Industrial Toxicology: Origins and Trends
Eula Bingham, Ph.D., John Zapp, Ph.D., (deceased)

1 Introduction

Industrial toxicology is a comparatively recent discipline, but its roots are shadowed in the mists of time. The beginnings of toxicology, the knowledge or science of poisons, are prehistoric. Earliest human beings found themselves in environments that were at the same time helpful and hostile to their survival. They found their food among the plants, trees, animals, and fish in their immediate surroundings, their clothing in the skins of animals, and their shelter mainly in caves. Their earliest tools and weapons were of wood and stone.

It was in the very early period of prehistory that humans must have become aware of the phenomenon of toxicity. Some fruits, berries, and vegetation could be eaten with safety and to their benefit, whereas others caused illness or even death. The bite of the asp or adder could be fatal, whereas the bite of many other snakes was not. Humans learned from experience to classify things into categories of safe and harmful. Personal survival depended on recognition and avoidance, so far as possible, of the dangerous categories.

In a unique difference from other animals, humans learned to construct tools and weapons that facilitated their survival. Stone and wood gave way in time to bronze and then to iron as materials for constructing these tools and weapons. The invention of the bow and arrow was a giant step forward in weaponry, for it gave humans a chance to kill animals or other people from a safe distance. And humans soon used their knowledge of the poisonous materials they found in their natural environment to enhance the lethality of their weapons.

One of the earliest examples of the deliberate use of poisons in weaponry was smearing arrowheads and spear points with poisons to improve their lethal effectiveness. In the *Old Testament* we find at Job 6:4, “The arrows of the Almighty find their mark in me, and their poison soaks into my spirit” (*The New English Bible* version). *The Book of Job* is generally dated at about 400 B. C.

L. G. Stevenson (1) cites the Presidential Address of F. H. Edgeworth before the Bristol Medico-Chirurgical Society in 1916, to the effect that Odysseus is credited in Homer's *Odyssey* with obtaining a man-killing poison from Anchialos, king of the Taphians, to smear on his bronze-tipped arrows. This particular passage does not occur in modern translations of the *Odyssey* and, according to Edgeworth, was probably expurgated from the text when Greece came under the domination of Athens, at which time the use of poisons on weapons was considered barbaric and not worthy of such a hero as Odysseus.

Because the earliest literature reference to Homer is dated at 660 B. C., well before the Pan-Athenian period, an early origin of the use of poisoned arrows can be assumed. Indeed, the word “toxic” derives from the early Greek use of poisoned arrows.

The Greek word for the bow was toxon and for a drug was pharmakon. Therefore, an arrow poison was called toxikon pharmakon, or drug pertaining to the bow. Many Latin words are derived from the Greek, but the Romans took only the first of the two Greek works as their equivalent of “poison,” that is, toxicum. Other Latin words for poison were venenum and virus. In the transition to English, toxicum became “toxin,” and the knowledge or science of toxins becomes “toxicology.”

There were practicing toxicologists in Greece and Rome. Stevenson (1) refers to a book by Sir T. C. Albutt (2) according to which the professional toxicologists of Greece and Rome were purveyors of poisons and dealt in three kinds: those that acted quickly, those that caused a lingering illness, and those that had to be given repeatedly to produce a cumulative effect. These poisons were of vegetable or animal origin, except for arsenic. Although the toxicity of lead was described by Hippocrates, and of mercury by Pliny the Elder, these metals were apparently not deliberately employed as poisons before the Renaissance.

There is little doubt that the customers of the early toxicologists were interested in assassination or suicide. Poisons offered a safer means for the assassin of disposing of an enemy than the more visible alternatives that posed the risk of premature discovery and possibly effective retaliation. As a means of suicide, poison often seemed more acceptable than other available means of self-destruction. Although poisons have continued to be used for both homicide and suicide, their popularity for these purposes has decreased as the popularity of firearms has increased.

The use of poisons as adjuncts to other weapons such as the spear or arrow ceased in Western Europe long before the discovery of firearms. It has persisted to this day in primitive civilizations such as those of the African pygmies and certain tribes of South American Indians. The use of poison on a large scale as a primary weapon of war occurred during World War I, when both sides employed poison gases. In the interval between World War I and World War II, the potential of chemical and biological agents as a means of coercion was thoroughly studied by most of the powers, and both sides were prepared to use them, if necessary, in World War II. Although their use in future wars has apparently been renounced, it should not be forgotten that the chemical and biological toxins remain viable means of coercion that could be utilized under appropriate circumstances in future conflicts. It would not be prudent to forget this in thinking about national defense.

The early and sinister uses of poisons did result in contributions to toxicology. Furthermore, the knowledge obtained did not require extrapolation to the human species, for humans were the subjects in early experimentation.

As mentioned earlier, the professional toxicologists of Greece and Rome had recognized and dealt with poisons that produced acute effects, those that produced lingering effects, and those that produced cumulative effects. We recognize these categories today. The “dose-effects” relationship was also recognized. In Plato's well-known description of the execution of Socrates, Socrates is required to drink a cup of hemlock, an extract of a parsley-like plant that bears a high concentration of the alkaloid coniine. When Socrates asks whether it is permissible to pour out a libation first to any god, the jailer replies, “We only prepare, Socrates, just as much as we deem enough.”

The ancients also had some concept of the development of tolerance to poisons. There have come down through the ages the poison damsel stories. In one of these, related by Stevenson (1), a king of India sent a beautiful damsel to Alexander the Great because he guessed rightly that Alexander was about to invade his kingdom. The damsel had been reared among poisonous snakes and had become so saturated with their venom that all of her secretions were deadly. It is said that Aristotle dissuaded Alexander from doing what seemed natural under the circumstances until Aristotle performed a certain test. The test consisted in painting a circle on the floor around the girl with an extract of dittany, believed to be a powerful snake poison. When the circle was completed, the girl is said to have collapsed and died. The poison damsel stories continued to appear from time to time, and even Nathaniel Hawthorne wrote a short story about one entitled “Rappaccini's Daughter.”

Kings and other important personages, fearing assassinations, sometimes tried to protect themselves from this hazard by attempting to build up an immunity to specific poisons by taking gradually increasing doses until able to tolerate lethal doses, sometimes—it is said—with results disastrous to the queen. Other kings took the precaution of having slaves taste their food before they ate. When slaves became too scarce or expensive, they substituted dogs as the official tasters and found that it worked about as well. Perhaps we have here the birth of experimental toxicology in which a nonhuman species was deliberately used to predict human toxicity.

Little of importance to the science of toxicology developed during the Middle Ages. Such research as was done was largely empirical and involved the search for such things as the Philosopher's Stone, the Universal Solvent, the Elixir of Life, and the Universal Remedy. The search for the Universal Remedy is rumored to have been abandoned in the twelfth century when the alchemists learned how

to make a 60% solution of ethyl alcohol through improved techniques of distillation and found that it had some remarkable restorative properties.

Although modern science is generally held to have had its beginnings in the seventeenth century with the work of Galileo, Descartes, and Francis Bacon, there was a precursor in the sixteenth century of some importance to toxicology. This was the physician-alchemist Phillipus Aureolus Theophrastus Bombastus von Hohenheim, known as Paracelsus. Born in 1490, the son of a physician, Paracelsus studied medicine with his father and alchemy at various universities. He was not impressed with the way that either medicine or alchemy was being taught or practiced and decided that more could be learned from the study of nature than from studying books by ancient authorities.

Through travel and observation, Paracelsus learned more than his contemporaries about the natural history of diseases, to whose cure he applied his knowledge of both medicine and alchemy. He advocated that the natural substances then used as remedies be purified and concentrated by alchemical methods to enhance their potency and efficacy. He also attempted to find specific therapeutic agents for specific diseases and became highly successful as a practicing physician; in 1526 he was appointed Town Physician to the city of Basel, Switzerland, and a lecturer in the university. Being of an egotistical and quarrelsome disposition, Paracelsus quickly antagonized the medical and academic establishment.

In the sixteenth century, syphilis was a more lethal disease than it was to become later, and the medical profession had no interest in it or cures for it. Paracelsus introduced and advocated the use of mercury for treating syphilis, and it worked. The establishment, however, was outraged and denounced Paracelsus for using a poison to treat a disease. Paracelsus loved an argument and responded to this and other accusations with a series of "Defenses," of which the Third Defense (3) contained this statement with respect to his advocacy of the use of mercury or any other poison for therapeutic purposes: "What is it that is not poison? All things are poison and none without poison. Only the dose determines that a thing is not poison." Paracelsus lectured and wrote in German, which was also contrary to prevailing academic tradition. When his works were eventually translated into Latin, the last sentence of the above quotation was usually rendered, "Dosis sola facit venenum" or "The dose alone makes a poison." This principle is the keystone of industrial hygiene and is a basic concept in toxicology.

Mercury soon became and remained the therapy of choice for syphilis for the next 300 years until Ehrlich discovered on his 606th trial an arsphenamine, Salvarsan, which was superior. Antimony was widely used as a therapeutic agent from the seventeenth to the nineteenth century, and with the medical profession was sharply divided as to whether it was more poison than remedy or more remedy than poison.

The period from the seventeenth to the nineteenth century witnessed little decline in the use of human subjects for the initial evaluation of remedies. In 1604, a book said to have been written by a monk named Basile Valentine, but more probably by an anonymous alchemist, was published under the title *The Triumphant Chariot of Antimony*. The book states that the author had observed that some pigs fed food containing antimony had become fat. Therefore, he gave antimony to some monks who had lost considerable weight through fasting, to see if it would help them to regain weight faster. Unfortunately, they all died. Up to this time, the accepted name for the element had been stibium (from which we retain the symbol Sb), but it was renamed antimony from the words auti-moine meaning "monk's bane." The *Oxford English Dictionary* agrees that this might be the popular etymology of the word. This anecdote can be credited to H. W. Haggard (4).

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2 Experimental Toxicology

Experimental toxicology, as we know, it followed the rise of organic chemistry, which is usually dated at around 1800. The rise was very rapid, and it is estimated that by 1880 some 12,000 compounds had been synthesized, and of these some turned out to be very toxic, in some cases proving fatal to the chemists who prepared them. Two of the war gases employed on a large scale in World War I, that is, phosgene ($COCl_2$) and mustard gas, bis(b-chloroethyl) sulfide, had been prepared in 1812 and 1822, respectively.

Early organic chemists were not deliberately looking for poisons, but for dyes, solvents, or pharmaceuticals. For example, toxicity was an unwanted side effect, but if it was there, it had to be recognized. The sheer number of new organic compounds synthesized in the laboratory, along with a growing public disapproval of the practice of letting toxicity be discovered by its effects on people, led to a more extensive use of convenient and available animals such as dogs, cats, or rabbits as surrogates for human beings, much as some of the ancient kings used dogs instead of slaves to test their food before they dined.

Loomis (5) credits M. J. B. Orfila (6) with being the father of modern toxicology. A Spaniard by birth, Orfila studied medicine in Paris. According to Loomis:

He is said to be the father of modern toxicology because his interests centered on the harmful effects of chemicals as well as therapy of chemical effects, and because he introduced quantitative methodology into the study of the action of chemicals on animals. He was the author of the first book devoted entirely to studies of the harmful effects of chemicals (6). He was the first to point out the valuable use of chemical analyses for proof that existing symptomatology was related to the presence of the chemical in the body. He criticized and demonstrated the inefficiency of many of the antidotes that were recommended for therapy in those days. Many of his concepts regarding the treatment of poisoning by chemicals remain valid today, for he recognized the value of such procedures as artificial respiration, and he understood some of the principles involved in the elimination of the drug or chemical from the body. Like many of his immediate followers, he was concerned primarily with naturally occurring substances for which considerable folklore existed with respect to the harmfulness of such compounds.

A reading of some of the earlier nineteenth century reports indicates a lack of recognition of and concern with either intraspecies or interspecies variation. Sometimes it is not possible to determine from the report which species of animal was tested. Some reports were based on dosage of only one animal, it being assumed that all others would react similarly. In reports of inhalation toxicity, a lethal concentration might be identified without designating the length of the exposure time.

The initial recognition of biological variability comes from the study of the action of drugs rather than from the study of the action of chemicals as such. The increased interest in the action of drugs resulted from the availability of so many new organic compounds that could be explored for possible therapeutic activity.

In the second half of the nineteenth century, the phenomenon of biological variability was recognized by pharmacologists, as was also the necessity for establishing the margin of safety between a therapeutically effective dose and a toxic dose of a drug. Clinical trials of new drugs with adequate controls began to be accepted as good science. The traditional wisdom and beliefs about therapeutic practice were reexamined by pharmacologists.

Early European efforts are credited by Warren Cook to Gruber (7) who used animals and himself in 1883 to set the boundaries for carbon monoxide poisoning. Lehmann and his colleagues (8) performed toxicity testing on numerous compounds using animals, and these provided the basis for establishing many exposure limits. Korbert (9) provided dose response data on acute exposures for twenty substances that gave information on levels that produced minimal symptoms after several hours, ½ to 1 hour exposures without serious disturbances, and ½ to 1 hour exposures that range from dangerous to rapidly fatal to man and animals. Many of these evaluations are still valid today.

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3 Industrial Toxicology
Concerns for the safety of the workplace drove the development of industrial toxicology. The British physician, C.T. Thackrah, noted that, "Most persons who reflect on the subject will be inclined to admit that our employments are to a considerable degree injurious to health ... " and "Evils are suffered to exist, even when the means of correction are known and easily applied. Thoughtlessness or apathy is the only obstacle to success" (10).

In the United States, the first recognition of occupational disease by Benjamin McCready appeared (11) in an essay published by the Medical Society of New York. Illnesses including dermatoses were noted as well as long hours, poor ventilation, and child labor. Certainly, some of the illnesses were from chemical exposures and dust, but it should be noted that ergonomic and human performance concepts are raised in these early writings. Working conditions became a cause for concern among social movements mainly because of child labor. More than a century and a half later we still are concerned about child labor.

Recognition of the relationship between chemical agents and disease (industrial toxicology) moved rapidly in Europe during the last decade of the nineteenth century. This activity may have been stimulated in Germany by the passage during Bismarck's rule of the Workingmen's Insurance Law, which set up an insurance fund into which both employers and employees contributed that amounted to about 6% of total wages paid out. For this, the workers obtained free medical care, as well as some compensation during periods of disability.

Industrial toxicology in the United States grew out of work in occupational and industrial health by such investigators as Hamilton and Hardy (12), the Drinkers at Harvard (13, 14), Hatch at Pittsburgh (15), and Kehoe (16) and Heyroth (17) at Cincinnati. Government and industry provided financial support for these efforts.

There had been no organic chemical industry in the United States before World War I. It was born just after the war, because during the war, the United States felt the lack of useful products such as aniline dyes (used for printing our stamps and currency, among other things) and pharmaceuticals (e.g., aspirin), which had been imported from Germany. Manpower and facilities used during the war for manufacturing munitions became available after 1918, and several companies decided to use them to get into the organic chemical business. Because neither employers nor workers had any previous experience in making and handling organic chemicals, the effects of unanticipated toxicity began to be encountered. That toxicity was not wanted because it was counterproductive and, along with other problems, had to be managed if the industry was to survive.

To manage a problem, it must be anticipated, the causes must be identified and analyzed, and practical means of overcoming the problem must be available. As a means to this end, industrial preventive medicine, industrial toxicology, and industrial hygiene became valuable tools. By the mid-1930s, several large chemical companies in the United States had established in-house

laboratories of industrial toxicology, e.g., DuPont, Dow, and Union Carbide. The purpose of these laboratories was to provide management with sufficient information about the toxicity of new chemicals to enable prudent business decisions.

Another important source of experimental toxicological data that was used to inform the workplace was from work by Hueper at one time, a pathologist at DuPont and chemists who were interested in chemical carcinogenesis and mechanistic research, e.g., the Millers (18) at Wisconsin and Ray (19) at Cincinnati. Early experimental data captured in Hartwell (20) "Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Federal Security Agency, U.S. Public Health Service" eventually provided the bases for the first early lists of carcinogenic chemicals prepared by the American Standards Association and the American Conference of Governmental and Industrial Hygienists in the 1940s.

It should be emphasized that although these beginning efforts in industrial toxicology were occurring in the United States, in Europe experimental toxicology and studies in occupational disease were well underway. For example, early work of the British on coal tars, mineral oils, and other carcinogens (aromatic amines) were widely available (22–25).

It is important to recognize that by the 1930s the data from experimental studies in animals, human case reports, and early epidemiological studies reported the causes of many occupationally induced cancers. Table 1.1 (26–36) presents data and references from several of these early studies, and although more investigations have added to the knowledge regarding these carcinogens, these early observations remain valid.

Table 1.1. Early Studies in Chemical Carcinogenesis

Year	First Reported by	Reported Agent or Process	Site
1775	Pott (26)	Soot	Scrotum
1822	Paris (27)	Arsenic	Skin
1873	Volkmann (28)	Crude wax from coal	Skin
1876	Bell (29)	Shale oil	Skin
1879	Härting and Hesse (30)	Ionizing radiation	Lung
1894	Unna (31)	Ultraviolet radiation	Skin
1895	Rehn (32)	Aromatic amines	Bladder
1898	Mackenzie (33)	Creosote	Skin
1935	Pfeil (34)	Chromate production	Lung
1917	Leymann (35)	Crude anthracene (coal tar?)	Skin
1929	Martland (36)	Radium	Bone

In the United States, a dramatic change occurred in 1935 with the passage of the Social Security Act. Financial and technical support from the Federal Government were given to the States, mostly to Health Departments, to develop health programs to protect workers. New York and Massachusetts maintained their programs in the Labor Department. This effort was very important in industrial toxicology because all of these programs performed investigations into chemical and physical agents in the workplace and the development of disease.

It is important to mention the work of the National Safety Council, which began a series of articles in the 1920s that described the toxicology of certain chemicals in the workplace and provided

recommendations for medical and industrial hygiene monitoring. Recognized leaders in the field wrote these guidelines, usually as a committee document. One example is the classic document on benzol toxicity (37).

Although not called “industrial toxicology,” the emergence of industrial medicine and industrial hygiene as significant public health disciplines became embedded in the basic principles of industrial toxicology, that is, connecting chemical exposures with development of disease through measuring exposures, developing dose-response relationships for adverse health effects, and recommending interventions to reduce exposures and disease. From these early beginnings, guidelines to prevent illness (and injuries) were developed as part of recommendations issued by the National Safety Council, American National Standards Institute in the 1920s, and later by the American Conference of Government Industrial Hygiene (TLVs).

By 1938, there were enough government-affiliated personnel engaged in the practice of industrial hygiene at the federal, state, and local levels to make possible the formation of the American Conference of Governmental Industrial Hygienists (ACGIH). In 1939, the American Industrial Hygiene Association (AIHA) was founded. These societies sought to bring collective knowledge regarding the toxicology of workplace hazards, mainly chemicals, and the necessary skills to reduce exposures. In the early period, industrial toxicologists were involved in recognizing, evaluating, and controlling hazards of the workplace that cause occupational illness and disability. Eventually, as investigators working in industrial toxicology became more specialized, they formed their own society in the 1960s, the Society of Toxicology, and eventually began to meet separately from the American Industrial Hygiene Association.

At the turn of the twentieth century, most industrial toxicological information was gleaned from observations of workers employed in various industries. By the 1930s, experimental industrial toxicology was expanding rapidly with the introduction of studies using animals. Most early studies focused either on cancer or acute toxic responses such as asphyxiation and acute lung injury or neurological symptoms such as dizziness, tremors, convulsions, etc., and death. Probably the development of certain chronic lung diseases resulting from industrial exposures over several years, such as silicosis, coal workers' pneumoconiosis, asbestosis, beryllioses, and the recognition of lead poisoning as a chronic disease, led to the development and use of experimental chronic toxicity studies.

Between 1920 and 1970 (i.e., before most environmental and occupational health laws), industrial toxicology was performed mainly by industry in its own laboratories, e.g., DuPont's Haskell Laboratory where one of the authors of this chapter worked, at Dow Chemical Company where V. K. Rowe was a pioneer investigator, and at various university laboratories, such as Harvard, University of Pittsburgh, New York University, University of Cincinnati, and Johns Hopkins University, where the work was supported by industry. The arrangements at these laboratories ranged from contracts to grant relationships and although the interpretation of the results may have involved some controversy, by and large, the experimental results have stood the test of time. A great deal of toxicological data came from industries where physicians, industrial hygienists, or toxicologists reported adverse health responses in certain occupations where a specific chemical was used. It was this collection of industrial toxicological data that was brought together and formed the basis of the first two editions of Patty's. For example, it is common over the years to see the names of industry leaders in health and safety provide “personal communication” as the source of certain toxicological data (e.g., Dr. D. Fassett, Eastman Kodak) in this volume.

Often these early references are to industry data or observations and were not published in the peer-reviewed literature but remain in files as unpublished reports. Fortunately, some of the reports of early studies are filed in libraries and are public documents (38).

3.1 Acute and Chronic Tests

It is interesting to note the role that World War I played in early toxicology. World War I stimulated a great many studies of acute inhalation toxicity for chemical warfare purposes. The number of

compounds examined during World War I as possible chemical warfare agents is estimated to have been between 3,000 and 4,000, and of these, 54 were used in the field at one time or another. During World War I, chemical warfare agents were selected for their irritancy to skin or eyes, rather than for systemic toxicity, and both the techniques developed for their study, as well as the information gained, were useful to postwar industrial toxicology.

Although chronic, or cumulative, toxicity had been recognized for centuries, it received much less attention than acute toxicity until more recent times, possibly because acute toxic effects were more likely to be recognized than chronic effects. Chronic toxicity could, however, be investigated by any relevant route of exposure, provided that the dosages used were small enough to permit the chronic damage to appear. The most perplexing question was, “How long should a prolonged exposure be to gain all the necessary information?” Opinions differed, but the majority of toxicologists seemed to feel that 90 days of repeated exposure would be sufficient to elicit all of the important manifestations of chronic toxicity in the rat or mouse, provided that the daily doses were sufficiently high but still consistent with survival. This effort was given impetus by the Food and Drug Administration as it began to require such tests for food additives and pesticides. It should be recalled that until 1970 FDA not EPA prescribed the testing requirements for pesticides.

In 1938, as a consequence of the elixir of sulfanilamide tragedy, in which a number of persons died from taking a solution of sulfanilamide in diethylene glycol for therapeutic purposes, the U.S. Food and Drug Administration undertook a comprehensive investigation of the toxicity of the glycols. This investigation culminated in a “lifetime” feeding study with diethylene glycol in rats. In 1945, Nelson et al. (39) reported the results at a meeting of the Federation of American Societies for Experimental Biology. A surprising result of the study was the finding that some of the rats fed a diet containing 4% diethylene glycol had developed bladder stones and that some of those with bladder stones had also developed fibropapillomatous tumors of the bladder. Because neither bladder stones nor tumors had been found in tests of shorter duration, it became obvious that, for some lesions, 90 days was not a sufficient time of exposure. By 1950, the FDA had begun recommending lifetime studies, for which they considered two years in the rat as proper, as part of proof of safety of proposed new intentional and unintentional food additives and pesticides. As a guide to the perplexed, members of the FDA staff prepared an article entitled “Procedures for the Appraisal of the Toxicity of Chemicals in Foods, Drugs, and Cosmetics,” which was published in the September, 1949, issue of Food Drug cosmetic Law Journal (40). It contained a section on how to do long-term chronic toxicity studies and recommended a period of two years for the rat, plus one year for a nonrodent species such as the dog.

Although not an official regulation, the article advised every one of the FDA's expectations with respect to data submitted to it as proof of safety of the proposed new food additive or pesticide. A revision of the article appeared in 1955 (41), and a third revision was published in 1959 as a monograph by the Association of Food and Drug Officials of the United States (42).

During the same period, the Food Protection committee of the National Academy of Science/National Research Council was publishing and revising “Principles and Procedures for Evaluating the Safety of Food Additives” (43) which were, in general, consistent with the FDA staff's guidelines. One common thread ran through both sets of recommendations. With each revision, the complexity of the tests increased and so did the cost.

The FDA's recommended protocol in 1959 (42) for a “lifetime” test with rats called for four groups of a minimum of 25 males and 25 females each. There would be a control group, a low-dose group (a no-effect level, it was hoped), a high-dose group (chosen to be an effect level), and a mid-dose group. All animals would be necropsied for gross pathology. Selected organs would be weighed, and selected organs would be preserved for histopathology. During the course of the experiment, food consumption and weight gains would be measured, blood and urine would be monitored for deviations from normality, and nay-behavioral changes would be noted. A three-generation reproduction study would be carried out at all dose levels. A similar experiment would also be

carried out with four groups of six to eight dogs each for an exposure period of two years to determine whether a nonrodent species responded differently from the rat. Dog reproduction studies were not required. The lifetime of the rat was considered to be two years for the purposes of the test.

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4 Trends
4.1 Toxicological Testing
Concerns raised 20 years ago about the costs and validity of toxicological information that may be used for making risk assessments to protect workers and for business decisions on product development are still valid today.

When John Zapp wrote the first part of this chapter, it was the late 1970s and the other author, Eula Bingham, Assistant Secretary of Labor for Occupational Safety and Health, was grappling with the need for toxicological data on which to base occupational health and safety standards. It was during this period (1978) that the National Toxicology Program (NTP) began. This effort was intended to expand the carcinogen testing program of the National Cancer Institute that began during the 1960s.

Today, the National Toxicology Program (44) provides a significant portion of all new data on industrial chemicals used in the United State and in other countries. At present, 80,000 chemicals are used in the United States and an estimated 2,000 new ones are introduced annually to be used in products such as foods, personal care products, prescription drugs, household cleaners, and lawn care products. The effects of many of these chemicals on human health are unknown, yet people may be exposed to them during their manufacture, distribution, use, and disposal or as pollutants in our air, water, or soil.

The National Toxicology Program (NTP) was established by the Department of Health and Human Services (DHHS) in 1978 and charged with coordinating toxicological testing programs within the Public Health Service of the Department; strengthening the science base in toxicology; and providing information about potentially toxic chemicals to health regulatory and research agencies, scientific and medical communities, and the public (See Fig. 1.1). The NTP is an interagency program whose mission is to evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology. In carrying out its mission, the NTP has several goals:

- to provide toxicological evaluations of substances of public health concern;
- to develop and validate improved (sensitive, specific, rapid) testing methods;
- to develop approaches and generate data to strengthen the science base for risk assessment; and
- to communicate with all stakeholders, including government, industry, academia, the environmental community, and the public.

Nationally, the NTP rodent bioassay is recognized as the standard for identifying carcinogenic agents. However, the NTP has expanded its scope beyond cancer to include examining the impact of chemicals on noncancer toxicities such as those affecting reproduction and development, inhalation, and the immune, respiratory, and nervous systems. Recently a Center for Evaluation of Risks to Human Reproduction and a Center for the Evaluation of Alternative Toxicological Methods were created.

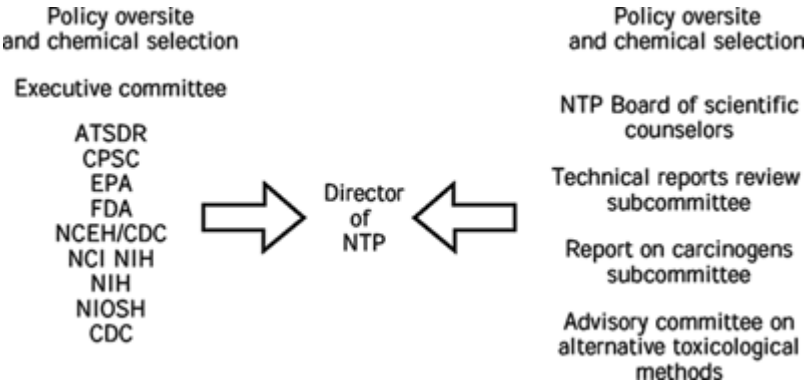

Figure 1.1. National Toxicology Program. The National Toxicology Program (NTP) is headquartered at the NIEHS/NIH, and its director serves as director of the NTP. The Executive Committee composed of the heads of key research and regulatory Federal agencies provides oversight for policy issues. Science oversight and peer review are provided through a mix of Federal, academic, industrial, and public interest science experts.

NTP's testing program seeks to use mechanism-based toxicology studies to enhance the traditional approaches. Molecular biology tools are used to characterize interactions of chemicals with critical target genes. Examples of mechanism-based toxicology include identification of receptor-mediated toxicants, molecular screening strategies, use of transgenic animal models, and the development of alternative or complementary *in vivo* tests to use with rodent bioassays. Inclusion of such strategies can provide insight into the molecular and biological events associated with a chemical's toxic effect and provide mechanistic information that is useful in assessing human risk. Such information can also lead to the development of more specific and sensitive (and often less expensive) tests for use in risk assessment. There is a strong linkage between mechanism-based toxicology and the development of more biologically based risk assessment models. Such models are useful in clarifying dose–response relationships, making species comparisons, and identifying sources of interindividual variability.

Genetically altered or “transgenic” mouse models carry activated oncogenes or inactivated tumor suppressor genes involved in neoplastic processes in both humans and rodents. This trait may allow them to respond to carcinogens more quickly than conventional rodent strains. The advantage provided by such an approach compared with standard rodent models is that in addition to chemicals undergoing metabolism, distribution, and relevant pharmacokinetics, the neoplastic effects of agents can be observed in the transgenic models within a time frame in which few if any spontaneous tumors would arise.

During the past few years, the NIEHS/NTP has evaluated transgenic strains in toxicological testing strategies. The response for 38 chemicals was compared in two genetically altered mouse strains ($p53^{def}$: p53+/– heterozygous and Tg.AC: n-*Ha-ras* transgene) with that of wild-type mice tested in chronic two-year bioassays. Findings from these studies were evaluated by the NTP Board of Scientific Counselors for their suitability in NTP toxicological evaluations. Based upon the NIEHS/NTP review, the transgenic models performed largely according to predictions; they identified all known human carcinogens and most of the multisite/multispecies rodent carcinogens but failed to identify completely rodent carcinogens that produced tumors in selected organs in two-year studies.

The use of these genetically altered mouse models holds promise in carcinogenesis research and testing and clearly is more rapid and less expensive than traditional NTP two-year bioassay studies. The challenge still facing the NTP is to design studies that address remaining questions and concerns and to explore how these models can be used in risk assessment.

The NIEHS Environmental Genome Project is a multicenter effort to identify systematically the alleles of 200 or more environmental disease susceptibility genes in the U.S. population. Information from this human exposure assessment initiative together with the environmental genome project will provide the science base essential for future, meaningful studies of gene/environment interactions in disease etiology.

As a part of an interagency human exposure assessment initiative, the NTP and the NCEH/CDC are collaborating on a pilot project to quantify approximately 70 chemicals in either human blood or urine that are considered endocrine disrupters. Biological samples from the National Health and Nutrition Examination Surveys (NHANES) are being tested. These data will be used to estimate human exposure to endocrine disrupting agents within the U.S. population and to identify those of greatest public health concern. This information can be used in prioritizing chemicals for study and in developing biologically based models for estimating human risks.

4.2 Human Genome

The revolution in genetics and specifically in mapping the human genome, as well as the development of transgenic animals, will radically change the way we evaluate chemical and physical agents. See chapter 7 by Dan Nebert in this volume.

The need to keep toxicologists apprised of the current thinking regarding many new advances in certain toxicological fields has led us to include a special chapter on genetics. Although human variability was recognized as a phenomenon during the last half of the nineteenth century, pharmacogenetics has now become a significant and critical element in understanding dose-response curves in every aspect of toxicology from predicting who can metabolize a chemical to a carcinogen to determining which patient may be at risk of death from a prescribed doses of an anticancer drug. This area will probably bring about the greatest changes in our understanding of worker responses to occupational exposures.

4.3 Global Workplaces

The workplaces of concern in early editions of Patty's were mainly those in U.S. factories where chemicals and certain processes occurred. Today, many of those activities and chemicals have moved overseas, and the scene is dynamic and changing as we write. Hopefully, the toxicological information contained in these volumes will be useful in global workplaces. We have welcomed authors from outside the United States, many of whom are outstanding toxicologists in their own countries and are known internationally. It is the hope of the editors that this trend will continue for Patty's in future editions. Without modern telecommunications and E-mail, we would not have the courage to propose such authors.

4.4 Mixtures

Mixtures have reemerged as a special concern in toxicology. Mainly during the period (1930–1970) when complex mixtures, particularly those derived from fossil fuels (petroleum fractions, coal tar) were being actively investigated, the issues revolved around finding the critical chemical in the complex mix that was responsible for its toxicology. Chemicals in these mixtures enhanced or inhibited the critical chemical. When chemical exposures occurred either together or in sequence as in chemical carcinogenesis, the concepts of initiation and promotion became part of understanding mixtures. Recognition that contributions from several chemicals affecting the same target organ could be at least additive and perhaps of concern in the workplace led the ACGIH to develop a methodology for simple mixtures.

As more information has been produced during the last 10 years regarding the content of hazardous waste sites, once again there are efforts to develop methodologies to account for multiple chemical exposures in attempting to assess risk. One of the most notable is the dioxins and the use of "equivalency factors." However, the way to determine any potential for interactions among a mixture of chemical exposures remains a problem in toxicology and will continue to require investigation in the future.

4.5 Training and Personnel

Current training programs in toxicology place heavy emphasis on genetics. Courses in genetics and molecular biology have largely replaced other fundamental medical disciplines such as biochemistry,

physiology, and pharmacology. Sometimes, aspects of these elements are covered to a small extent in a toxicology course. Courses in risk assessment are usually elective. Most graduate programs in toxicology today provide little background for individuals seeking to work in industrial toxicology. On the other hand, the practical elements that remain as staples in industrial hygiene programs provide much that is useful in industrial toxicology. The deficiency in these programs is the lack of training in the biological sciences, since most industrial hygiene graduates have little or no toxicology unless they take it as an elective. The result is that industry today must be prepared to provide current graduates with on-the-job training equivalent to 2–3 years of a postdoctoral fellowship if they are to work in industrial toxicology.

Industrial Toxicology: Origins and Trends

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Pathways and Measuring Exposure To Toxic Substances
Morton Lippmann, Ph.D., CIH

1 Introduction

For toxic substances in the environment to exert adverse effects on humans, they must deposit on and/or penetrate through a body surface and reach target sites where they can alter normal functions and/or structures. The critical pathways and target sites can vary greatly from substance to substance and, for a given substance, can vary with its chemical and physical form. A further complication arises from the fact that chemical and/or metabolic transformations can take place between deposition on a body surface and the eventual arrival of a toxic substance or metabolite of that substance at a critical target site. A critical target site is where the toxic effect of first or greatest concern takes place.

This chapter reviews and summarizes current knowledge concerning the generic aspects of the environmental pathways and processes leading to (1) deposition of toxicants on body surfaces (skin, respiratory tract, gastrointestinal tract); (2) uptake of toxicants by epithelial cells from environmental media (air, waste, food); (3) translocation and clearance pathways within the body for toxicants that penetrate a surface epithelium; and (4) the influence of chemical and physical form of the toxicant on the metabolism and pathways of the chemical of concern. Where the physical attributes of the toxicant such as the length and biopersistence of airborne fibers are of generic concern, these are also discussed in this chapter. Other aspects of the pathways and the fates of toxicants that are specific to the chemical species that are the subject of the following chapters of this volume are discussed, as appropriate, in those chapters.

This chapter also summarizes and discusses techniques for measuring personal and population exposures to environmental toxicants and their temporal and spatial distributions. Quantitative exposure assessment, as a component of risk assessment, involves consideration of (*1*) the nature and properties of chemicals in environmental media, (*2*) the presence in environmental media of the specific chemicals that are expected to exert toxic effects, (*3*) the temporal and spatial distributions of the exposures of interest, and (*4*) the ways that ambient or workplace exposure measurements or models can be used to draw exposure inferences. In this context, the knowledge of deposition, fate, pathways, and rates of metabolism and transport within the body, to be reviewed later in this chapter, provide appropriate rationales for size-selective aerosol sampling approaches and/or usage of biomarkers of exposure. Finally, this chapter discusses the choices of sampling times, intervals, rates, durations, and schedules most appropriate for exposure measurements and/or modeling that are most relevant to risk assessment strategies that reflect data needs for (*1*) documenting compliance with exposure standards; (*2*) performing epidemiological studies of exposure–response relationships; (*3*) developing improved exposure models; and (*4*) facilitating secondary uses of exposure data for epidemiological research, studies of the efficacy of exposure controls, and analyses of trends.

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2 Nature of Toxic Substances

2.1 Physical Properties of Toxic Air Contaminants

Chemicals can be dispersed in air at normal ambient temperatures and pressures in gaseous, liquid, and solid forms. The latter two represent suspensions of particles in air and were given the generic term “aerosols” by Gibbs (1) by analogy with the term “hydrosol,” used to describe dispersed systems in water. Although hydrosols generally have uniformly sized particles, aerosols do not.

Gases and vapors, which are present as discrete molecules, form true solutions in air. Particles composed of moderate- to high-vapor-pressure materials evaporate rapidly because those small enough to remain suspended in air for more than a few minutes (i.e., those smaller than about 10 mm) have large surface to volume ratios. Some materials with relatively low vapor pressures can have appreciable fractions in both vapor and aerosol forms simultaneously.

Once dispersed in air, contaminant gases and vapors generally form mixtures so dilute that their physical properties, such as density, viscosity, and enthalpy, are indistinguishable from those of clean air. Such mixtures follow ideal gas law relationships. There is no practical difference between a gas and a vapor except that the latter is generally the gaseous phase of a substance that can exist as a solid or liquid at room temperature. While dispersed in the air, all molecules of a given compound are essentially equivalent in their size and capture probabilities by ambient surfaces, respiratory tract surfaces, and contaminant collectors or samplers.

Aerosols are dispersions of solid or liquid particles in air and have the very significant additional variable of particle size. Size affects particle motion and, hence, the probabilities of physical phenomena such as coagulation, dispersion, sedimentation, impaction onto surfaces, interfacial phenomena, and light-scattering. It is not possible to characterize a given particle by a single size parameter. For example, a particle's aerodynamic properties depend on density and shape, as well as linear dimensions, and the effective size for light scattering depends on refractive index and shape.

In some special cases, all of the particles are essentially the same size. Such aerosols are considered *monodisperse*. Examples are natural pollens and some laboratory-generated aerosols. More typically, aerosols are composed of particles of many different sizes and hence are called *heterodisperse* or *polydisperse*. Different aerosols have different degrees of size dispersion. Therefore, it is necessary to specify at least two parameters in characterizing aerosol size: a measure of central tendency, such as a mean or median, and a measure of dispersion, such as an arithmetic or geometric standard deviation.

Particles generated by a single source or process generally have diameters that follow a log-normal distribution, i.e., the logarithms of their individual diameters have a Gaussian distribution. In this case, the measure of dispersion is the geometric standard deviation, which is the ratio of the 84.16th percentile size to the 50th percentile size. When more than one source of particles is significant, the resulting mixed aerosol will usually not follow a single log-normal distribution, and it may be necessary to describe it by the sum of several distributions.

2.1.1 Particle and Aerosol Properties Many properties of particles, other than their linear size, can greatly influence their airborne behavior and their effects on the environment and health. These include

Surface: For spherical particles, the surface varies as the square of the diameter. However, for an aerosol of given mass concentration, the total aerosol surface increases with decreasing particle size. For nonspherical or aggregate particles, the particles may have internal cracks or pores, and the ratio of surface to volume can be much greater than for spheres.

Volume: Particle volume varies as the cube of diameter; therefore, the few largest particles in an aerosol dominate its volume (or mass) concentration.

Shape: A particle's shape affects its aerodynamic drag, as well as its surface area, and therefore its motion and deposition probabilities.

Density: A particle's velocity in response to gravitational or inertial forces increases as the square root of its density.

Aerodynamic diameter: The diameter of a unit-density sphere that has the same terminal settling velocity as the particle under consideration is equal to its aerodynamic diameter. Terminal settling velocity is the equilibrium velocity of a particle that is falling under the influence of gravity and

fluid resistance. Aerodynamic diameter is determined by the actual particle size, the particle density, and an aerodynamic shape factor.

2.1.2 Types of Aerosols Aerosols are generally classified in terms of their processes of formation. Although the following classification is neither precise nor comprehensive, it is commonly used and accepted in the industrial hygiene and air pollution fields.

Dust: An aerosol formed by mechanical subdivision of bulk material into airborne fines that have the same chemical composition. Dust particles are generally solid and irregular in shape and have diameters greater than 1 mm.

Fume: An aerosol of solid particles formed by condensation of vapors formed at elevated temperatures by combustion or sublimation. The primary particles are generally very small (less than 0.1 mm) and have spherical or characteristic crystalline shapes. They may be chemically identical to the parent material, or they may be composed of an oxidation product such as a metal oxide. Because they may be formed in high concentrations, they often coagulate rapidly and form aggregate clusters of low overall density.

Smoke: An aerosol formed by condensation of combustion products, generally of organic materials. The particles are generally liquid droplets whose diameters are less than 0.5 mm.

Mist: A droplet aerosol formed by mechanical shearing of a bulk liquid, for example, by atomization, nebulization, bubbling, or spraying. The droplet size can cover a very large range, usually from about 2 to greater than 50 mm.

Fog: An aqueous aerosol formed by condensation of water vapor on atmospheric nuclei at high relative humidities. The droplet sizes are generally larger than 1 mm.

Smog: A popular term for a pollution aerosol derived from a combination of smoke and fog. The term is commonly used now for any atmospheric pollution mixture.

Haze: A submicrometer-sized aerosol of hydroscopic particles that take up water vapor at relatively low relative humidities.

Aitken or condensation nuclei (CN): Very small atmospheric particles (mostly smaller than 0.05 mm) formed by combustion processes and by chemical conversion from gaseous precursors.

Accumulation mode: A term given to the particles in the ambient atmosphere ranging in diameter from 0.1 to about 1.0 mm. These particles generally are spherical, have liquid surfaces, and form by coagulation and condensation of smaller particles that derive from gaseous precursors. Too large for rapid coagulation and too small for effective sedimentation, they accumulate in the ambient air.

Coarse particle mode: Ambient air particles larger than about 2.5 mm in aerodynamic diameter and generally formed by mechanical processes and surface dust resuspension.

2.1.3 Physical Properties of Toxic Liquid and Solid Components For liquids and solids deposited on human skin or taken into the gastrointestinal (GI) tract by ingestion, penetration to and through the surface epithelium depends upon their physical form, their solubility in the fluids on the surface, and the structure and nature of the epithelial barrier. Dissolved chemicals can penetrate by diffusion, whereas chemicals present as particles or droplets must find access via pores or defects in the barrier associated with injury caused by trauma or corrosive chemicals or by dissolution in solvents that alter the barrier function.

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3 Human Exposure Pathways and Dosimetry

People can be exposed to chemicals in the environment in numerous ways. The chemicals can be inhaled, ingested, or taken up by and through the skin. Effects of concern can take place at the initial epithelial barrier, i.e., the respiratory tract, the gastrointestinal (GI) tract, or the skin, or can occur in other organ systems after penetration and translocation by diffusion or transport by blood, lymph, etc. As illustrated in Fig. 2.1, exposure and dose factors are intermediate steps in a larger continuum ranging from the release of chemicals into an environmental medium to an ultimate health effect in an exposed individual. There are, of course, uncertainties of varying magnitude at each stage. The diagram could also be applied to populations as well as to individuals. In that case, each stage of the figure would include additional variance for the interindividual variability within a population associated with age, sex, ethnicity, size, activity patterns, dietary influences, use of tobacco, drugs, alcohol, etc.

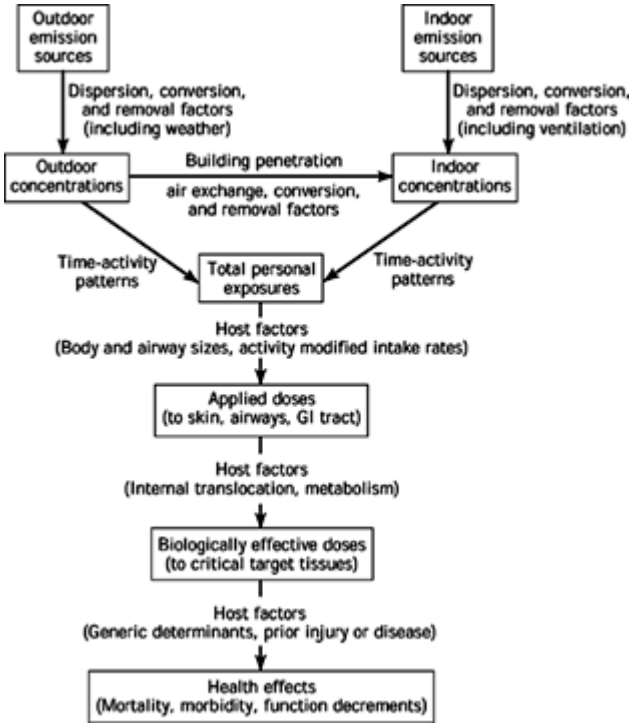

Figure 2.1. Framework for personal exposure assessment and exposure-response (modified from Ref. 1a).

Exposure is a key and complex step in this continuum. The concept of total human exposure developed in recent years is essential to the appreciation of the nature and extent of environmental health hazards associated with ubiquitous chemicals at low levels. It provides a framework for considering and evaluating the contribution to the total insult from dermal uptake, ingestion of food and drinking water, and inhaled doses from potentially important microenvironments such as workplace, home, transportation, recreational sites, etc. More thorough discussions of this key concept have been prepared by Sexton and Ryan (2), Lioy (3), and the National Research Council (4). Guidelines for Exposure Assessment have been formalized by the U.S. Environmental Protection Agency (5).

Figure 2.2 outlines possible approaches for estimating contaminant exposures of populations, as well as individuals, in a conceptual sense, and Fig. 2.3 indicates terminologies used by EPA to describe exposures and their distributions within a population.

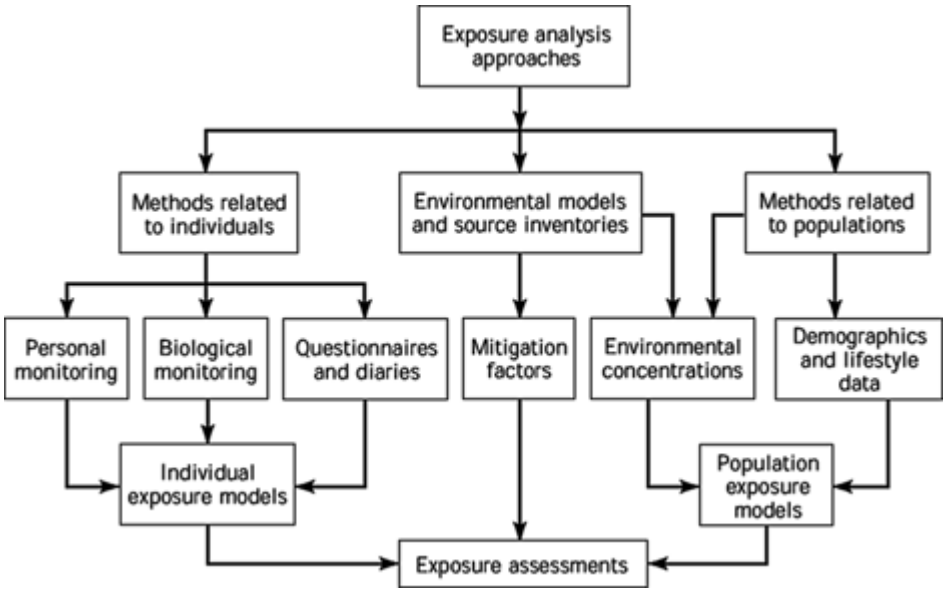

Figure 2.2. Possible approaches for analyzing contaminant exposures.

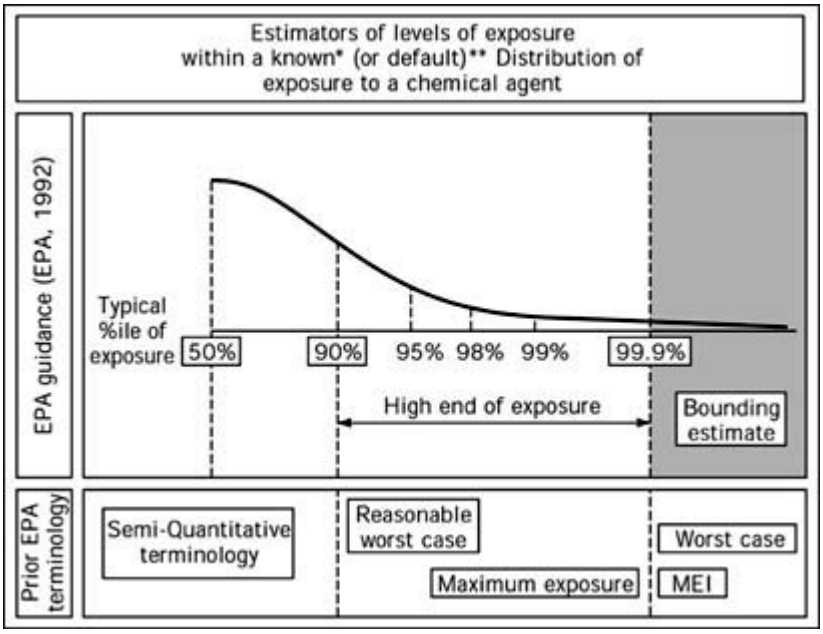

Figure 2.3. EPA guidance on terminology for exposures in the general population.

Toxic chemicals in the environment that reach sensitive tissues in the human body can cause discomfort, loss of function, and changes in structure leading to disease. This section addresses the pathways and transport rates of chemicals from environmental media to critical tissue sites, as well as retention times at those sites. It is designed to provide a conceptual framework as well as brief discussions of (*1*) the mechanisms for—and some quantitative data on—uptake from the environment; (*2*) translocation within the body, retention at target sites, and the influence of the physicochemical properties of the chemicals on these factors; (*3*) the patterns and pathways for exposure of humans to chemicals in environmental media; and (*4*) the influence of age, sex, size, habits, health status, etc.

3.1 Terminology

An agreed on terminology is critically important when discussing the relationships among toxic chemicals in the environment, exposures to individuals and populations, and human health. Key terms used in this chapter are defined as follows:

Exposure: Contact with external environmental media containing the chemical of interest. For fluid media in contact with the skin or respiratory tract, both concentration and contact time are critical. For ingested material, concentration and amount consumed are important.

Microenvironments: Well-defined locations that can be treated as homogeneous (or well characterized) in the concentrations of a chemical or other stressor.

Deposition: Capture of the chemical at a body surface site on the skin, the respiratory tract, or the GI tract.

Clearance: Translocation from a deposition site to a storage site or depot within the body or elimination from the body.

Retention: Presence of residual material at a deposition site or along a clearance pathway.

Dose: The amount of chemical deposited on (applied dose) or translocated to a site on or within the body where toxic effects can take place (delivered dose).

Target tissue: A site within the body where toxic effects lead to damage or disease. Depending on the toxic effects of concern, a target tissue can extend from whole organs to specific cells and to subcellular constituents within cells.

Exposure surrogates or indices: Indirect measures of exposure, such as: (*1*) concentrations in environmental media at times or places other than those directly encountered; (*2*) concentrations of the chemical of interest, a metabolite of the chemical, or an enzyme induced by the chemical in circulating or excreted body fluids, generally referred to as a biomarker of exposure; and (*3*) elevations in body burden measured by external probes.

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4 Pathways

4.1 Respiratory Tract

The respiratory system extends from the breathing zone just outside of the nose and mouth through the conductive airways in the head and thorax to the alveoli, where respiratory gas exchange takes place between alveoli and the capillary blood flowing around them. The prime function of the respiratory system is to deliver oxygen (O_2) to the gas-exchange region of the lung, where it can diffuse to and through the walls of the alveoli to oxygenate the blood passing through the alveolar capillaries, as needed over a wide range of work or activity levels. In addition, the system must also: (*1*) remove an equal volume of carbon dioxide (CO_2) that enters the lungs from the alveolar capillaries; (*2*) maintain body temperature and water vapor saturation within the lung airways (to maintain the viability and functional capacities of the surface fluids and cells); (*3*) maintain sterility (to prevent infections and their adverse consequences); and (*4*) eliminate excess surface fluids and debris, such as inhaled particles and senescent phagocytic and epithelial cells. It must accomplish all of these demanding tasks continuously during a lifetime and do so with highly efficient performance and energy utilization. The system can be abused and overwhelmed by severe insults, such as high concentrations of cigarette smoke and industrial dust, or by low concentrations of specific pathogens that attack or destroy its defense mechanisms or cause them to malfunction. Its ability to overcome and/or compensate for such insults as competently as it usually does is a testament to its elegant combination of structure and function.

4.2 Mass Transfer

The complex structure and numerous functions of the human respiratory tract have been summarized concisely by a Task Group of the International Commission on Radiological Protection (6), as shown in Fig. 2.4. The conductive airways, also known as the respiratory dead space, occupy about 0.2 liter

(L). They condition the inhaled air and distribute it by convective (bulk) flow to approximately 65,000 respiratory acini that lead off the terminal bronchioles. As tidal volumes increase, convective flow dominates gas exchange deeper into the respiratory bronchioles. In any case, within the respiratory acinus, the distance from the convective tidal front to alveolar surfaces is short enough so that efficient CO_2–O_2 exchange takes place by molecular diffusion. By contrast, submicrometer sized airborne particles whose diffusion coefficients are smaller by orders of magnitude than those for gases, remain suspended in the tidal air and can be exhaled without deposition.

Functions	Cytology (epithelium)	Histology (walls)	Generation number	Anatomy
Air conditioning; temperature and humidily, and cleaning; fast particle clearance; air conduction	Respiratory epithelium with goblet cells: cell types: – Ciliated cells – Nonciliated cells: • Goblet cells • Mucous (secretoey) cells • Serous cells • Brush cells • Endocrine cells • Basal cells • Intermediate cells	Mucous membrane, respiratory epithelium (pseudostratified, ciliated, mucous), glands Mucous membrane, respiratory or stratified epithelium, glands		Anterior nasal passages Nose mouth Pharynx posteric Larynx Esophagu
		Mucous membrane, respiratory epithelium, cartilage rings, glands	0 1	Trachea main bronchi
		Mucous membrane, respiratory epithelium, cartilage plates, smooth muscle layer, glands	2 - 8	Bronchi
	Respiratory epithelium with clara cells (no goblet cells) cell types: – Ciliated cells – Nonciliated cells • Clara (secretory) cells	Mucous membrane, respiratory epithelium, no cartilage, no glands, smooth muscle layer	9 - 14	Bronchioles
		Mucous membrane, single-layer respiratory epithelium, less ciliated, smooth muscle layer	15	Terminal bronchioles
Air conduction; gas exchange; slow particle clearance	Respiratory epithelium consisting mainly of clara cells (secretory) and few ciliated cells	Mucous membrane, single-layer respiratory epithelium of cubodial cells, smooth muscle layers	16 - 18	Respiratory bronchioles
Gas exchange; very slow particle clearance	Squamous alveolar epithelium cells (type I), covering 93% of alveolar surface areas	Wall consists of alveolar entrance rings, squamous epithelium layer, surfactant	**	Alveolar ducts
	Cuboidal alveolar epithelial cells (type II. Surfactant-producing), covering 7% of alveolar surface area Alveolar macrophages	Interalveolar septa covered by squamous epithelium, containing capillaries, surfactant	**	Alveolar ducts
				Lymphatics

* Previous ICRP model
** Unnumbered because of imprecise information
† Lymph nodes are located only in BB region but drain the bronchial and alveolar interstitial regions as well as the bronchial region.

Figure 2.4. Structure and function of the human respiratory tract.

A significant fraction of the inhaled particles do deposit within the respiratory tract. The mechanisms that account for particle deposition in the lung airways during the inspiratory phase of a tidal breath are summarized in Fig. 2.5. Particles larger than about 2 mm in aerodynamic diameter (the diameter of a unit density sphere that has the same terminal settling (Stokes) velocity) can have significant momentum and deposit by impaction at the relatively high velocities present in the larger conductive airways. Particles larger than about 1 mm can deposit by sedimentation in the smaller conductive airways and gas-exchange airways where flow velocities are very low. Particles smaller than 0.1 mm are in Brownian motion, and their random walk while in small airways causes them to diffuse to and deposit on small airway walls at a rate that increases with decreasing size. Finally, particles whose diameters are between 0.1 and 1 mm, which have a very low probability of depositing during a

single tidal breath, can be retained within the approximately 15% of the inspired tidal air that is exchanged with residual lung air during each tidal cycle. This volumetric exchange occurs because of the variable time constants for airflow in the different segments of the lungs. Because of the much longer residence times of residual air in the lungs, the low intrinsic particle displacements of 0.1 to 1 mm particles within such trapped volumes of inhaled tidal air become sufficient to cause their deposition by sedimentation and/or diffusion over the course of successive breaths.

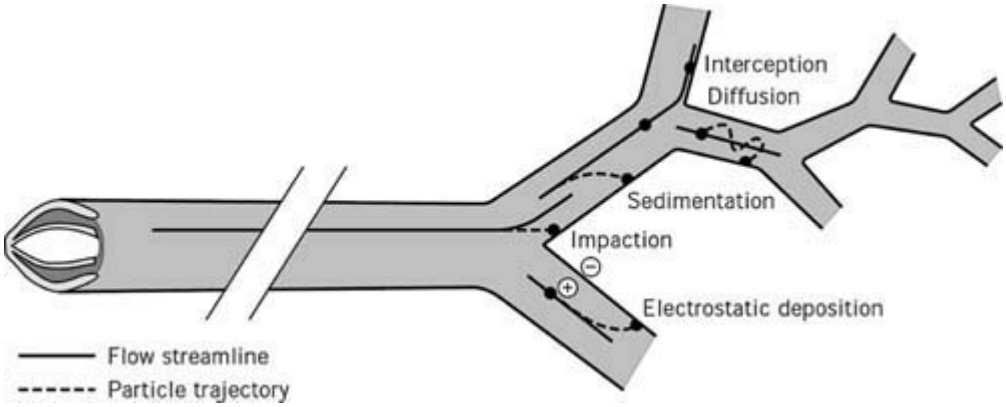

Figure 2.5. Mechanism for particle deposition in lung airways.

The essentially particle-free residual lung air that accounts for about 15% of the expiratory tidal flow acts like a clean-air sheath around the axial core of distally moving tidal air, so that particle deposition in the respiratory acinus is concentrated on interior surfaces such as airway bifurcations, whereas interbranch airway walls have relatively little particle deposition.

The number of particles deposited and their distribution along the respiratory tract surfaces, along with the toxic properties of the material deposited, are the critical determinants of pathogenic potential. The deposited particles can damage the epithelial and/or the mobile phagocytic cells at or near the deposition site or can stimulate the secretion of fluids and cell-derived mediators that have secondary effects on the system. Soluble materials deposited as, on, or within particles can diffuse into and through surface fluids and cells and be rapidly transported throughout the body by the bloodstream.

The aqueous solubility of bulk materials is a poor guide to particle solubility in the respiratory tract. Generally solubility is greatly enhanced by the very large surface to volume ratio of particles small enough to enter the lungs. Furthermore, the ionic and lipid contents of surface fluids within the airways are complex and highly variable and can lead to enhanced solubility or to rapid precipitation of aqueous solutes. In addition the clearance pathways and residence times for particles on airway surfaces are very different in the different functional parts of the respiratory tract.

The ICRP (6) Task Group's clearance model identifies the principal clearance pathways within the respiratory tract that are important in determining the retention of various radioactive materials and thus the radiation doses received by respiratory tissues and/or other organs after translocation. The ICRP deposition model is used to estimate the amount of inhaled material that enters each clearance pathway. These discrete pathways are represented by the compartment model shown in Fig. 2.6. They correspond to the anatomic compartments illustrated in Figure 2.4 and are summarized in Table 2.1, along with those of other groups that provide guidance on the dosimetry of inhaled particles.

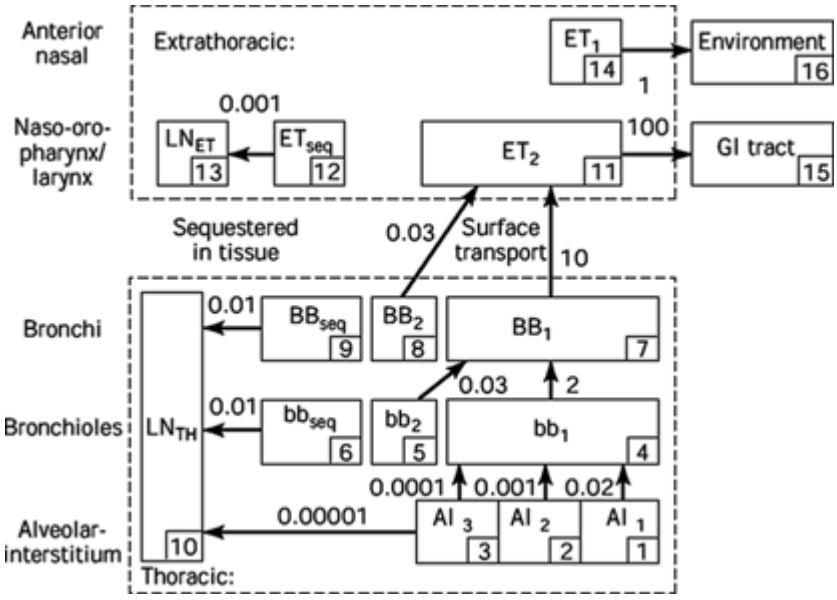

Figure 2.6. Compartment model.

Table 2.1. Respiratory Tract Regions as Defined in Particle Deposition Models

Anatomic Structures Included	ACGIH Region	ISO and CEN Regions	1966 ICRP Task Group Region	1994 ICRP Task Group Region
Nose, nasopharynx	Head airways (HAR)	Extrathoracic (E)	Nasopharynx (NP)	Anterior nasal passages (ET_1)
Mouth, oropharynx, laryngopharynx				All other extrathoracic (ET_2)
Trachea, bronchi, and conductive bronchioles (to terminal bronchioles)	Tracheobronchial (TBR)	Tracheobronchial (B)	Tracheobronchial (TB)	Trachea and large bronchi (BB) Bronchioles (bb)
Respiratory bronchioles, alveolar ducts, alveolar sacs, alveoli	Gas exchange (GER)	Alveolar (A)	Pulmonary (P)	Alveolar-interstitial (Al)

4.3 Extrathoracic Airways

As shown in Figure 2.4, the extrathoracic airways were partitioned by ICRP (6) into two distinct clearance and dosimetric regions: the anterior nasal passages (ET_1) and all other extrathoracic

airways (ET_2), i.e., the posterior nasal passages, the naso- and oropharynx, and the larynx. Particles deposited on the surface of the skin that lines the anterior nasal passages (ET_1) are assumed to be subject only to removal by extrinsic means (nose blowing, wiping, etc.). The bulk of material deposited in the naso-oropharynx or larynx (ET_2) is subject to fast clearance in the layer of fluid that covers these airways. The 1994 ICRP model recognizes that diffusional deposition of ultrafine particles in the extrathoracic airways can be substantial, whereas earlier ICRP models did not (7–9).

4.4 Thoracic Airways

Radioactive material deposited in the thorax is generally divided between the tracheobronchial (TB) region, where deposited particles are subject to relatively fast mucociliary clearance (duration in hours to 1 or 2 days), and the alveolar-interstitial (AI) region, where macrophage-mediated particle clearance is much slower (duration up to several weeks), and dissolution rates for insoluble particles not cleared by macrophages can have half-times measured in months or years.

For purposes of dosimetry, the ICRP (6) divided the deposition of inhaled material in the TB region between the trachea and bronchi (BB) and in the more distal, small conductive airways, known as bronchioles (bb). However, the subsequent efficiency with which mucociliary transport in either type of airway can clear deposited particles is controversial. To be certain that doses to bronchial and bronchiolar epithelia would not be underestimated, the ICRP Task Group assumed that as much as half the number of particles deposited in these airways is subject to relatively "slow" mucociliary clearance that lasts up to about 1 week. The likelihood that an insoluble particle is cleared relatively slowly by the mucociliary system depends on its size.

4.5 Gas-Exchange Airways and Alveoli

The ICRP (6) model also assumed that material deposited in the AI region is subdivided among three compartments (AI_1, AI_2, and AI_3) each of which is cleared more slowly than TB deposition, and the subregions clear at different characteristic rates.

4.6 Regional Deposition Estimates

Figure 2.7 depicts the predictions of the ICRP (6) Task Group Model in terms of the fractional deposition in each region as a function of the size of the inhaled particles. It reflects the minimal lung deposition between 0.1 and 1 mm, where deposition is determined largely by the exchange in the deep lung between tidal and residual lung air. Deposition increases below 0.1 mm as diffusion becomes more efficient with decreasing particle size. Deposition increases with increasing particle size above 1 mm as sedimentation and impaction become increasingly effective.

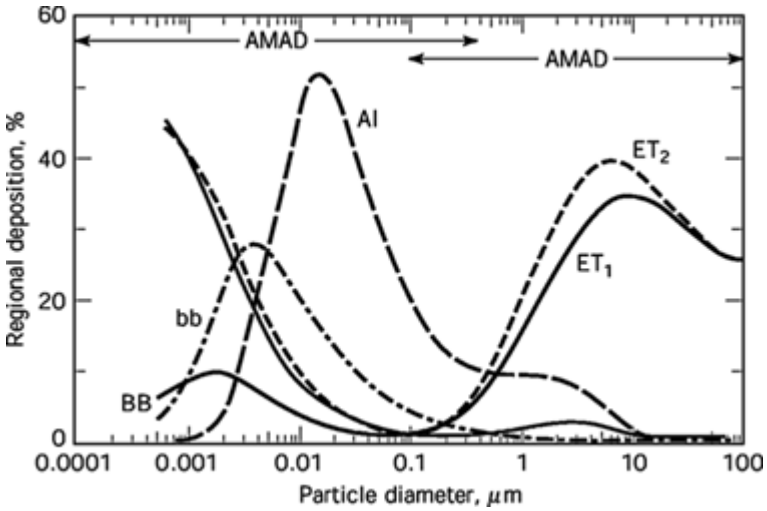

Figure 2.7. Fractional deposition in each region of the respiratory tract for a reference light worker (normal nose breather) in the 1994 ICRP model.

Although aerodynamic diameter is an excellent index of particle behavior for relatively compact

particles that differ greatly in shape and density, it is inadequate for fibers that deposit by interception, as well as by inertia, gravitational displacement, or diffusion. The aerodynamic diameter of mineral or vitreous fibers whose aspect ratio (length/width) is greater than 10 is about three times their physical diameter. Fibers whose diameters are less than 3 mm can penetrate into bronchioles whose diameters are less than 500 mm. For thin fibers longer than 10 or 20 mm, interception, whereby an end of the fiber touches a surface and is collected, accounts for a significant enhancement of deposition (10).

Less complex models for size-selective regional particle deposition have been adopted by occupational health and community air pollution professionals and agencies, and these have been used to develop inhalation exposure limits within specific particle size ranges. Distinctions are made between: (*1*) those particles that are not aspirated into the nose or mouth and therefore represent no inhalation hazard; (*2*) the inhalable (aka inspirable) particulate mass (IPM), i.e., those that are inhaled and are hazardous when deposited anywhere within the respiratory tract; (*3*) the thoracic particulate mass (TPM), i.e., those that penetrate the larynx and are hazardous when deposited anywhere within the thorax; and (*4*) the respirable particulate mass (RPM), i.e., those particles that penetrate through the terminal bronchioles and are hazardous when deposited within the gas-exchange region of the lungs. These criteria are described in more detail later in this chapter in the sections devoted to exposure assessment.

4.7 Translocation and Retention

Particles that do not dissolve at deposition sites can be translocated to remote retention sites by passive and active clearance processes. Passive transport depends on movement on or in surface fluids that line the airways. There is a continual proximal flow of surfactant to and onto the mucociliary escalator, which begins at the terminal bronchioles, where it mixes with secretions from Clara and goblet cells. Within midsized and larger airways are additional secretions from goblet cells and mucus glands that produce a thicker mucous layer that has a serous subphase and an overlying more viscous gel layer. The gel layer that lies above the tips of the synchronously beating cilia is found in discrete plaques in smaller airways and becomes more of a continuous layer in the larger airways. The mucus that reaches the larynx and the particles carried by it are swallowed and enter the GI tract.

The total transit time for particles cleared during the relatively rapid mucociliary clearance phase varies from ~2 to 24 hours in healthy humans (11). Macrophage-mediated particle clearance via the bronchial tree takes place during a period of several weeks. Compact particles that deposit in alveolar zone airways are ingested by alveolar macrophages within about 6 hours, but the movement of the particle-laden macrophages depends on the several weeks that it takes for the normal turnover of the resident macrophage population. At the end of several weeks, the particles not cleared to the bronchial tree via macrophages have been incorporated into epithelial and interstitial cells, from which they are slowly cleared by dissolution and/or as particles via lymphatic drainage pathways, passing through pleural and eventually hilar and tracheal lymph nodes. Clearance times for these later phases depend strongly on the chemical nature of the particles and their sizes, and half-times range from about 30 to 1,000 days or more.

All of the characteristic clearance times cited refer to inert, nontoxic particles in healthy lungs. Toxicants can drastically alter clearance times. Inhaled materials that affect mucociliary clearance rates include cigarette smoke (12, 13), sulfuric acid (14, 15), ozone (16, 17), sulfur dioxide (17a), and formaldehyde (18). Macrophage-mediated alveolar clearance is affected by sulfur dioxide (19), nitrogen dioxide and sulfuric acid (20), ozone (16, 20), silica dust (21), and long mineral and vitreous fibers (22, 23). Cigarette smoke affects the later phases of alveolar zone clearance in a dose-dependent manner (24). Clearance pathways and rates that affect the distribution of retained particles and their dosimetry can be altered by these toxicants.

Long mineral and manufactured vitreous fibers cannot be fully ingested by macrophages or epithelial cells and can clear only by dissolution. Most glass and slag wool fibers dissolve relatively rapidly within the lung and/or break up into shorter length segments. Chrysotile asbestos is more

biopersistent than most vitreous fibers and can subdivide longitudinally, creating a larger number of long fibers. The amphibole asbestos varieties (e.g., amosite, crocidolite, and tremolite) dissolve much more slowly than chrysotile. The close association between the biopersistence of inhaled long fibers and their carcinogenicity and fibrogenicity has been described by Eastes and Hadly (25), and additional data on the influence of fiber length on the biopersistence of vitreous fibers following inhalation was described by Bernstein et al. (26).

4.8 Ingestion Exposures and Gastrointestinal (GI) Tract Exposures

Chemical contaminants in drinking water or food reach human tissues via the GI tract. Ingestion may also contribute to the uptake of chemicals that were initially inhaled, because material deposited on or dissolved in the bronchial mucous blanket is eventually swallowed.

The GI tract may be considered a tube running through the body, whose contents are actually external to the body. Unless the ingested material affects the tract itself, any systemic response depends on absorption through the mucosal cells that line the lumen. Although absorption may occur anywhere along the length of the GI tract, the main region for effective translocation is the small intestine. The enormous absorptive capacity of this organ results from the presence in the intestinal mucosa of projections, termed *villi*, each of which contains a network of capillaries; the villi have a large effective total surface area for absorption.

Although passive diffusion is the main absorptive process, active transport systems also allow essential lipid-insoluble nutrients and inorganic ions to cross the intestinal epithelium and are responsible for the uptake of some contaminants. For example, lead may be absorbed via the system that normally transports calcium ions (27). Small quantities of particulate material and certain large macromolecules such as intact proteins may be absorbed directly by the intestinal epithelium.

Materials absorbed from the GI tract enter either the lymphatic system or the portal blood circulation; the latter carries material to the liver, from which it may be actively excreted into the bile or diffuse into the bile from the blood. The bile is subsequently secreted into the intestines. Thus, a cycle of translocation of a chemical from the intestine to the liver to bile and back to the intestines, known as the *enterohepatic circulation*, may be established. Enterohepatic circulation usually involves contaminants that undergo metabolic degradation in the liver. For example, DDT undergoes enterohepatic circulation; a product of its metabolism in the liver is excreted into the bile, at least in experimental animals (28).

Various factors modify absorption from the GI tract and enhance or depress its barrier function. A decrease in gastrointestinal mobility generally favors increased absorption. Specific stomach contents and secretions may react with the contaminant and possibly change it to a form with different physicochemical properties (e.g., solubility), or they may absorb it, alter the available chemical, and change the translocation rates. The size of ingested particulates also affects absorption. Because the rate of dissolution is inversely proportional to particle size, large particles are absorbed to a lesser degree, especially if they are fairly insoluble in the first place. Certain chemicals, e.g., chelating agents such as EDTA, also cause a nonspecific increase in the absorption of many materials.

As a defense, spastic contractions in the stomach and intestine may eliminate noxious agents via vomiting or by accelerating the transit of feces through the GI tract.

4.9 Skin Exposure and Dermal Absorption

The skin is generally an effective barrier against the entry of environmental chemicals. To be absorbed via this route (*percutaneous absorption*), an agent must traverse a number of cellular layers before gaining access to the general circulation (Fig. 2.8) (29). The skin consists of two structural regions, the epidermis and the dermis, which rest on connective tissue. The epidermis consists of a number of layers of cells and varies in thickness depending on the region of the body; the outermost layer is composed of keratinized cells. The dermis contains blood vessels, hair follicles, sebaceous and sweat glands, and nerve endings. The epidermis represents the primary barrier to percutaneous absorption, the dermis is freely permeable to many materials. Passage through the epidermis occurs

by passive diffusion.

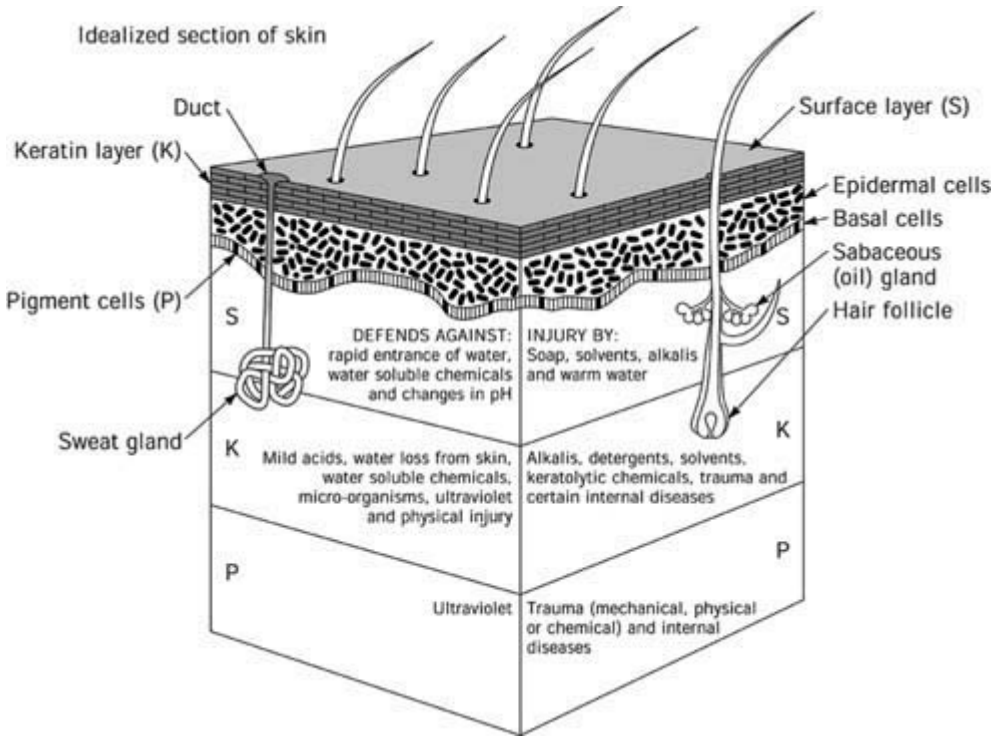

Figure 2.8. Idealized section of skin. The horny layer is also known as the stratum corneum. From Birmingham (29).

The main factors that affect percutaneous absorption are the degree of lipid solubility of the chemicals, the site on the body, the local blood flow, and the skin temperature. Some environmental chemicals that are readily absorbed through the skin are phenol, carbon tetrachloride, tetraethyl lead, and organophosphate pesticides. Certain chemicals, e.g., dimethyl sulfoxide (DMSO) and formic acid, alter the integrity of skin and facilitate penetration of other materials by increasing the permeability of the stratum corneum. Moderate changes in permeability may also result following topical applications of acetone, methyl alcohol, and ethyl alcohol. In addition, cutaneous injury may enhance percutaneous absorption.

Interspecies differences in percutaneous absorption are responsible for the selective toxicity of many insecticides. For example, DDT is about equally hazardous to insects and mammals if ingested but is much less hazardous to mammals when applied to the skin. This results from its poor absorption through mammalian skin compared to its ready passage through the insect exoskeleton. Although the main route of percutaneous absorption is through the epidermal cells, some chemicals may follow an *appendageal* route, i.e., entering through hair follicles, sweat glands, or sebaceous glands. Cuts and abrasions of the skin can provide additional pathways for penetration.

4.10 Absorption Through Membranes and Systemic Circulation

Depending upon its specific nature, a chemical contaminant may exert its toxic action at various sites in the body. At a portal of entry—the respiratory tract, GI tract, or skin—the chemical may have a topical effect. However, for actions at sites other than the portal, the agent must be absorbed through one or more body membranes and enter the general circulation, from which it may become available to affect internal tissues (including the blood itself). Therefore, the ultimate distribution of any chemical contaminant in the body is highly dependent on its ability to traverse biological membranes. There are two main types of processes by which this occurs: passive transport and active transport.

Passive transport is absorption according to purely physical processes, such as osmosis; the cell has

no active role in transfer across the membrane. Because biological membranes contain lipids, they are highly permeable to lipid-soluble, nonpolar, or nonionized agents and less so to lipid-insoluble, polar, or ionized materials. Many chemicals may exist in both lipid-soluble and lipid-insoluble forms; the former is the prime determinant of the passive permeability properties of the specific agent.

Active transport involves specialized mechanisms, and cells actively participate in transfer across membranes. These mechanisms include carrier systems within the membrane and active processes of cellular ingestion, phagocytosis and pinocytosis. Phagocytosis is the ingestion of solid particles, whereas pinocytosis refers to the ingestion of fluid containing no visible solid material. Lipid-insoluble materials are often taken up by active-transport processes. Although some of these mechanisms are highly specific, if the chemical structure of a contaminant is similar to that of an endogeneous substrate, the former may also be transported.

In addition to its lipid-solubility, the distribution of a chemical contaminant also depends on its affinity for specific tissues or tissue components. Internal distribution may vary with time after exposure. For example, immediately following absorption into the blood, inorganic lead localizes in the liver, the kidney, and in red blood cells. Two hours later, about 50% is in the liver. A month later, approximately 90% of the remaining lead is localized in bone (30).

Once in the general circulation, a contaminant may be translocated throughout the body. In this process it may (*1*) become bound to macromolecules, (*2*) undergo metabolic transformation (biotransformation), (*3*) be deposited for storage in depots that may or may not be the sites of its toxic action, or (*4*) be excreted. Toxic effects may occur at any of several sites.

The biological action of a contaminant may be terminated by storage, metabolic transformation, or excretion; the latter is the most permanent form of removal.

4.11 Accumulation in Target Tissues and Dosimetric Models

Some chemicals concentrate in specific tissues because of physicochemial properties such as selective solubility or selective absorption on or combined with macromolecules such as proteins. Storage of a chemical often occurs when the rate of exposure is greater than the rate of metabolism and/or excretion. Storage or binding sites may not be the sites of toxic action. For example, carbon monoxide produces its effects by binding with hemoglobin in red blood cells; on the other hand, inorganic lead is stored primarily in bone but exerts its toxic effects mainly on the soft tissues of the body.

If the storage site is not the site of toxic action, selective sequestration may be a protective mechanism because only the freely circulating form of the contaminant produces harmful effects. Until the storage sites are saturated, a buildup of free chemical may be prevented. On the other hand, selective storage limits the amount of contaminant that is excreted. Because bound or stored toxicants are in equilibrium with their free form, as the contaminant is excreted or metabolized, it is released from the storage site. Contaminants that are stored (e.g., DDT in lipids and lead in bone) may remain in the body for years without effect. However, upon weight loss and mobilization of body reserves, the stored chemicals can enter the circulation and produce toxic effects. For example, pregnant women who had prior excessive exposure to lead can increase their own blood lead levels and also create high and possibly damaging levels of lead exposures to their fetus. Accumulating chemicals may also produce illnesses that develop slowly, as occurs in chronic cadmium poisoning.

A number of descriptive and mathematical models have been developed to permit estimation of toxic effects from knowledge of exposure and one or more of the following factors: translocation, metabolism, and effects at the site of toxic action.

More complex models that require data on translocation and metabolism have been developed for inhaled and ingested radionuclides by the International Commission on Radiological Protection (6–9).

Pathways and Measuring Exposure To Toxic Substances
Morton Lippmann, Ph.D., CIH

5 Measuring and Modeling Human Exposures
Direct measurement data on personal exposures to environmental toxicants would be ideal for risk assessments for individuals, and personal exposure data on large numbers of representative individuals would be ideal for performing population-based risk assessments. However, considerations of technical feasibility, willingness and ability to participate in extensive measurement studies among individuals of interest, and cost almost invariably preclude this option. Instead, more indirect measures of exposure and/or exposure models are relied on that combine a limited number of direct measurements with general background knowledge, historic measurement data believed to be relevant to the particular situation, and some reasonable assumptions based on first principles and/or expert judgements.

When monitoring exposures, it is highly desirable to have benchmarks (exposure limits) as references. There are well-established occupational exposure limits for hundreds of air contaminants, including legal limits such as the Permissible Exposure Limits (PELs) established by the U.S. Occupational Safety and Health Administration (OSHA), as well as a larger number of Threshold Limit Values (TLVs) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) as professional practice guidelines.

For ingested chemicals, there are acceptable daily intake values (ADIs), such as those adopted by the Food and Drug Administration (FDA) and the U.S. Department of Agriculture.

Until now, comparable exposure limits have not been available for dermal exposure. However, Bos et al. (31) recently proposed a procedure for deriving such limits, and Brouwer et al. (32) performed a feasibility study following the Bos et al. proposal. Table 2.2 from Bos et al. (31) summarizes the nature and applications of such dermal exposure limits.

Table 2.2. Some Characteristics of Available Exposure Limits[a]

	Route of Entry			
	Respiratory Tract	**Gastrointestinal Tract**	**Skin**	**Miscellaneous or Combined**
Name	Maximum accepted concentration (MAC) Threshold limit value (TLV)	Acceptable daily intake (ADI)	Skin denotation	Biological limit value; (BEI, BAT-Werte, biological monitoring guidance value)
Qualitative or quantitative	Quantitative	Quantitative	Qualitative	Quantitative

Target population	Working population	General population	Working population	Working population or general population
Dimensions	mg/m^3	mk/kg/food	Not applicable; however	(a) mg/L blood, mg/L urine, mg/m^3 exhaled air
	parts per million (ppm)	mg/kg body weight	likely to be assessed as mg	(b) cholinesterase inhibition, zinc protoporphyrin, DNA adducts,
	fibres n/m^3		(mg/cm^2)	mutations, etc.
Monitoring methods	Environmental monitoring (EM)	Food residues or contaminants in combination with food intake data	For example, environmental surface wipe-off; patches, gloves, coveralls; tracer methods; skin	Biological media: blood, urine, exhaled air, feces, hair
	Personal air sampling (PAS)	No specific worker monitoring method	washings; or skin stripping	

[a] From Bos et al. (31).

In routine monitoring of occupational exposures, it is quite common to collect shift-long (~ 8 hour) integrated breathing zone samples using passive diffusion samplers (for gases and vapors) or battery-powered personal samplers that draw a continuous low flow rate stream of air from the breathing zone through a filter or cartridge located in the breathing zone that captures essentially all of the air contaminants of interest for subsequent laboratory analyses. Such sampling is typically performed on only a single worker or at most on a small fraction of the workforce on the basis that the exposures of the sentinel worker(s) represent the exposures of other, unmonitored workers in the same works environment. In this case, the modeling of the other worker's exposures is relatively simple.

Shift-long sampling can provide essential information for cumulative toxicants, but that information may be inadequate when peak exposure levels are important (as for upper respiratory irritants or asphyxiants). Continuous readout monitors would be ideal for evaluating such exposures, but may be impractical because of their size and/or cost. Spot or grab samples can be informative for evaluating of such exposures but require prior knowledge of the timing and locations of peak exposures. In such situations, peak exposures can be estimated using fixed-site continuous monitors in the general vicinity and supplementary information or experience-based models that relate breathing zone levels to general air levels in the room. Time-activity pattern data on each worker can be combined with measured or estimated concentrations at each work site or with specific work activities to construct a time-weighted average exposure (TWAE) for that worker to supplement estimates of peak exposures. The characteristics of equipment used for air sampling in industry are described in detail in *Air Sampling Instruments* (33).

In constructing exposure estimates or models for community air or indoor air exposures for the general population, this time-weighted averaging approach is generally known as

microenvironmental exposure assessment. For community air pollutants of outdoor origin, data are often available on the concentrations measured at central monitoring sites, and population exposures to these pollutants are based on models incorporating time-activity patterns (indoors and outdoors), as well as factors representing the infiltration and persistence of the pollutants indoors. Such models should recognize the substantial variability of time-activity patterns among and between subsegments of the population (children, working adults, elderly and/or disabled adults, etc.).

5.1 Biomonitoring

An alternate approach to measuring exposures directly is the use of biomarkers of exposures, determined from analyses of samples of blood, urine, feces, hair, nails, or exhaled air. The levels of the contaminant, its metabolites, changes in induced enzyme or protein levels, or characteristic alterations in DNA may be indicative of recent peak or past cumulative exposures. Exposure biomarkers may be complementary to and, in some cases, preferable to direct measures of environmental exposures. In any case, they are more biologically informative than indirect measures based on models and knowledge of sources or qualitative measures of exposure such as questionnaires about work and/or residential histories. There are diverse types of biomarkers that range from simple to complex in measurement requirements, and they are diverse in their relationships to either remote or recent exposures. There is also a range of biological relevance among exposure biomarkers: some provide indices that are directly biologically relevant, e.g., the level of carbon monoxide in end-tidal air samples and the risk of myocardial ischemia, whereas others, although broadly related, may not cover the temporally appropriate exposure window, e.g., nicotine levels in biological fluids and lung cancer risk from smoke exposure.

For the near term, extensive development of new molecular level biomarkers relevant to malignant and nonmalignant diseases can be anticipated. However, most of these new exposure biomarkers remain to be validated, and few will be ready for translation to the population in the short term. Anticipated applications include epidemiological studies of responses to low-level exposures to environmental agents. Biomarkers will also be used to validate other exposure assessment methods and to provide more proximate estimates of dose.

Exposure biomarkers may be applied to groups that have unique exposure or susceptibility patterns, to monitor the population in general, and to document the consequences of exposure assessment strategies designed to reduce population exposures.

Exposure biomarkers validated against the end point of disease risk and used in conjunction with other measurements and metrics of exposure should prove particularly effective in risk assessment. However, biomarkers of exposure may pose new and unanticipated ethical dilemmas. Information gained from biomolecular markers of exposure may provide an early warning of high risk or preclinical disease; capability for early warning will require a high level of, and an accepted social-regulatory framework for follow-up actions. They may also cause false alarms and needless stress for individuals warned about the presence of uncertain signals.

In summary, exposure represents contact between a concentration of an agent in air, water, food, or other material and the person or population of interest. The agent is the source of an internal dose to a critical organ or tissue. The magnitude of the dose depends on a number of factors: (1) the volumes inhaled or ingested; (2) the fractions of the inhaled or ingested material transferred across epithelial membranes of the skin, the respiratory tract, and the GI tract; (3) the fractions transported via circulating fluids to target tissues; and (4) the fractional uptake by the target tissues. Each of these factors can have considerable intersubject variability. Sources of variability include activity level, age, sex, and health status, as well as such inherent variabilities as race and size.

With chronic or repetitive exposures, other factors affect the dose of interest. When the retention at, or effects on, the target tissues are cumulative and clearance or recovery is slow, the dose of interest can be represented by cumulative uptake. However, when the agent is rapidly eliminated or when its effects are rapidly and completely reversible on removal from exposure, the rate of delivery may be the dose parameter of primary interest.

5.2 Determining Concentrations of Toxic Chemicals in Human Microenvironments

The technology for sampling air, water, and food is relatively well developed, as are the technologies for sample separation from copollutants, media, and interferences and for quantitative analyses of the components of interest. However, knowing when, where, how long, and at which rate and frequency to sample to collect data relevant to the exposures of interest is difficult and requires knowledge of the temporal and spatial variability of exposure concentrations. Unfortunately, we seldom have enough information of these kinds to guide our sample collections. Many of these factors that affect occupational exposures are discussed in detail in the chapters of Patty's *Industrial Hygiene*, 5th ed. (33) The following represents a very brief summary of some general considerations.

5.3 Water and Foods

Concentrations of environmental chemicals in food and drinking water are extremely variable, and there are further variations in the amounts consumed because of the extreme variability in dietary preferences and food sources. The number of foods for which up-to-date concentration data for specific chemicals are available is extremely limited. Relevant human dietary exposure data are sometimes available in terms of market basket survey analyses. In this approach, food for a mixed diet is purchased, cleaned, processed, and prepared as for consumption, and one set of specific chemical analyses is done for the composite mixture.

The concentrations of chemicals in potable piped water supplies depend greatly on the source of the water, its treatment history, and its pathway from the treatment facility to the tap. Surface waters from protected watersheds generally have low concentrations of dissolved minerals and environmental chemicals. Well waters usually have low concentrations of bacteria and environmental chemicals but often have high mineral concentrations. Poor waste disposal practices may contribute to groundwater contamination, especially in areas of high population density and/or industrial sources of wastes. Treated surface waters from lakes and rivers in densely populated and/or industrialized areas usually contain a wide variety of dissolved organics and trace metals, whose concentrations vary greatly with the season (because of variable surface runoff), with proximity to pollutant sources, with upstream usage, and with treatment efficacy.

The uptake of environmental chemicals in bathing waters across intact skin is usually minimal compared to uptake via inhalation or ingestion. It depends on both the concentration in the fluid surrounding the skin surface and the polarity of the chemical; more polar chemicals have less ability to penetrate intact skin. Uptake via skin can be significant for occupational exposures to concentrated liquids or solids.

5.4 Air

Although chemical uptake through ingestion and the skin surface is generally intermittent, inhalation provides a continuous means of exposure. The important variables that affect the uptake of inhaled chemicals are the depth and frequency of inhalation and the concentration and physicochemical properties of the chemicals in the air.

Exposure to airborne chemicals varies widely among inhalation microenvironments, whose categories include workplace, residence, outdoor ambient air, transportation, recreation, and public spaces. There are also wide variations in exposure within each category, depending on the number and strength of the sources of the airborne chemicals, the volume and mixing characteristics of the air within the defined microenvironment, the rate of air exchange with the outdoor air, and the rate of loss to surfaces within the microenvironment.

For community air pollutants that have national ambient air quality standards, particulate matter (PM), sulfur dioxide (SO_2), carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), and lead (Pb), there is an extensive network of fixed-site monitors, generally on rooftops. Although the use of these monitors generates large volumes of data, the concentrations at these sites may differ substantially from the concentrations that people breathe, especially for tailpipe pollutants such as CO. Data for other toxic pollutants in the outdoor ambient air are not generally collected routinely.

5.5 Workplace

Exposures to airborne chemicals at work are extremely variable in composition and concentration and depend on the materials being handled, the process design and operation, the kinds and degree of engineering controls applied to minimize release to the air, the work practices followed, and the personal protection provided.

5.6 Residential

Airborne chemicals in residential microenvironments are attributable to air infiltrating from out of doors and to the release from indoor sources. The latter include unvented cooking stoves and space heaters, cigarettes, consumer products, and volatile emissions from wallboard, textiles, carpets, etc. Indoor sources can release enough nitrogen dioxide (NO_2), fine particle mass (FPM), and formaldehyde (HCHO) that indoor concentrations for these chemicals can be much higher than those in ambient outdoor air. Furthermore, their contributions to the total human exposure are usually even greater because people usually spend much more time at home than outdoors.

5.7 Conventions for Size-Selective Inhalation Hazard Sampling for Particles

In recent years, quantitative definitions of Inhalable particulate matter (IPM), Thoracic particulate matter (TPM), and Respirable particulate matter (RPM) have been internationally harmonized. The size-selective inlet specifications for air samplers that meet the criteria of ACGIH (34), ISO (35), and CEN (36) are enumerated in Table 2.3 and illustrated in Figure 2.9. They differ from the deposition fractions of ICRP (6), especially for larger particles, because they take the conservative position that protection should be provided for those engaged in oral inhalation and thereby bypass the more efficient filtration efficiency of the nasal passages.

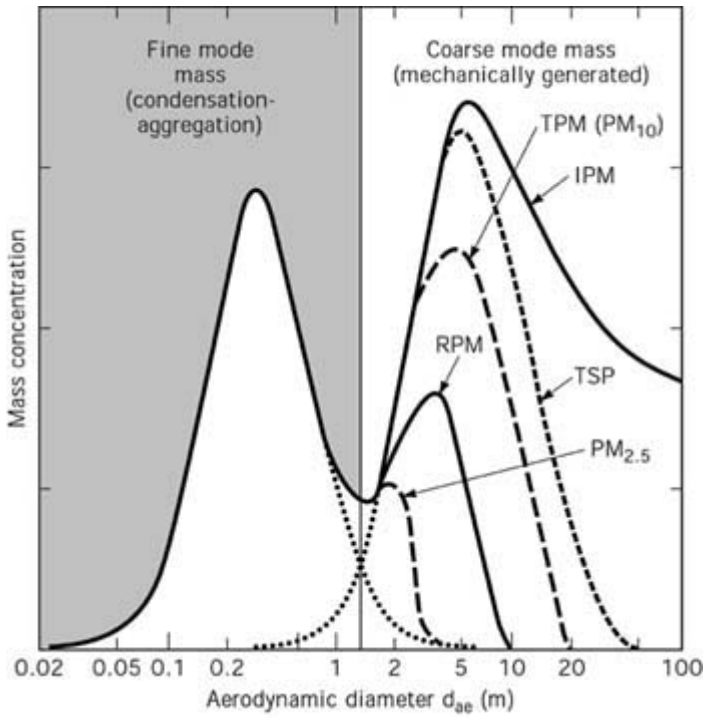

Figure 2.9. Effect of size-selective inlet characteristic on the aerosol mass collected by a downstream filter. IPM = inhalable particulate matter; TSP = total suspended particulate; TPM = thoracic particulate matter; (aka PM_{10}); RPM = respirable particulate matter; and $PM_{2.5}$ = fine particulate matter in ambient air.

Table 2.3. Inhalable, Thoracic and Respirable Dust Criteria of ACGIH, ISO and CEN, and Criteria of U.S. EPA

Inhalable		Thoracic		Respirable		PM_{10}	
Particle Aerodynamic Diameter (mm)	Inhalable Particulate Mass (IPM) (%)	Particle Aerodynamic Diameter (mm)	Thoracic Particulate Mass (TPM) (%)	Particle Aerodynamic Diameter (mm)	Respirable Particulate Mass (RPM) (%)	Particle Aerodynamic Diameter (mm)	T Pa Ma (T
0	100	0	100	0	100		0
1	97	2	94	1	97		2
2	94	4	89	2	91		4
5	87	6	80.5	3	74		6
10	77	8	67	4	50		8
20	65	10	50	5	30		10
30	58	12	35	6	17		12
40	54.5	14	23	7	9		14
50	52.5	16	15	8	5	16	
100	50	18	9.5	10	1		
		20	6				
		25	2				

The U.S. Environmental Protection Agency (36a) set a standard for ambient air particle concentration known as PM_{10}, i.e., for particulate matter less than 10 mm in aerodynamic diameter. It replaced a poorly defined size-selective criterion known as total suspended particulate matter (TSP), whose actual inlet cut varied with wind speed and direction. PM_{10} has a sampler inlet criterion that is similar (functionally equivalent) to TPM but, as shown in Table 2.3, has somewhat different numerical specifications.

In 1997, following its most recent thorough review of the literature on the health effects of ambient PM, the EPA concluded that most of the health effects attributable to PM in ambient air were more closely associated with the fine particles in the fine particle accumulation mode (extending from about 0.1 to 2.5 mm) than with the coarse mode particles within PM_{10} and promulgated new National Ambient Air Quality Standard (NAAQS) based on fine particles, defined as particles whose aerodynamic diameters (d_{ae}) are less than 2.5 mm ($PM_{2.5}$), to supplement the PM_{10} NAAQS that was retained (37). The selection of d_{ae} = 2.5 mm as the criterion for defining the upper bound of fine particles in a regulatory sense was, inevitably, an arbitrary selection made from a range of possible options. It was arrived at using the following rationales:

- Fine particles produce adverse health effects more because of their chemical composition than their size (see Table 2.4) and need to be regulated using an index that is responsive to control measures applied to direct and indirect sources of such particles.

Table 2.4. Comparisons of Ambient Fine and Coarse Mode Particles[a]

	Fine Mode	Coarse Mode

Formed from	Gases	Large solids/droplets
Formed by	Chemical reaction; nucleation; condensation; coagulation; evaporation of fog and cloud droplets in which gases have dissolved and reacted	Mechanical disruption (e.g., crushing, grinding, abrasion of surfaces); evaporation of sprays; suspension of dusts
Composed of	Sulfate, SO_4^{2-}; nitrate, NO_3^-; ammonium, NH_4^+; hydrogen ion, H^+; elemental carbon; organic compounds (e.g., PAHs, PNAs); metals (e.g., Pb, Cd, V, Ni, Cu, Zn, Mn, Fe); particle-bound water	Resuspended dusts (e.g., soil dust, street dust); coal and oil fly ash; metal oxides of crustal elements (Si, Al, Ti, Fe); $CaCO_3$, NaCl, sea salt; pollen, mold spores; plant/animal fragments; tire wear debris
Solubility	Largely soluble, hygroscopic, and deliquescent	Largely insoluble and non hygroscopic.
Sources	Combustion of coal, oil, gasoline, diesel, wood; atmospheric transformation products of NO_x, SO_2, and organic compounds including biogenic species (e.g., terpenes); high temperature processes, smelters, steel mills, etc.	Resuspension of industrial dust and soil tracked onto roads; suspension from disturbed soil (e.g., farming, mining, unpaved roads); biological sources; construction and demolition; coal and oil combustion; ocean spray
Lifetimes	Days to weeks	Minutes to hours
Travel distance	100s to 1000s of kilometers	<1 to 10s of kilometers

[a] Source: USEPA (36).

- Any separation by aerodynamic particle size that attempts to separate fine mode from coarse mode particles cannot include all fine mode particles and exclude all coarse mode particles because the modes overlap (see Figure 2.9).
- The position of the "saddle point" between the fine mode and coarse mode peaks varies with aerosol composition and climate. Data from Michigan indicates a volumetric saddle point at d_{ae} ~2 mm. If the data were corrected for particle density, it might be somewhat higher. Data from Arizona have a lower saddle point at d_{ae} ~1.5 mm.
- Evidence of a need for a fine particle NAAQS came from studies based on $PM_{2.5}$ or $PM_{2.1}$. If $PM_{2.5}$ errs, it also does so on the conservative side with respect to health protection. Further, it was deemed to be impractical to have different cut sizes in different parts of the United States.
- The intrusion of coarse mode mass into $PM_{2.5}$ can be minimized by specifying a relatively sharp cut characteristic for the $PM_{2.5}$ reference sampler (i.e., s_g=1.5).

5.8 Indirect Measures of Past Exposures

Documented effects of environmental chemicals on humans seldom contain quantitative exposure data and only occasionally include more than crude exposure rankings based on known contact with or proximity to the materials believed to have caused the effects. Reasonable interpretation of the

available human experience requires some appreciation of the uses and limitations of the data used to estimate the exposure side of the exposure–response relationship. The discussion that follows is an attempt to provide background for interpreting data and for specifying the kinds of data needed for various analyses.

Both direct and indirect exposure data can be used to rank exposed individuals by exposure intensity. External exposure can be measured directly by collecting and analyzing environmental media. Internal exposure can be estimated from analyses of biological fluids and *in vivo* retention. Indirect measures generally rely on work or residential histories based on some knowledge of exposure intensity at each exposure site and/or some enumeration of the frequency of process upsets and/or effluent discharges that result in high-intensity, short-term exposures.

5.9 Concentrations in Air, Water, Food, and Biological Samples

Historic data may occasionally be available for the concentrations of materials of interest in environmental media. However, they may or may not relate to the exposures of interest. Among the more important questions to be addressed in attempts to use such data are,

1. How accurate and reliable were the sampling and analytical techniques used in collecting the data? Were they subjected to any quality assurance protocols? Were standardized and/or reliable techniques used?
2. When and where were the samples collected, and how did they relate to exposures at other sites? Air concentrations measured at fixed (area) sites in industry may be much lower than those that occur in the breathing zone of workers close to the contaminant sources. Air concentrations at fixed (generally elevated) community air-sampling sites can be either much higher or much lower than those at street level and indoors as a result of strong gradients in source and sink strengths in indoor and outdoor air.
3. What is known or assumed about the ingestion of food and/or water containing the measured concentrations of the contaminants of interest? Time at home and dietary patterns are highly variable among populations at risk.

Many of the same questions that apply to the interpretation of environmental media concentration data also apply to biological samples, especially quality assurance. The time of sampling is especially critical in relation to the times of the exposures and to the metabolic rates and pathways. In most cases, it is quite difficult to separate the contributions to the concentrations in circulating fluids of levels from recent exposures and those from long-term reservoirs.

5.10 Exposure Histories

Exposure histories per se are generally unavailable, except in the sense that job or work histories, routine compliance data on air concentrations, and/or residential histories can be interpreted in terms of exposure histories. Job histories are often available in company and/or union records and can be converted into relative rankings of exposure groups with the aid of long-term employees and managers familiar with the work processes, history of process changes, material handled, tasks performed, and the engineering controls of exposure.

5.11 Occupational Exposure Data in the Information Age

There are increasing opportunities for obtaining technical information that can inform our exposure and risk assessments that arise from the development of: (*1*) sensitive passive monitors for time-weighted average analyses; (*2*) miniature direct-reading sensors for collecting time-resolved, as well as average personal and area concentration data; (*3*) long-path sensors for area monitoring; (*4*) computerized tomography techniques for developing concentration maps from long-path monitoring data; (*5*) biomarkers of exposure; (*6*) technical means of determining worker presence at workstations; and (*7*) an ever-growing toxicological and epidemiological database for relating exposure to risk.

5.12 Exposure Measurements

In the area of chemical sensors, there are multiple possibilities for developing automated and, in some cases, relatively inexpensive real-time microsensors for measuring gaseous and particulate pollutants in personal and microenvironmental measurements (see Table 2.5) (38). New materials

and coating technologies can provide the chemical specificity and selectivity needed for such sensors. These new technologies offer the means to do near real-time measurements to understand the variability of exposures over short and long time periods. Such sensors could also be used to directly reduce exposures by providing immediate exposure information to monitored populations or through linkages to control systems, e.g., air quality monitoring coupled with ventilation controls.

Table 2.5. A Few Examples of New Sensor Technologies with Potential Applications to Occupational and Air Pollutant Exposure Assessment[a]

Ultrasonic Flexural Plate Wave (FPW) Devices for Chemical Multiarray Microsensors. Highly sensitive flexural plate wave devices are being developed for *in situ*, real time analyses of particles and volatile organic compounds in indoor and outdoor air and clean rooms and in emissions sources. FPW sensors can be batch fabricated using well-developed and inexpensive silicon technology and interfaced with microprocessors that record and analyze the sensed measurements.
Computer Tomography/Fourier-Transform Infrared Spectrometry. This emerging technology will provide the means to characterize spatial distributions and movements of air pollutants in three dimensions in indoor and outdoor environments. Recent breakthroughs in computer algorithms for computer tomography have made it possible for this technology to be commercially available within three to five years.

[a] (From USEPA-SAB-IAQC) (38).

Sensor data from field measurements can be transmitted over telecommunications lines directly to computer systems for analysis. Such direct transmission reduces chances for errors in recording data.

Many different kinds of exposure-related models that take advantage of computer capabilities and large databases of information have already been developed and are currently available. These include exposure models that combine concentration data with time-activity patterns to estimate exposures, physiologically based pharmacokinetic models that describe the distribution and metabolism of toxic chemicals (including biomarkers) in the body, and health effects models (e.g., cancer risk models). Such models are typically developed as single models without considering linkages to other models and are often written in different computer languages and have system designs that are not readily compatible with other models. For more fully integrated exposure analysis, from sources to health effects, integrating frameworks must be developed that more readily allow the output from one model to serve easily as input into other models.

In the near future, new insights will inevitably come from combining measurements of the personal environment with measurements of the individual's capacity to interact with that environment. For example, it is technically possible to record simultaneous real-time measurements of specific airborne compounds in an individual's breathing zone, an individual's breathing and exercise rates, and geographic location. Such advanced technology is already being used in some large industries. For example, some combine location in a work area (accessible by coded badges) and continuous work area air monitoring outputs to automatically compute daily time-weighted average exposures of worker cohorts.

5.13 Expanded Applications of Occupational Exposure Databases

Hygienists tend to be compulsive about the quality of the data they collect when assessing occupational exposures and the influence of exposure determinants. They are likely to be careful and consistent in collecting data according to a rational sampling strategy that aids them in interpreting the data and the preparation of recommendations for remedial actions as needed. They also often use

a cumulative data set to document progress in reducing exposures and/or to identify evidence for actual or potential increases. However, they may not recognize additional ways that their carefully acquired data resources can be used by them or others for other important purposes.

Perhaps the single most important need to use such data more broadly is to collect and enter more data on exposure determinants into the databases. Another critical need is to devise means for censoring the data, so that specific individuals and companies do not incur legal or public relations problems because their data become available to others in a traceable form. There will need to be a long period of gradual development and experience with such systems before widespread donations of data can be expected. No matter how long it takes, it is important that the harmonization of the data elements to be entered into company-specific databases take place as soon as possible, so that it is at least feasible for disparate data to be used in a combined analysis. These could be used in corporatewide or industrywide analyses whose results end up in peer-reviewed scientific literature that can benefit all interested parties.

There are now opportunities for harmonizing data elements in occupational exposure databases that, when combined with the capabilities of our state-of-the-art hardware and software, will enable us to collect, assemble, and store very large amounts of data. If such consolidated databases are properly assembled and quality-assured, they could be used by individuals and companies that contributed data, by trade associations, and by research investigators to learn more about the distributions and determinants of occupational exposures, the efficacy of technical means of exposure controls, and the adequacy of current exposure limits for preventing health effects. A Workshop on Occupational Exposure Databases (39) reviewed the various activities that were underway. This was followed by the active development of Guidelines for the Development of Occupational Exposure Databases by both a Joint Ad Hoc Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) and the American Industrial Hygiene Association (AIHA) and by a Task Group appointed by the European Commission. Fortunately, both groups tried to harmonize their recommendations before they were completed. The final report of the ACGIH-AIHA Ad Hoc Committee appeared in *Applied Occupational and Environmental Hygiene* (40), along with a progress report from the European Community Task Group (41).

Important issues remain to be resolved before suitable arrangements can be made to establish a central exposure data repository or for other means of sharing proprietary data that are collected and stored using a common format. It is clear that, for at least some secondary uses of compatible data from different sources, means must be provided to ensure that the data elements cannot be traced back to individual workers, individual work sites, or even to employers.

5.14 Applications and Environmental Exposure and Effects Databases

The environmental health field has learned a great deal about some of the more subtle effects of environmental toxicants on human populations by studying the statistical associations between mortality and morbidity indices, on the one hand, and environmental exposure indices, on the other. Small, but statistically significant increases in population relative risks (RRs) have been demonstrated that link

- blood lead to blood pressure in U.S. adults (based on data from the second National Health and Nutrition Examination Survey (NHANES II) (42).
- blood lead and hearing acuity to neurobehavioral development in children, also based on NHANES II (43).
- blood lead to stature in children, also based on NHANES II (44).
- both ozone and sulfate particles to hospital admissions for respiratory diseases in various U.S. and Canadian communities (45–47).
- fine particles to hospital admissions for cardiovascular diseases in various U.S. and Canadian communities (48, 49).
- fine particles to daily mortality rates in various communities in the Americas and Europe (45, 50).

- fine particles and sulfate particles to annual mortality rates in various U.S. communities (45, 47, 51, 52).
- environmental tobacco smoke (ETS) to lung cancer mortality among spouses in various communities in the U.S., Asia, and Europe (53).
- ETS to 150,000 to 300,000 cases/year of lower respiratory tract infections in U.S. children (53).
- ETS to 200,000 to 1,000,000 additional asthma episodes/year in U.S. children (53).
- ETS to increased prevalence of fluid in the middle ear, symptoms of upper respiratory tract, irritation, reduced lung function in children, and as a risk factor for new cases of asthma in children (53).

In each of these cases, the risks are relatively low (≤1.3), and the biological mechanisms that may account for the associations are either only suggestive or unknown. However, the strength and consistency of the observations are compelling, and attempts to find confounding factors that can account for the associations have been unsuccessful. The U.S. Environmental Protection Agency (USEPA) (44, 45, 53) has used these findings for public health guidance and to set environmental standards. In some cases, detecting such small relative risks was possible only because of the large sizes of the populations studied, sometimes including the total populations of large cities, as for the daily mortality and hospital admissions studies (45). In other cases, stratified random samples of the whole U.S. population have been used, as in the NHANES studies (42–44). Another approach has been to obtain individual risk factor data on large cohorts of individuals. For example, the American Cancer Society study of the relationship between annual mortality and sulfate particle concentrations used data on more than a half million people in 151 U.S. communities (52).

For occupational health studies, the opportunities to study large populations in definable exposure groupings have been quite rare, and few epidemiological studies have had the statistical power to detect relative risks below about 2.

In the future, opportunities for access to data sets that have individual exposure data on relatively large numbers of workers for the study of exposure–response relationships characterized by small relative risks may eventually emerge if the Guidelines and Recommendations on Data Elements for Occupational Exposure Databases, recently endorsed by the Boards of ACGIH and AIHA, discussed previously, are adopted by industries, trade associations, and governmental agencies.

Pathways and Measuring Exposure To Toxic Substances
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Reproductive and Developmental Toxicology

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1.0 Introduction

Reproductive toxicology encompasses the study of a wide variety of chemical and physical agents and their effects on the structure and function of the male and female reproductive systems, the ability to conceive and reproduce, the nurture of the young during pregnancy and lactation, and the development of offspring to grow, mature, and reproduce (Fig. 3.1). Developmental toxicology involves the study of the effects of preconceptional, prenatal, and/or postnatal exposures up to the time of sexual maturity on developmental processes. Developmental toxicology is a subset of reproductive toxicology, although the subsequent effects of direct postnatal exposure of young animals or children traditionally have notx been considered part of reproductive toxicology. Reproductive dysfunction and developmental disorders are major public health issues that affect significant proportions of the population. Infertility in humans, defined as the inability to conceive after one year of unprotected intercourse, has been estimated to affect approximately 8% of all married couples in the United States (1). Billions of dollars are spent each year on fertility

treatments, including fertility drugs and the increased use of assisted reproductive techniques (e.g., *in vitro* fertilization). Although many of these technologies can improve fertility, some can also result in multiple births that put small and premature babies at risk. The causes of infertility are varied, and the impact of chemical and physical agents on the reproductive system is unclear. However, several reports in the 1990s of declining human sperm concentration, an increased incidence of cryptorchidism, hypospadias, and testicular cancer, as well as reports that some chemicals may act by disrupting endocrine function (2–5), have raised concerns that environmental chemicals might be causing some of these problems. These concerns have led to requirements, as part of the Food Quality Protection Act of 1996, for testing pesticides and industrial chemicals for their potential to cause endocrine disruption.

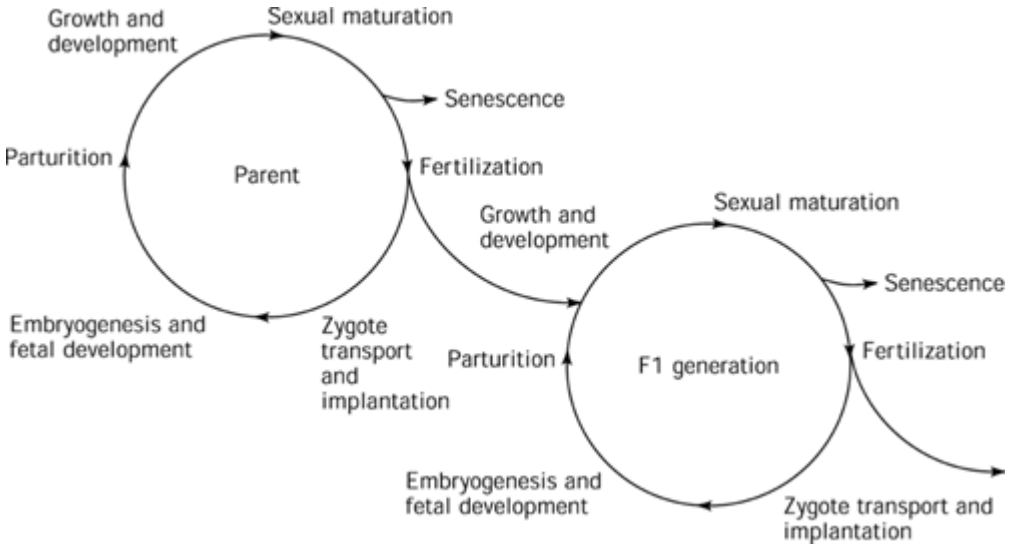

Figure 3.1. Reproductive life cycle of the parental and F1 generations showing the major stages in development, reproduction, and aging.

The incidence of spontaneous abortions in the population has been estimated to be as high as 50% of all conceptions (6, 7). Many of these occur before implantation in the uterus, are not detected, and cannot be distinguished from subfertility or infertility. Tests sensitive to the production of human chorionic gonadotropin as early as eight days after conception (before a woman may know she is pregnant) have shown a rate of 32–34% spontaneous abortions for postimplantation pregnancies (8, 9). The incidence of major birth defects in live-born children is 3–4%, and developmental disorders at school age affect approximately 12–14% of all children. The lifetime cost of caring for children born each year with the 17 most common birth defects and cerebral palsy has been estimated to be more than $8 billion. (10). This is a conservative estimate because these birth defects affect only 22% of children born with birth defects in a year and lost wages of caregivers were not considered. Developmental disorders also include the full gamut of functional effects such as neurobehavioral deficits, altered cardiovascular, pulmonary, renal, and other organ system dysfunction that result from prenatal or postnatal exposures.

The contribution of chemical and physical agents to the cases of reproductive dysfunction in humans is unknown, but there are some outstanding examples of environmental chemicals, pharmaceuticals, and other agents that can affect reproduction, development, and function; these include, for example, lead, methylmercury, polychlorinated biphenyls, diethylstilbestrol, thalidomide, cigarette smoking, and alcohol.

1.1 Definitions

Reproductive toxicology is the study of the occurrence of biologically adverse effects on the reproductive systems of females or males that may result from exposure to chemical or physical agents. The toxicity may be expressed as alterations to the female or male reproductive organs, the related endocrine system, or pregnancy outcomes. The manifestations of such toxicity may include,

but are not limited to, adverse effects on the onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, developmental toxicity, premature reproductive senescence, or modifications in other functions that depend on the integrity of the reproductive systems.

Fertility is defined as the capacity to conceive or induce conception.

Fecundity is the ability to produce offspring within a given time period. For litter-bearing species, the ability to produce large litters is also a component of fecundity.

Developmental toxicity is the occurrence of adverse effects on the developing organism that may result from exposure before conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

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Carole A. Kimmel, Ph.D., Judy Buelke-Sam

2.0 Overview of Normal Reproduction and Development Relevant to Toxicology
An appreciation of normal reproductive biology and development is important for understanding and evaluating the toxic effects of chemical and physical agents. This section provides an overview of these processes and a discussion of issues that are important in toxicology. Reference texts on reproductive and developmental biology and toxicology should be consulted for more detail (11–19).
2.1 Gametogenesis
The process by which germ cells (ova and sperm) are produced in both the male and female mammal is termed *gametogenesis* (Fig. 3.2) (20). The germ cells originate in both sexes from cells lining the embryonic yolk sac and, during the sixth week of gestation in humans, migrate into the gonadal ridges and become spermatogonia or oogonia, residing in the testis or ovary, respectively. Although many of the processes are similar in males and females, several differences are important for reproductive and developmental toxicology.

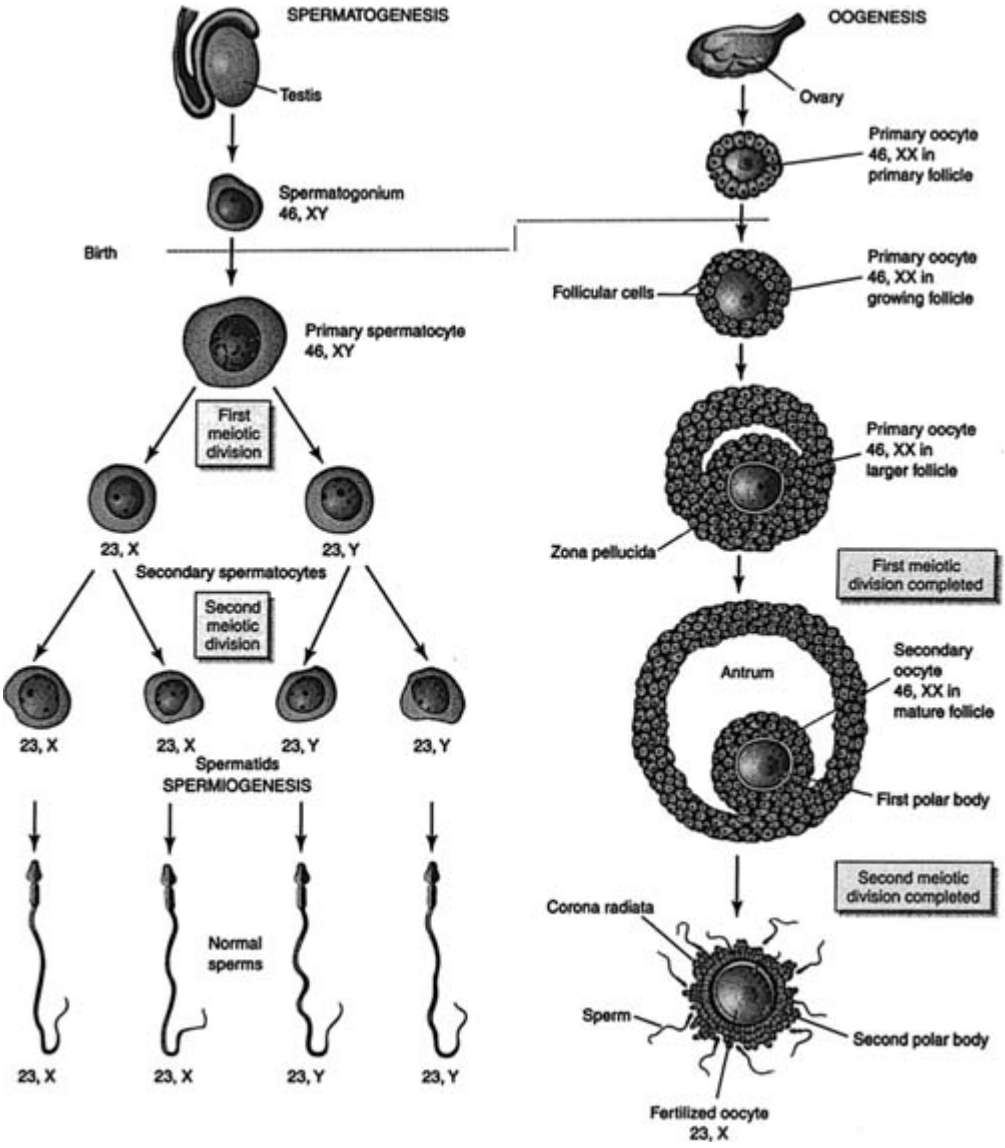

Figure 3.2. Gametogenesis in the male and female (used with permission of W. B. Saunders Co., and modified from Ref. 20).

Spermatogonia are dormant until after birth and up to the time of puberty when they begin to increase in number through mitosis and produce primary spermatocytes. These further divide by a process called *meiosis* to form two haploid (half the chromosome number) secondary spermatocytes, that further divide to form four spermatids. The process by which spermatids are transformed into mature sperm is called *spermiogenesis*. Mature sperm are released into the lumen of the seminiferous tubule of the testis. This transformation from spermatogonia to mature sperm, called *spermatogenesis*, lasts for 60 days in rats or 80 days in humans and continues throughout the life of the male, as long as undifferentiated A-type spermatogonia are present (21). Agents that affect spermatogonia are the most devastating because the effects may be permanent, whereas effects on later stages of spermatogenesis are more likely to be transient. For example, agents that affect DNA synthesis and cell division, such as the chemotherapeutic agents cyclophosphamide and cytosine arabinoside, affect spermatogonia and early spermatocytes (22, 23), whereas brief exposure to heat affects spermatocytes and early spermatids (24) and temporarily results in reduced fertility which is restored as later spermatocytes mature.

Oogenesis is the process of the development of mature ova in the female mammal. Before birth, the oogonia proliferate by mitotic division and form primary oocytes surrounded by follicular cells. The oocyte and its follicle cells are called a *primary follicle*. The first phase (Prophase I) of meiosis in the

oocyte begins before birth, and cells are then arrested until around puberty. At the onset of each estrous cycle, a pool of primordial follicles is recruited into a growing pool of primary follicles, one or more of which go on to form the large Graafian follicle and become an ovulatory follicle. In rodents and other polytocous species, several primary follicles become ovulatory follicles. No more primary oocytes are formed after birth. There is a normal process of atresia of oocytes throughout the prenatal and postnatal periods decreasing from approximately 7 million at 5 months of gestation to approximately 2.8 million at birth, with approximately 300,000 remaining at puberty (25). These continue to decrease so that no more follicles are present by around age 50. Damage to oogonia or primary oocytes before or after birth may be permanent, and an agent that increases atresia of primary oocytes reduces the complement of total ova available for ovulation and possibly decreases the time to onset of reproductive senescence (see later).

2.2 Fertilization

Fertilization involves the penetration of the ovum, its surrounding layers of granulosa cells, and the acellular zona pellucida by the mature sperm in the upper reaches of the oviducts (Fig. 3.3) (26). Fertilization requires a mature sperm that has undergone *capacitation* during its traverse of the female reproductive tract. The events required in capacitation are not well understood, but require plasma membrane modifications, decreases in net negative surface charge, changes in lipid components, alterations in fluidity/mobility of membranes, increased ion permeability, and other internal modifications. In addition, the *acrosome reaction*, which may facilitate penetration of the granulosa cells, and *activated motility*, to allow penetration of the zona pellucida, occur. Factors that can alter capacitation, the acrosome reaction, or activated motility may all play a role in preventing normal fertilization (27).

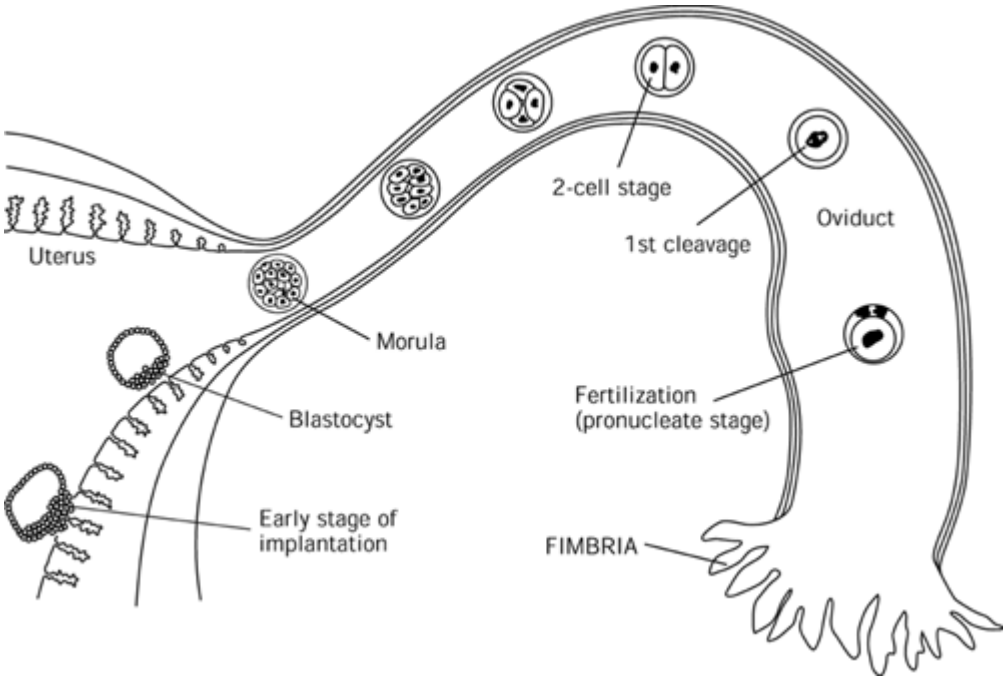

Figure 3.3. Development of the human embryo in the reproductive tract from fertilization to implantation (used with permission of Raven Press from Ref. 26, p. 47).

Several genetic aspects are determined at fertilization. First, the diploid number of chromosomes is restored when the male and female pronuclei fuse and chromosomes from the two become the chromosomal complement of the embyro. Second, by gaining genetic material from two different individuals, genetic diversity is maintained. Third, sex is determined at fertilization, in that a sperm bearing a Y chromosome results in a genetically male individual (XY zygote), whereas an X-bearing sperm results in a genetic female (XX zygote). Finally, fertilization stimulates rapid cell division or cleavage to form the embryo.

2.3 Female Reproduction

The female reproductive system involves the *ovaries, uterus, oviducts, cervix, vagina*, and *mammary glands*. The function of these is controlled by a carefully regulated interaction between the *hypothalmus*, the *anterior pituitary*, and the ovary. The hypothalmus secretes gonadotropin-releasing hormone (GnRH) which results in follicle stimulating hormone (FSH) and luteinizing hormone (LH) release from the anterior pituitary. A preovulatory surge of FSH and LH from the anterior pituitary stimulates differentiation of the granulosa cells and further meiotic division of the primary oocytes to a pre-ovulatory state (Fig. 3.4) (25).

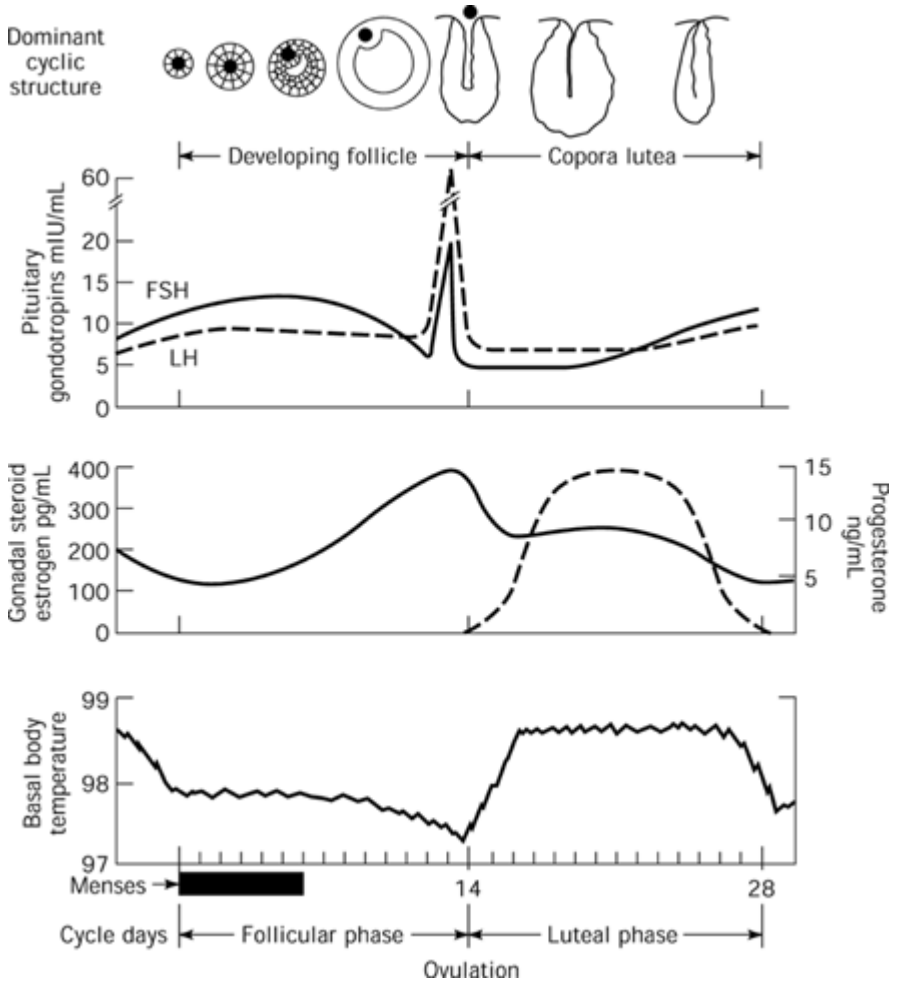

Figure 3.4. Endocrinology of the reproductive cycle in normal women. The dominant cycle structure, pituitary gonadotropins, gonadal steroids, and basal body temperature throughout the menstrual cycle are depicted. Note that in the follicular phase, the follicle enlarges as the serum estrogen rises. A midcycle gonadotropin surge heralds follicular rupture and release of the oocyte. Immediately after ovulation, the corpus luteum develops and secretes large amounts of progesterone with a resultant elevation in basal body temperature. In the absence of the conceptus, the luteal phase is 14 days long, and declining progesterone coincides with the onset of menses (used with permission of Raven Press from Ref. 25, p. 182).

The ovary is comprised of an outer cortex, which includes the *follicles*, and an inner medulla. The granulosa and thecal cells of the follicle secrete estrogen in a modulated fashion during the cycle and control secretion of FSH and LH through a negative feedback mechanism. As the estradiol level rises, it stimulates the release of LH and FSH, and possibly has direct effects on the LH releasing hormone (LHRH) which is released in a pulsatile fashion from the mediobasal hypothalamus. Once ovulation occurs, the follicle forms the corpus luteum, and progesterone is secreted, which stimulates the development of a secretory endometrium in the uterus in preparation for implantation. Progesterone secretion also causes an increase in basal body temperature. If fertilization occurs,

progesterone levels continue to rise. In humans, chorionic gonadotropin (hCG) secreted by the embryonic membranes is necessary to maintain the corpus luteum during early pregnancy. If fertilization does not occur, the ovum degenerates, and menses ensues.

Agents that interfere with the development of the reproductive system and the normal hormonal patterns necessary to regulate development may alter the intricate processes involved in a number of different ways. For example, the normal structure of the ovaries, uterus, oviducts, cervix, and vagina can be altered during development, resulting in interference with fertility and pregnancy. This was the case with the drug diethylstilbestrol (DES), a potent synthetic estrogen used in the 1950s and 1960s to prevent spontaneous abortion. Unfortunately, the drug was not effective in preventing labor but had profound effects on the development of the reproductive system in both boys and girls exposed before birth and produced a rare form of cancer (vaginal adenocarcinoma) in females not detected until after puberty (28). Synthetic androgens and antiandrogens also alter the structure of reproductive organs by interfering with the normal hormonal milieu during development. For example, ethinyl testosterone given to prevent spontaneous abortion resulted in masculinization (pseudohermaphrodism) of female offspring (29), and other androgenic compounds (e.g., danazole, methadriol, and methyltestosterone) prescribed for endometriosis, alopecia, hypotension, and other indications have shown similar effects. Because the endocrine activity of agents may be useful for their therapeutic value, it is sometimes difficult to separate pharmacological efficacy from toxicity. For example, raloxifene, a nonsteroidal selective estrogen receptor modulator (SERM) developed for treatment of postmenopausal osteoporosis acts as an estrogen in bone but functions in uterine tissue as a complete estrogen antagonist. Because estrogen is important in preparing for implantation, raloxifene was found, not unexpectedly, to cause delays in implantation (30); such effects have been seen with other compounds that are estrogen antagonists (reviewed in Ref. 30).

Mammary gland tissue is highly dependent on endocrine function. The mammary gland changes dramatically around the time of parturition as a result of a number of gonadal and extragonadal hormones. Milk letdown depends on suckling by the offspring, release of oxytocin from the posterior pituitary, and secretion of prolactin by the anterior pituitary. Agents that affect hormonal status, mammary gland development, and/or function may cause difficulties with milk production, milk quality, and indirectly result in adverse effects on offspring growth and development. Two neurotransmitters, dopamine and serotonin, play critical roles in the neuroendocrine modulation of prolactin secretion (31, 32), and prolactin is known to be mammotrophic and lactogenic, as well as luteotrophic and endometriotrophic (33, 34). Acute pharmacological doses of serotonin agonists stimulate prolactin release and enhance neonatal mouthing behavior, whereas acute doses of antagonists decrease these responses (35). It has long been known that bromocriptine, a preferential dopamine D_2 agonist, prevents postpartum onset of lactation in humans (36), inhibits established lactation in several species including rats (37), dogs (38), and humans (36, 39), and suppresses the suckling-induced secretion of prolactin in rats (40, 41).

Reproductive senescence occurs with advancing age, depletion of oocytes, and loss of normal ovarian cycling. As indicated earlier, agents that enhance atresia of oocytes may produce early depletion and untimely reproductive senescence. The long-term consequence of early menopause is an increased risk of a number of associated diseases, including heart disease and osteoporosis. Cigarette smoking has been shown to reduce the age at onset of menopause by as much as 2 years (42). In addition, Mattison and Thorgeirsson (43) showed that benzo[a]pyrene, which occurs in tobacco smoke, can kill oocytes in mice.

2.4 Male Reproduction

The male reproductive system is comprised of the *testis, accessory sex glands* (seminal vesicles, prostate, and bulbourethral or Cowper's glands), and the *duct system*. In rodents, there are two additional accessory sex glands, the coagulating glands and the preputial glands. The duct system is comprised of the *efferent ducts, epididymis* (consisting of three parts: head or caput epididymis, body or corpus epididymis, and tail or cauda epididymis), *ductus deferens*, and *ejaculatory duct*. A balanced interplay among the hypothalamus, anterior pituitary, and testis regulates the function of

the male reproductive system (Fig. 3.5) (44). As in the female, GnRH production by the hypothalmus permits release of FSH and LH by the anterior pituitary, which permits release of testosterone from the *Leydig cells*, and in turn is negatively regulated by increased levels of testosterone and dihydrotestosterone, the more active form of the androgen. Several important proteins are secreted by the *Sertoli cells*, including androgen-binding protein, activin which stimulates LH and FSH production by the pituitary, and inhibin and follistatin which have an inhibitory influence on the pituitary gonadotropins. Undernutrition, particularly a low protein diet (8% versus 27% in controls) started at weaning, can have a major impact on the development of the anterior pituitary–testicular axis and the feedback mechanism that controls gonadotropin secretion (45). Several antiandrogenic agents have been shown to interfere with normal development of the male reproductive system. For example, finasteride, a 5-alpha-reductase inhibitor, causes hypospadias in male offspring of rats exposed during pregnancy (46), and the most sensitive period for exposure was gestational days 16 and 17 in the rat (47). Several pesticides (e.g., vinclozolin and procymidone) are antiandrogenic and also cause hypospadias in male offspring (48–50).

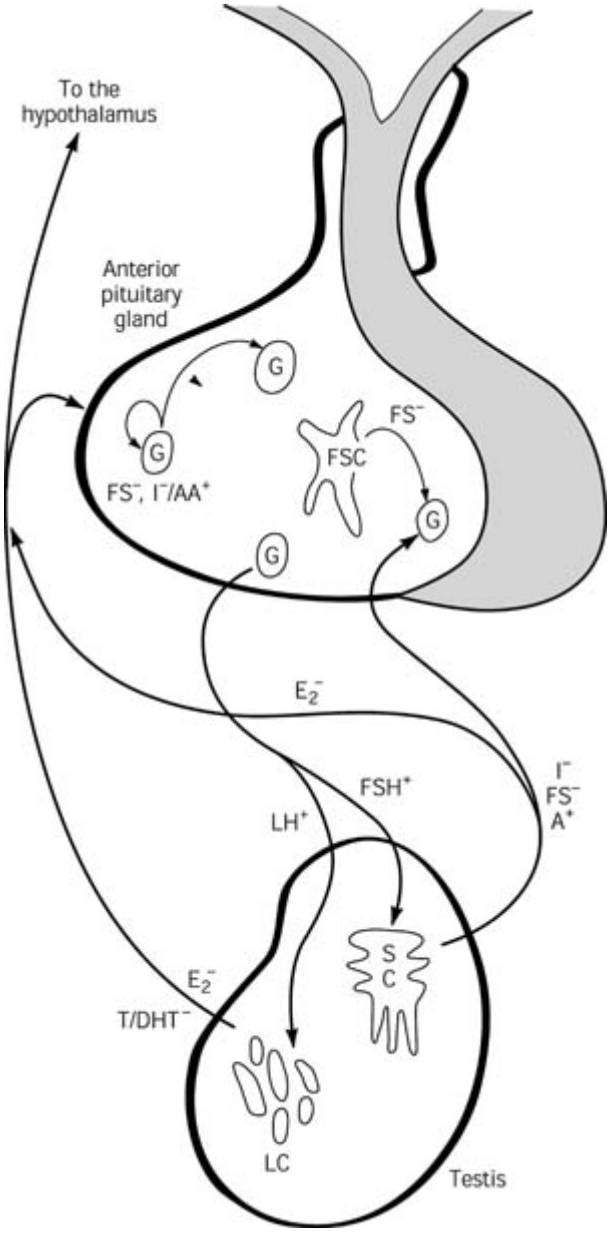

Figure 3.5. Diagram summarizing the anterior pituitary-testicular axis. LH and FSH are secreted by the gonadotrophs (G) to stimulate (+) either the Sertoli cells (SC) or Leydig cells (LC). These cells subsequently produce peptides [inhibin (I), follistatin (FS), and activin (A)] or sex steroid hormones [estradiol (E2), testosterone (T), or dihydrotestosterone (DHT)], which feed back principally at the

level of the anterior pituitary gland to regulate gonadotropin secretion. The modulatory role of these compounds is primarily inhibitory (–), although activin is known to stimulate FSH secretion. Autocrine/paracrine control over LH and FSH occurs at the level of the anterior pituitary gland via the peptides inhibin, follistatin, and activin, which are produced by the gonadotrophs and folliculostellate cells (FSC) (used with permission of Raven Press from Ref. 44, p. 6).

Approximately 90% of the testis is comprised of the *seminiferous tubules*, which are folded and refolded within the testis and contain the developing spermatozoa and Sertoli cells. The Sertoli cells extend from the basement membrane to the lumen of the seminiferous tubules and surround and support the developing germ cells. Tight junctions between the Sertoli cells near the basement membrane form the *blood-testis barrier*, which blocks access to the adluminal comparment. The interstitial tissue contains the Leydig cells (the primary source of testosterone), the vascular supply to the testis, and other cells. Testosterone is converted to dihydrotestosterone, the more active form of the androgen. Spermatogenesis takes place along the tubules in a wave form, so that cross sections of several tubules would reveal sperm in different stages of development. There are 14 distinct stages of development that have been identified in rats (51) (Fig. 3.6) (52), and six distinct stages have been described in humans (53). These stages can be used as a basis for determining the effect of an exogenous agent. A serial mating design can be used to identify site-specific lesions; this type of protocol involves mating males that have been exposed for a short time (5–7 days) with unexposed females for 4–5 day periods over several weeks. Cytosine arabinoside, a chemotherapeutic agent, caused reduced fertility 31 to 41 days post-exposure, indicating an effect on spermatogonia and early spermatocytes (22).

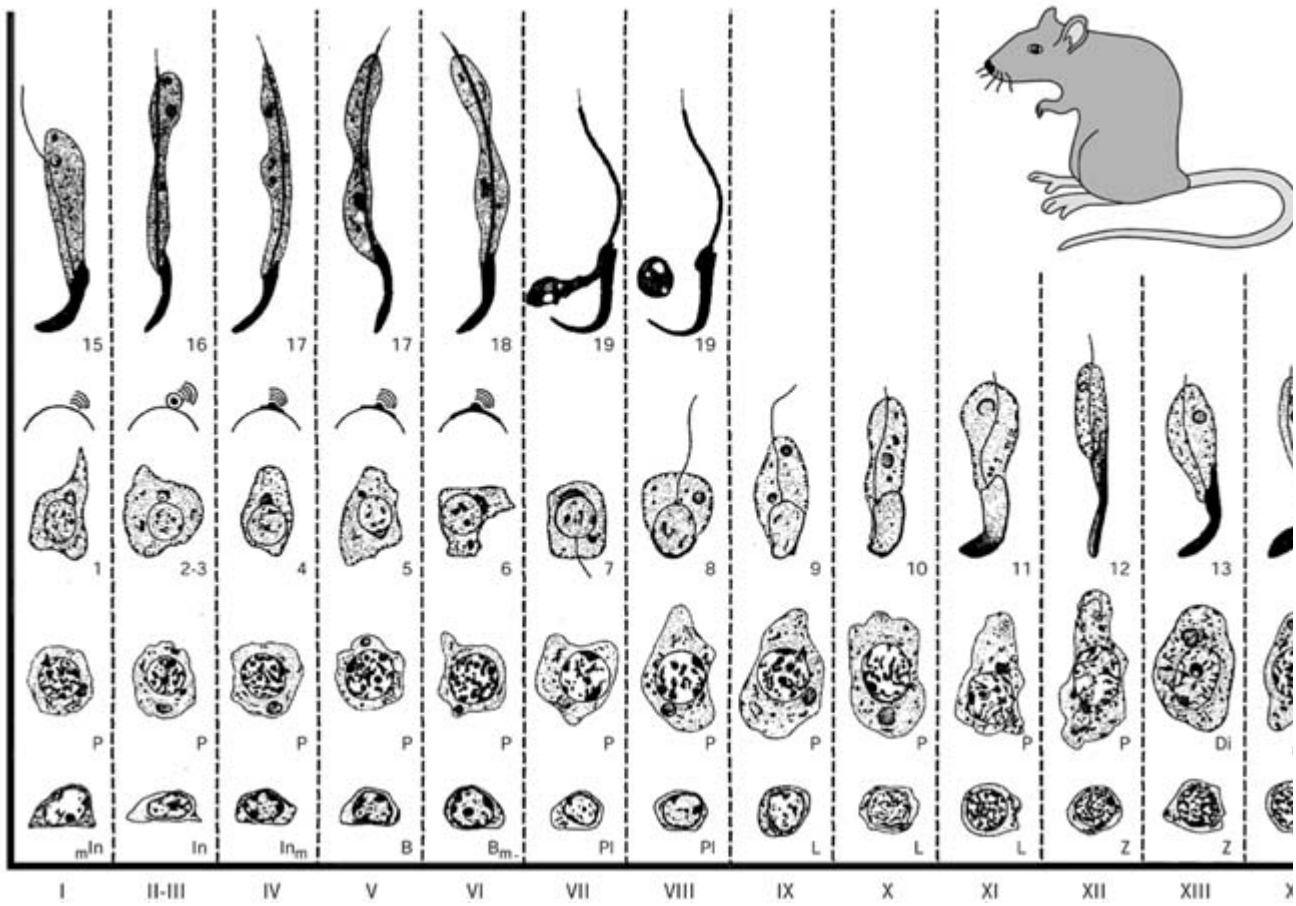

Figure 3.6. Cycle map of spermatogenesis for the rat. The vertical columns, designated by Roman numerals, depict cells associated with various stages. A cycle is a complete series of stages. The developmental progression of a cell is followed horizontally until the right hand border of the cycle map is reached and continues from left to right up the map, ending with spermiation (used with

permission of Cache River Press from Ref. 52, p. 43).

After sperm are released from the Sertoli cells into the lumen, they pass from the seminiferous tubules through the rete testis and efferent ducts into the epididymis, then through the ductus deferens and ejaculatory duct. The sperm undergo maturation in the epididymis and are stored there until ejaculation. The accessory sex glands contribute most of the volume to the semen, and their secretions may be involved in effective transport, survival, and function of the sperm through the female reproductive tract after ejaculation. The duct system and the accessory sex glands are androgen-dependent, and can be affected by agents that alter androgen levels (54).

2.5 Development

Development can be divided into the *prenatal* and *postnatal* periods. Prenatal development includes the *preimplantation* and *postimplantation* periods, and the latter encompasses the *embryonic* and *fetal* periods. Preimplantation is characterized by transport of the zygote from the upper ends of the oviduct into the uterine cavity during a period of 7–8 days in humans, or 5–6 days in rats or mice (Figure 3.3). Rapid cell division of the single-cell *zygote* (fertilized ovum) proceeds through the *morula* stage, a solid ball of approximately 16 cells, and further division results in a multicellular *blastocyst* that contains a cavity. The blastocyst implants in the uterine wall and develops into the definitive embryo. The embryo itself develops from a small group of cells in the blastocyst, the *inner cell mass.* The rest of the cells, the *extraembryonic cells*, form the *placenta* and surrounding membranes. Implantation occurs around gestational day (gd) 7 in humans, gd 5–6 in mice and rats, and gd 7 in rabbits. Agents that interfere with implantation result in apparent subfertility or infertility in humans. The type of effect produced on fertility can be determined in rodents by counting the number of corpora lutea (i.e., ovulated eggs) and the number of implantation sites in the uterine wall if there are enough viable implants to maintain active corpora lutea during pregnancy or if done early in gestation when there are no viable implants.

Placentation is a complex series of events that provides an intimate relationship between the embryonic and maternal tissues for the purpose of nutrition of the embryo and removal of wastes. Early on, before vascularization of the extraembryonic membranes and formation of the *chorioallantoic placenta*, the *yolk sac placenta* provides histiotrophic nutrition (breakdown and transfer of maternal macromolecules). The yolk sac placenta is the primary placenta in rodents through the early part of embryogenesis (when the early neural tube and limb buds are forming), and a gradual switchover to the chorioallantoic placenta occurs around gestation days 11–12 in the rat. In humans, the chorioallantoic placenta becomes functional around gestation day 21 when the neural tube is just beginning to form, an earlier embryonic stage than in rodents. Chorioallantoic placentation involves hemotrophic nutrition (transfer of nutrients via the circulation) and is somewhat different in different species, in that the number of maternal and embryonic layers differs. Although much has been made of these differences in terms of their role in placental transfer of toxicants, there is little evidence that these differences are important factors compared to maternal blood flow, plasma protein binding, molecular size and charge, placental metabolism, and the fetal elimination pathway. A more complete discussion of the morphology and function of the placenta can be found in embryology textbooks and excellent descriptions related to developmental toxicology are given by Beck (55), and Slikker and Miller (56).

Exposure to certain toxic agents during pregnancy may adversely affect placental function, which can in turn affect the developing embryo/fetus. Effects on the placenta may include alterations in blood flow and perfusion, metabolism, placental transfer of essential nutrients or compounds, and in extreme cases, may cause necrosis and separation from the uterine wall. Cadmium is an environmental contaminant associated with refineries, fossil fuel plants, and tobacco smoke and is a demonstrated placental toxicant in both rodents and humans (56). Although cadmium may cross the rodent yolk sac placenta very early in development and cause fetal malformations, it does not cross but accumulates in the chorioallantoic placenta. Adverse developmental effects, ranging from growth retardation to fetal death, observed following such accumulation result from placental dysfunction rather than direct actions on the embryo/fetus.

The embryonic inner cell mass forms a two-layered embryonic disc, consisting of *ectoderm* and *endoderm*. Around gestation day 17 in humans or gestation day 9 in rats, invagination of ectodermal cells occurs through a midline *primitive streak* to form the third intermediate layer of cells, the *mesoderm*. Figure 3.7 shows the major derivatives of each layer. The mesoderm cells form the viscera, blood vessels and cells, muscles, tendons, and bone. The endoderm forms the lining of the gut, respiratory system, thyroid, and pharynx. The ectoderm forms the surface layers of the body, including the skin, hair, and nails, enamel of the teeth, and the lens; a specialized portion of the ectoderm that forms along the edges of the primitive streak is the *neuroepithelium* consisting of the *neural tube* and the *neural crest cells*. The neural tube forms the brain and spinal cord, and the neural crest cells form the cranial and spinal ganglia and nerves, several components of the face and neck, the adrenal medulla, and contribute to the endocardial cushions that separate the chambers of the heart. Agents that interfere with the development and closure of the neural tube may result in anencephaly or spina bifida, and those that interfere with migration of neural crest cells to their ultimate site may result in craniofacial defects, cranial or spinal nerve defects, and/or cardiac septal defects. Retinoids, including excessive supplements of vitamin A or the drug Accutane (used in treating dermatologic disorders), interfere with neural crest cell migration, and both animals and children exposed during early development exhibit a number of these defects (57, 58). In addition, central nervous system malformations and a continuum of neurobehavioral disorders have been identified in animal fetuses and offspring and in children exposed early in pregnancy (59–64). Postnatal death, profound mental retardation, alterations in general learning ability, and other subtle behavioral alterations have been documented. These effects in animals and humans all depend on the dose and developmental stage at exposure, as well as the relative teratogenic potency of the individual retinoid (64).

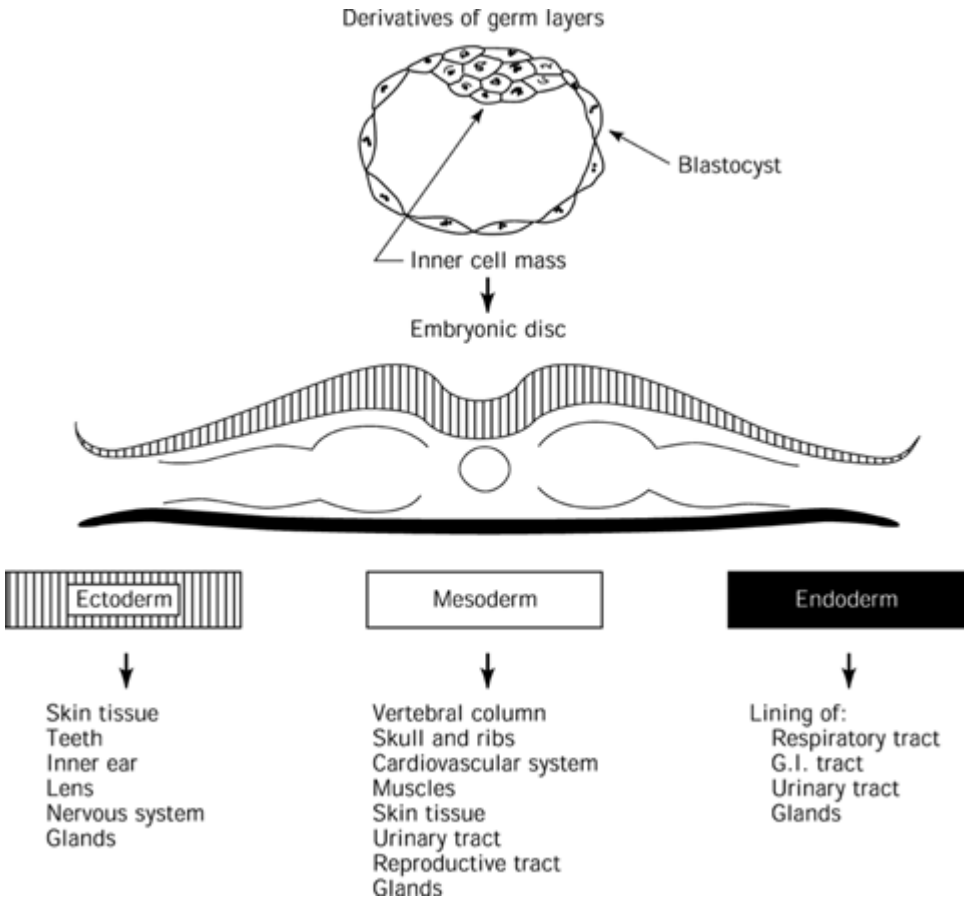

Figure 3.7. Derivatives of the germ layers in the mammalian embryo. Cells of the inner cell mass form the embryonic disc consisting initially of ectoderm and endoderm. During gastrulation, a mesodermal layer is formed in between the ectoderm and endoderm. The primary derivatives of the three germ layers are shown.

The period during which the major conformation of organ systems occurs, called *organogenesis*, encompasses the period from the primitive streak stage until palate closure (gestation days 6–15 in rats and mice, gestation days 17–57 in humans). The *fetal period* consists of the time after major organogenesis until birth, during which organization continues at the histological level in most organ systems.

There are a number of *critical periods* when cells or organ systems are particularly sensitive to exposure to toxic agents. Because of this, the manifestations of developmental toxicity vary depending on the timing of exposure. As examples, exposure before conception may cause chromosomal or DNA changes in germ cells that result in heritable effects, including death, malformations, growth retardation, functional deficits, or cancer in the offspring. During very early embryogenesis when cells are multiplying at a rapid rate and are relatively undifferentiated, exposure tends to result in death or compensation and continued normal development. For several genotoxic agents (e.g., ethylene oxide, ethylnitrosourea, ethyl methanesulfonate) (65–71), exposure during this period also results in malformations and growth retardation. As organogenesis begins, cells become more and more differentiated and the major structure of organs is formed, although not all organs develop at the same time or rate. Exposure during this period may cause major structural defects, as well as death, growth retardation, or postnatal functional changes. As major organ structure is completed, organization and differentiation at the histological, physiological, and biochemical levels proceed; in most mammals, these processes occur to varying extents during pre- and postnatal development. However, there are important differences at birth among experimental animal species and humans in the staging of developmental events that must be recognized in designing studies and interpreting experimental outcome data for potential human risk. Exposure during this late gestational or fetal period may result in alterations that are detected as histopathology, growth retardation, functional changes, or cancer. Subsequent stages of development include further growth and functional maturation of organs/systems, some of which are not completed until after puberty. Exposure during this period may affect the same target organs as in adults but have different consequences because of the immaturity of the target organ itself. Additionally, other immature organ systems may be targets, and relative sensitivities may be greater or lesser due to immaturity of processes responsible for metabolism and excretion of the chemical.

Less work has been done to discern the critical timing for exposure during the postnatal period, but there are examples of neonatal exposures and effects on the developing reproductive system (72–74), and developing nervous system (75). This is an area of current interest to provide adequate guidance for pediatric use of pharmaceuticals and also for environmental exposures that may affect children where they live and play. One area that has received attention recently is the significant increase in childhood asthma (76, 77). As a result, a number of studies are being pursued to discern genetic and/or environmental factors that may be involved or responsible both prenatally and postnatally.

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3.0 Testing Procedures and Guidelines

Standard testing procedures have been used to identify reproductive toxicity since the mid-1950s. However, the first testing guidelines in the United States were not written until 1966 by the U.S. Food and Drug Administration (FDA) for testing the developmental effects (with particular emphasis on teratogenicity) of potential new pharmaceutical agents (78). In 1982, the FDA published testing guidelines (Redbook I) for food additives (79). The Organization for Economic Cooperation and Development (OECD) issued international testing guidelines in the early 1980s for reproductive and developmental toxicity of industrial chemicals (80, 81). In 1982, EPA published its first guidelines

for testing pesticides (82) and in 1985 for industrial chemicals (83).

During the last several years, many of these guidelines have been updated. The FDA participated as a member of the International Committee on Harmonization (ICH), which finalized a revised set of global testing guidelines for preclinical assessment of pharmaceuticals (84, 85). In 1993, the FDA published the draft Redbook II (86) and in 1997 clarified the approach to toxicity testing that had been outlined in Redbook I (79) based on level of concern. The 1997 publication is available at www.vcm.cfsan.fda.gov/~dms/opa-tg1.html. (site currently unavailable) The EPA has recently updated and expanded testing guidelines to include a more comprehensive evaluation of the reproductive toxicity of pesticides and industrial chemicals (87–89). The OECD guidelines are currently being revised. The most recent testing guidelines for pharmaceuticals and for pesticides and industrial chemicals are briefly described here.

3.1 Testing Pharmaceutical Agents for Reproductive Toxicity

Testing of potential new pharmaceuticals is conducted for three reasons: (1) to provide scientifically and ethically appropriate support for clinical trials, (2) to provide data used to establish exposure guidelines for worker safety, and (3) to provide information relevant to risk:benefit assessments in the product label for use by prescribing physicians. Before international acceptance of the ICH testing guidelines (84), preclinical testing for reproductive and developmental toxicity was conducted following different guidelines for U.S., European, or Japanese registration of a new pharmaceutical (90, 91). Harmonization has not altered the overall requirements to evaluate reproductive and developmental outcomes following parental exposure before mating and during pregnancy and lactation, and assessment of effects on the entire parental reproductive process. However, it has reduced testing redundancy and provided the flexibility necessary to design studies most appropriate for assessing the toxicity of individual compounds. Exposure periods, dose selection, and end points evaluated within these studies are chosen based on the following: (1) pharmacology of the compound; (2) the plan for clinical trials, including duration of treatment; (3) known or expected toxicity of the therapeutic class; and (4) the target medical condition and therapeutic population(s).

Preclinical reproductive and developmental studies traditionally have been designated as Segment I, Segment II, and/or Segment III studies based on timing of initiation and duration of parental exposure (Fig. 3.8). These studies are routinely conducted in rodents, although a second Segment II study in a nonrodent species, most often the rabbit, usually is required. Segment I studies are intended to evaluate estrous cycling, mating, testicular and sperm parameters, fertility parameters, and early embryonic development; parental treatment begins before mating (generally 2 weeks for females, 4 weeks for males) and continues in females through implantation (gd 5 or 6). Segment II studies are intended to evaluate embryo and organ development; maternal treatment is initiated once implantation has occurred (gd 6 in rodents, gd 7 in rabbits) and continues throughout the period of major organogenesis (to gd 15 in mice, gd 15–17 in rats, and gd 18–19 in rabbits). Segment III studies are intended to evaluate maternal processes of parturition and lactation, as well as fetal and offspring development through sexual maturity; maternal treatment begins at the end of organogenesis and continues through to weaning of the offspring (usually postpartum day 21 in rodents).

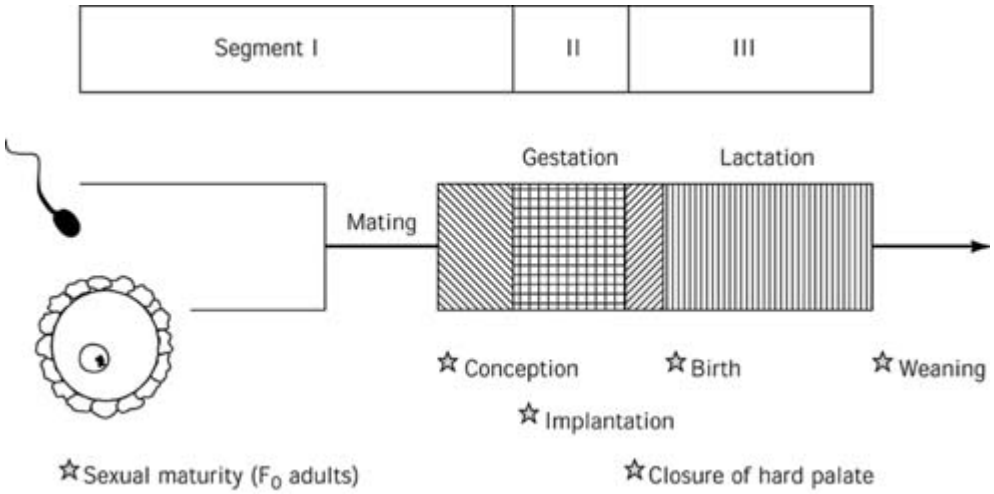

Figure 3.8. Exposure conventions for reproductive and developmental toxicity testing of pharmaceuticals. The Segment I, II, and III designations for these studies refer primarily to the reproductive and developmental events that occur during the discrete parental treatment period. The parameters monitored in any single-Segment or combined-Segment study may include relevant end points which are measured during and/or following the treatment period (diagram developed by J. A. Hoyt and J. Buelke-Sam, included with permission).

Currently, four studies are usually conducted for the majority of potential new pharmaceuticals: a Segment I study in treated male and female rodents; Segment II studies in rodents and rabbits; and a combined Segment II/III study in rodents which includes postnatal assessments of growth, physical development, and behavioral and reproductive performance of the offspring.

However, alternative exposure periods may be more appropriate to assess individual agents. These alternatives may include additional exposure period combinations (e.g., a combined Segment I/II study in rodents for compounds with no anticipated effects on mating and fertility and a single rodent combined Segment I/II/III study for compounds with no expected reproductive or developmental toxicity and anticipated long-term clinical exposures) (92). Other alternatives include more discrete exposure periods (e.g., gd 0–5 of pregnancy for agents that have anticipated adverse effects on implantation processes) (30). The standard reproductive and developmental assessments in these studies may be supplemented with any additional outcome parameters deemed appropriate for individual agents, based on considerations listed before (e.g., progressive histopathological evaluations or functional assessments of suspected target organs or systems) (93).

An additional component of these studies involves determining maternal blood levels and/or toxicokinetic parameters. Most often, such determinations are made within the Segment II exposure period but also may be applicable to other segments. These data allow a more direct comparison of maternal animal and human exposures and may also aid in interpreting reproductive outcome. Maternal blood level data are particularly valuable in verifying that maternal exposure did occur for studies in which no adverse maternal or developmental findings were seen. Placental transfer studies or milk excretion studies also may be conducted to determine embryo/fetal or neonatal exposures more directly.

Another aspect of testing is providing adequate preclinical support for pediatric testing and guidance in the product label for using many pharmaceuticals in the pediatric population (94, 95). Only 20% of the pharmaceutical products currently marketed in the United States include labeling information on safety and effectiveness in infants or children. The ICH guidelines (84) indicate that additional studies involving direct treatment of neonatal and young animals may be necessary to support pediatric clinical trials, in addition to appropriate repeated-dose toxicity studies, standard genotoxicity studies, a complete reproductive and developmental toxicity package (Segments I, II

and III studies), as well as safety data from previous adult human trials. The FDA (95) has defined four human age categories of concern: infant, neonate, child, and adolescent. Table 3.1 provides a general comparison for these categories in humans and several test species, although the comparable age ranges in these species vary depending on the developmental schedules of individual organs or systems. The need for preclinical juvenile studies, the test species for such studies, age categories to be covered, duration of exposure(s), as well as the parameters and ages for assessment of effects within any particular study, are currently being determined compound by compound.

Table 3.1. Comparative Age Categories

Category	Rat (days)	Mini-Pig (weeks)	Dog (weeks)	Primate (months)	Human (years)
Neonate	<10	<2	<3	<0.5	<1 month
Infant	10–21	2–4	3–6	0.5–6	1–2 months
Child	21–30	4–14	6–20	6–36	2–12
Adolescent	30–60	14–26	20–28	36–48	12–18

3.2 Testing Pesticides and Industrial Chemicals for Reproductive Toxicity

Several testing protocols are used to evaluate the reproductive toxicity of pesticides and industrial chemicals. The EPA testing guidelines published in 1998 were harmonized for pesticides and industrial chemicals, so that there are no differences in the testing protocols themselves. The requirements for pesticide testing specifically defined in 40 CFR Part 158. 340 Subpart F include reproductive and developmental toxicity testing for all food-use pesticides or those for which a reference dose (RfD) will be set. For industrial chemicals regulated under the Toxic Substances Control Act, the process involves defining the appropriate tests to be done according to the testing guidelines in test rules for specific chemicals, or testing approaches may be developed under consent agreements with industry for specific chemicals.

In general, the testing guidelines for pesticides and industrial chemicals are more specifically defined than those for pharmaceuticals in terms of number of animals, days of treatment, outcomes, and the methods for measuring them, and reporting of data. There are three major protocols used for pesticide and industrial chemical testing of reproductive and developmental toxicity. These include the prenatal developmental toxicity study, the two-generation reproduction study, and the developmental neurotoxicity study (87–89). These guidelines are available at http://www.epa.gov/docs/OPPTS_Harmonized_870_Health_Effects_Test_Guidelines/Series/. The developmental neurotoxicity study has not been routinely required for most pesticides and industrial chemicals, as discussed futher later. Data from adult toxicity studies are reviewed to determine which target organs might be of concern and whether additional testing of other organ systems may be appropriate, for example, immunotoxicity evaluations in developing animals or perinatal carcinogenic testing.

The prenatal developmental toxicity study (Fig. 3.9) (87) involves exposure of time-mated animals (usually rats and rabbits) to an agent throughout pregnancy or at least from implantation (around gd 6) to the day before parturition (gd 20 in rats, 28–29 in rabbits). Clinical signs and body weights throughout the dosing period are recorded for maternal animals, which are then killed on the day before parturition and examined for gross pathology. Fetuses are harvested from the pregnant uterus, weighed, and examined for external, visceral, and skeletal defects. In addition, the number of implantations and incidence of resorptions or fetal deaths are recorded.

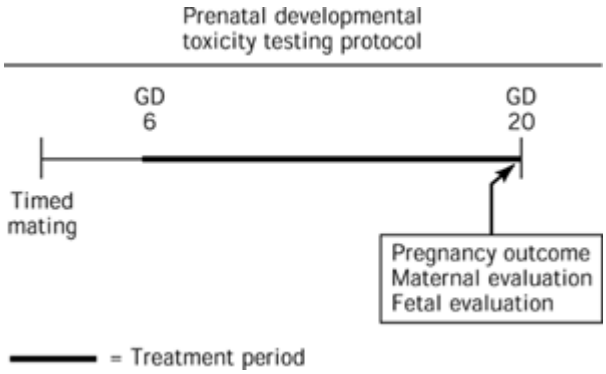

Figure 3.9. Schematic of the prenatal developmental toxicity testing protocol (87). The treatment period is shown by the heavy black line. GD = gestation day; the numbers shown refer to the days of gestation in the rat. Treatment begins on GD 6 around the time of implantation or can be started as soon as animals are mated. The protocol can be conducted in other species with appropriate adjustment of treatment times.

The developmental neurotoxicity study (Fig. 3.10) (89) is currently triggered based on observing malformations of the central nervous system in the prenatal developmental toxicity study, adult neurotoxicity/neuropathology, alterations in brain weight in the two-generation study, or other indicators of potential developmental neurotoxicity, for example, evidence that an agent may cause hormonal effects. A recent evaluation of the literature on developmental neurotoxicity concluded that this study should be conducted as a standard part of reproductive toxicity testing because such triggers may not be inclusive enough to indicate all chemicals that may cause such effects (96). This study can be done as a separate study, in conjunction with the prenatal developmental toxicity study, or preferably with the two-generation reproduction study in the second generation. As a stand-alone study, time-mated pregnant animals (usually rats) are dosed from gd 6 at least through postnatal day (PND) 10 or to weaning. Pups are weighed at various postnatal ages and examined for clinical signs, and several developmental landmarks (e.g., vaginal opening, preputial separation), as well as several behaviors, are evaluated. These include motor activity at PND 13, 17, 21, and 60, auditory startle habituation at weaning and at PND 60, and learning and memory at weaning and around PND 60. Brain weights are recorded from pups killed on PND 11 and at termination of the study neuropathology including a simple morphometric analysis is done.

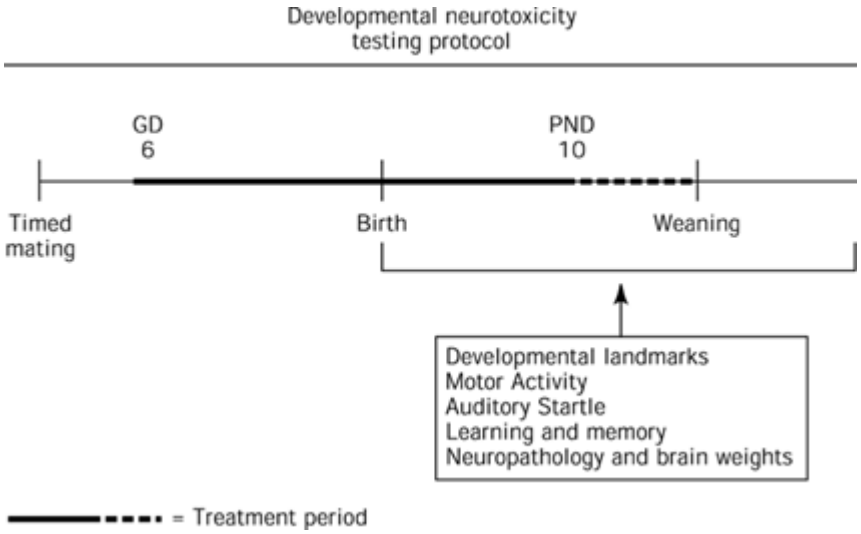

Figure 3.10. Schematic of the developmental neurotoxicity testing protocol (89). The treatment period is shown by the heavy black line, although treatment is currently being extended to weaning in some cases (dashed line). GD = gestational day, PND = postnatal day. This study is typically done in rats but can be conducted in other species. The study can be conducted as a stand-alone protocol

or can be done in conjunction with a prenatal developmental toxicity study or a two-generation reproductive study.

The two-generation reproduction study (Fig. 3.11) (88) involves exposing the parental (P) male and female animals (usually rats) for 10 weeks before mating, through the mating period, and to females during pregnancy. Exposure continues to the lactating females postpartum and to selected F1 males and females for 10 weeks after weaning. F1 males and females are mated and exposure continues to the F1 females during pregnancy and lactation. A second litter may be obtained in each generation for additional studies; for example, a standard fetal examination similar to that done in the prenatal developmental toxicity study may be conducted or the developmental neurotoxicity study may be conducted on a second F2 litter. A number of end points of reproductive toxicity are evaluated in this study. For example, estrous cyclicity is evaluated for three weeks in the P and F1 females before and throughout mating, and semen quality (sperm number, motility, and morphology) is evaluated in the P and F1 males before mating. Reproductive development is evaluated in the F1 and F2 offspring by observing the age at vaginal opening and preputial separation. If there is a treatment-related effect in the F1 sex ratio or sexual maturation, the anogenital distance is measured in F2 pups at birth. Reproductive organs, as well as other potential target organs, from animals in each generation are weighed and examined histologically. In addition, brain, spleen, and thymus weights are recorded for F1 and F2 pups terminated at weaning.

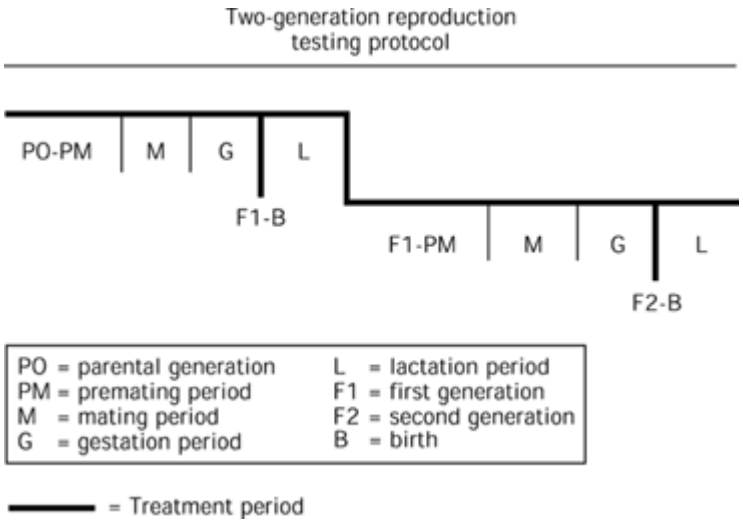

Figure 3.11. Schematic of the two-generation reproduction testing protocol (88). The treatment period is shown by the heavy black line. Males and females are exposed for 10 weeks before mating, and females are continued through gestation and lactation. F1 offspring continue treatment until they are old enough to be mated, and treatment continues through gestation and lactation.

3.3 Other Reproductive Toxicity Testing Procedures

Additional studies may also be used to determine the potential for reproductive toxicity of a drug or chemical. For example, Chapin (97) and Morrissey et al. (98) described the addition of improved testicular histopathology and assessment of estrous cyclicity and sperm quality to standard subchronic testing studies. Such data can provide valuable information on reproductive effects that can then be followed up in further reproductive toxicity testing studies.

The single mating trial, modified from the original FDA two-litter test (90), provides a basic test of fertility and reproductive function. In this type of study, a single mating occurs after a 60–70 day exposure period for males and a 14-day exposure period for females. The longer period of exposure in males is to ensure exposure to all stages of the spermatogenic cycle. If the only effects seen are those on fertility or pregnancy outcome, the contribution of male- or female-specific effects cannot be determined. If estrous cyclicity and ovarian/reproductive tract histopathology are included in

females and sperm measures and reproductive tract histopathology in males, the contribution of an effect of an agent on either gender may be characterized. However, there may still be questions as to which sex is affected. For this reason, some laboratories run separate studies in which only one gender is treated to characterize any gender-specific effects.

The continuous breeding protocol, also known as the Fertility (or Reproductive) Assessment by Continuous Breeding (FACB or RACB), was developed by the National Toxicology Program (99). This protocol was based on an older protocol used to determine full reproductive capacity in which females were mated repeatedly to determine how many litters and offspring they could produce. The RACB, as currently designed, can be conducted in mice or rats and involves dosing before mating and through several pregnancies over a 14-week period. Offspring are removed shortly after birth, counted and examined for viability, litter and/or pup weight, sex, and external abnormalities, and then discarded. Up to five litters can be produced during a 14-week period, and the number of litters, pups, and spacing of litters are recorded. The last litter may remain with the dam until weaning to study the effects of prenatal, as well as postnatal exposures, and to raise for production of an F2 litter. If effects are observed in the parental and F1 animals, crossover matings may be conducted between the treated and control animals (treated females with control males, treated males with control females), to define the affected gender and the site of toxicity. In addition, sperm measures (number, motility, and morphology) and vaginal smear cytology to detect changes in estrous cyclicity can be added at the end of the mating trial and used to detect changes (100, 101). This testing approach allows observing the timing of the onset of effects on fertility, as well as the ability to detect subfertility with measures of number of litters, litter spacing, and litter size.

Gray et al. (102) also proposed a test protocol (the Alternate Reproductive Test—ART) that includes many of the advantages of the RACB, but in addition monitors morphological and physiological changes associated with puberty in the F1 animals, making it useful for detecting compounds that have hormonally mediated effects on reproductive function. Chapin et al. (103) developed a protocol for evaluating several adult functional outcomes following perinatal and juvenile exposures.

Other protocols have been developed to screen and set priorities for further testing. In particular, the Reproductive/Developmental Toxicity Screening Test, which is part of the Screening Information Data Set (SIDS) protocol developed by the Organization for Economic Cooperation and Development (104), was developed to screen a large number of commercial industrial chemicals that have not been tested for potential toxicity. This protocol involves exposing a small number of males and females (8/dose group) during the premating, pregnancy, and lactation periods and then determining any effects on fertility, pregnancy outcome, and sperm measures. This protocol may be combined with the repeated dose toxicity study (105). An effect in this protocol raises concerns about the toxicity of a chemical, but lack of an effect cannot be interpreted as no effect because of the relative insensitivity of the testing protocol.

3.4 Tests of Germ Cell Toxicity

Tests of germ cell toxicity are important for assessing reproductive toxicity, because effects on fertility and pregnancy outcome are often the result. Two types of assays are generally used: measurements of heritable damage (e.g, the dominant lethal test, the specific locus test, and the heritable translocation assay) and measurements of effects in germ cells that may be related to alteration of DNA but may not actually represent heritable damage (e.g., DNA damage and/or repair, chromosomal abnormalities, and abnormal sperm morphology).

The male dominant lethal test was designed to detect the mutagenic effects of agents on the spermatogenic process that are lethal to offspring. It may be conducted in one of two ways: (1) exposure of males for a few days to one week, then mating with one or more females per week for the duration of the spermatogenic cycle; or (2) exposure of males for 10 weeks, then mating to one or more females immediately after exposure. In either case, a decrease in the number of implantation sites, the number of live fetuses, and/or an increase in the number of resorptions at necropsy 15–18 days later indicate a genotoxic effect. This type of testing paradigm can be expanded to follow animals to term and postnatally for longer term effects of male germ cell toxicity. For example,

Anderson et al. (106, 107) conducted dominant lethal studies of 1,3-butadiene in which one-half the pregnant animals were killed on gestation day 17, the other half were allowed to litter, and the pups were followed for 75 weeks to determine viability, growth, and tumorigenicity. A similar exposure and mating protocol was used to characterize male-mediated alterations in the postnatal function of surviving offspring after paternal treatment with drugs and chemical agents (108).

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4.0 Risk Assessment

Risk assessment for reproductive and developmental toxicity has developed during the past 20 years and is currently a focus for a number of efforts in research and development, as well as in the regulatory setting. The focus by several regulatory and funding agencies on children's environmental health issues in the 1990s has heightened the awareness of special concerns involving pre- and postnatal exposures and effects. For example, the Food Quality Protection Act (FQPA) of 1996 which updated the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) for regulating pesticides focused much greater attention on children's exposures to and the potential health effects of pesticides. Also in 1996, a Presidential Executive Order (No. 13045) was issued that requires Federal agencies to make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children and ensure that agency policies, programs, activities and standards address disproportionate risk to children. Another major law affecting children was the Food and Drug Administration Modernization Act of 1997, requiring the FDA to provide a list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population and, for certain new products, requires sufficient data and information to support directions for pediatric use for the claimed indications.

The U.S. Environmental Protection Agency published Guidelines for Developmental Toxicity Risk Assessment in 1991 (109), Reproductive Toxicity Risk Assessment in 1996 (110), and Neurotoxicity Risk Assessment in 1998 (111). These detailed guidelines describe a process for evaluating data and setting reference values for reproductive and developmental effects resulting from environmental exposures. No other similar risk assessment guidelines have been published by U.S. federal regulatory agencies. Recently, the Food and Drug Administration's Center for Drug Evaluation and Research made available for public comment two draft documents that discuss the evaluation of human pregnancy outcome data (available at http://www.fda.gov/cder/guidance/2377dft.pdf) and the evaluation of animal data for reproductive toxicity (available at http://www.fda.gov/cder/meeting/advcomm/paper.pdf). All of these guidance documents include many of the same principles as those in the EPA guidelines but are written for the specific regulatory mandate of each agency.

The EPA guidelines were based on the risk assessment paradigm outlined by the National Research Council (112). The process described by the NRC is comprised of four components, the first two are *hazard identification* and *dose–response assessment*. These two parts of the process constitute the toxicological evaluation that is aimed at characterizing the sufficiency and strength of the available toxicity data and may indicate a level of confidence in the data. Dose–response modeling may be included, if data are sufficient. Another component, *exposure assessment*, derives estimates of potential human exposure based on various environmental and/or occupational scenarios. The integration of human and animal data with the exposure assessment is termed *risk characterization* and constitutes the final step in the risk assessment process. Risk characterization is used along with social, economic, engineering and other factors in weighing alternative regulatory options and in making regulatory and public health decisions. This latter process, called risk management, is purposely separated from the scientific evaluation (i.e., risk assessment) to allow full evaluation of the scientific data without bias from other nonscientific influences.

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5.0 Summary

This chapter provides a brief overview of normal reproduction and development, as well as examples of how toxic agents may impact these processes. It summarizes the types of studies conducted and data collected as part of routine toxicity testing. Assumptions that must be made in the risk assessment process and an evaluation of data from both animal and human studies used in this process are discussed. The integration of hazard data (both animal and human) and dose–response information is described, and exposure estimates in the final characterization of risk are summarized. Advances have been made in our understanding of reproductive and developmental toxicity, particularly as the integration of molecular biology and toxicology has grown. However, there are still many gaps in our knowledge of both normal and abnormal reproductive and developmental processes. Further research will continue to fill these gaps and enhance our ability to identify more specific susceptible events in these processes and ultimately reduce adverse reproductive and developmental outcomes due to chemical exposures.

The views expressed in this chapter are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency. Mention of trade names of commercial products does not constitute endorsement or recommendation for use.

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1.0 Introduction

1.1 General Concepts of Multistage Carcinogenesis

Cancer is not a single disease, but rather is a general term applied to a multitude of diseases and stages of disease, each of clonal origin, that elicit uncontrollable tissue growth. There are more than 100 different types of cancer. In normal tissue the balance between cell reproduction and cell death determines the ultimate size of an organ. This balance is clearly represented after partial hepatectomy where, following removal of as much as two-thirds of the liver, regeneration results in restoration of the liver to its original size. If a normal cell incurs a defect in its growth regulating processes and acquires a growth advantage over other cells in a particular tissue or organ, it may multiply out of control producing a mass of altered cells; this abnormal overgrowth of new tissue is called a tumor or neoplasm.

The multistep process of carcinogenesis is thought to involve at least four stages (1): (1) initiation—the induction of a heritable change in a cell resulting from DNA damage (from endogenous processes or by a DNA reactive environmental agent or its metabolites) that can lead to point mutations, insertions, deletions, or chromosomal aberrations; (2) promotion—the clonal expansion of the initiated cell population; (3) progression—the process whereby benign neoplasms become malignant, as a consequence of increased genomic instability in neoplastic cells that gives rise to additional genetic alterations (i.e., mutations, chromosomal deletions, and/or rearrangements), and (4) metastasis—the spread of cancerous cells to other parts of the body. With increasing knowledge of the number of genes altered in human cancers, it is evident that even a four-stage model is not adequate to describe the carcinogenic process (2).

Two groups of genes control normal tissue growth; protooncogenes promote growth while suppressor genes halt growth. Normal protooncogenes of which there are 300–400 within the human genome regulate cell division and differentiation (3). If a protooncogene is mutated it may become an activated oncogene that causes the normal regulated cycling pattern of the affected cell to proceed out of control. Similarly a mutation in a suppressor gene may damage the growth-halting program of the cell and thereby allow unabated cell division. *p53* is the most commonly found mutated tumor suppressor gene in human cancers. The proliferating mass of altered cells may undergo additional changes during the progression stage that allow these cells to metastasize, that is, escape from their site of origin and invade surrounding tissues or remote organs of the body. The abnormal cells of a benign tumor become malignant (i.e., cancerous) when they acquire additional genetic changes that enable them to invade and destroy adjacent normal tissue or to metastasize to distant sites. Thus, the cancer cell is one that has lost the ability to respond to signals to differentiate into specialized cells, stop dividing, or even die. Carcinogenesis is the multistep process that leads to the production of cancers or malignant neoplasms that elicit uncontrollable growth and dissemination.

Most tumors are defined by their cell of origin and their behavior or appearance. Benign neoplasms of epithelial origin are referred to as adenomas or papillomas, and benign neoplasms of mesenchymal origin are referred to as fibromas, osteoma, gliomas, etc. Malignant tumors of epithelial cells are carcinomas, and malignant tumors of mesenchymal tissues are sarcomas.

Environmental insults, including ionizing or UV radiation, certain viruses, or various chemical agents can cause genetic damage that converts protooncogenes to oncogenes or inactivates tumor suppressor genes. Genes involved in regulating cell division, differentiation, adaptive responses, signal transduction, and programmed cell death could be adversely affected by exposure to certain chemicals. Thus, environmental pollutants can pose a persistent cancer risk, especially to workers who may be exposed to higher levels of these agents than the general population. The simplest definition of a carcinogen is an agent that can cause cancer. However, identifying an agent as a human carcinogen and assessing human risk associated with environmental or occupational exposure is complicated because of the multitude of factors that must be considered: the induction of benign or malignant neoplasms, animal-to-human extrapolations, the influence of mechanistic information on low-dose risk, and the variability in susceptibility among individuals in an exposed population.

Tumor induction by occupational chemicals is a multistep process that may involve activation of the compound to a DNA reactive form, binding of the active metabolite (or parent compound, e.g., ethylene oxide) to DNA forming a DNA adduct, faulty repair of the adduct leading to a gene mutation, replication of the altered cell to fix the mutation in the genome, and further genetic alterations (including gene mutations, gene rearrangements and gene or chromosome deletions) that lead to progression to a metastatic cancer. Alternatively, some chemicals or their metabolites may act by “nongenotoxic” mechanisms whereby normal cell cycling patterns are disregulated as a consequence of altered gene expression, perhaps through receptor mediated processes (4). In this case, changes in cellular function occur without the chemical producing a direct effect on the normal DNA base sequence. Impacting on these considerations is the recognition that humans are exposed to a multitude of chemicals that have mixed mechanisms of action, and humans vary considerably more than inbred or outbred laboratory animals with respect to genetic factors that influence cancer

susceptibility. Thus, the predicted effect of a single agent may be affected by the mechanism of tumor induction, genetic differences among individuals, health status, and other exposure circumstances.

The first issue in cancer hazard identification is to determine whether exposure to a particular agent can cause a carcinogenic response. Hueper and Conway (5) defined carcinogens as "chemical, physical and parasitic agents of natural and man-made origin which are capable under proper conditions of exposure, of producing cancers in animals, including man, in one or several organs and tissues, regardless of the route of exposure and the dose and physical state of the agent used." Similarly, an Interdisciplinary Panel on Carcinogenicity (6) stated that "the carcinogenicity of a substance in animals is established when administration in adequately designed and conducted experiments results in an increase in the incidence of one or more types of malignant (or, where appropriate, a combination of benign and malignant) neoplasms in treated animals as compared to untreated animals maintained under identical conditions except for exposure to the test compound." In addition to causing an increase in incidence of tumors in treated animals versus controls, a chemical may be considered carcinogenic if it causes tumors earlier in treated animals than in controls or if it causes an increase in the number of tumors per organ (i.e., tumor multiplicity).

Concerning the issue of whether benign neoplasms are indicators of human risk, the National Cancer Advisory Board (7) stated that "benign neoplasms may endanger the life of the host by a variety of mechanisms including hemorrhage, encroachment on a vital organ, or unregulated hormone production" and that "benign neoplasms may represent a stage in the evolution of a malignant neoplasm and in other cases may be 'end points' which do not undergo transition to malignant neoplasms." A similar view was given by an Interdisciplinary Panel on Carcinogenicity (6) and by the Office of Science and Technology Policy (8) which reported that "truly benign tumors in rodents are rare and that most tumors diagnosed as benign really represent a stage in the progression to malignancy." Furthermore, it is not yet known whether benign neoplasms in rodents correspond to benign or malignant neoplasms in other species, including humans. Accordingly, chemically induced benign neoplasms in rodents should be considered important indicators of a chemical's carcinogenic activity, and they should continue to be made an integral part of the overall weight-of-the-evidence evaluation process for identifying potential human carcinogens (9).

The identification of an agent as a carcinogen is based on information from epidemiological studies, experimental animal studies, *in vitro* evaluations, and assessments of mechanistic data and structure–activity relationships. Data from these sources have shown that carcinogens may act by very different mechanisms (e.g., direct acting or requiring metabolic activation; genotoxic or nongenotoxic) and that carcinogens are not equal in their potential to cause human cancer. In addition, most carcinogens operate by a combination of mechanisms that may vary in different target tissues (2). Consequently, there has been much debate on the identification of human carcinogens and in particular on the characterization of human risk associated with exposure to such agents. The term "risk" is used in this chapter to indicate the probability of developing cancer from a particular exposure. Because most known human carcinogens are also carcinogenic in animals when adequately tested, the International Agency for Research on Cancer (10) considers that unless there is convincing data in humans to the contrary, "it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans."

Individuals may respond differently to similar exposures to a particular carcinogen. The likelihood of an individual developing cancer in an exposed population depends on extrinsic factors including the intensity, route, frequency, and duration of exposure, as well as on host factors including age, sex, health, nutritional status, and inherited characteristics. Hence, this chapter reviews issues related to the identification of carcinogens and factors that influence human risk. We also provide an update on agents that have been identified as "known" human carcinogens or "probable/reasonably anticipated" human carcinogens by IARC and the National Toxicology Program (NTP), as well as exposure standards developed by the Occupational Safety and Health Administration (OSHA) to

reduce worker exposure to these agents.

1.2 U.S. Occupational Safety and Health Laws Related to Risks from Exposures to Hazardous Substances

During the past 30 years, several laws have been promulgated to protect workers from the harmful effects of hazardous agents in the workplace (11). The Occupational Safety and Health Act of 1970, administered by OSHA, includes the following: (1) requires employers to provide safe working conditions for their employees, (2) prescribes mandatory occupational safety and health standards including exposure limits for toxic chemicals, (3) requires assessment of chemical hazards and notification to workers of their exposure to such hazards, and (4) establishes the National Institute for Occupational Safety and Health (NIOSH) "to develop and establish recommended safety and health standards." The Act authorized OSHA to promulgate occupational safety and health standards for toxic materials that ensure "to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life."

Based on the belief that any exposure to a carcinogen is not safe, OSHA interpreted the Congressional mandate to mean that carcinogens should be regulated to the lowest level feasible. However, in the 1980 benzene decision (448 US 607, 1980), the U.S. Supreme Court ruled that before OSHA "can promulgate any health or safety standard, the Secretary (of Labor) is required to make a threshold finding that a place of employment is unsafe—in the sense that significant risks are present and can be lessened by a change in practices." The Supreme Court did not define "significant risks" but wrote "if the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are 1 in a 1000 that regular inhalation of gasoline vapors that are 2% benzene will be fatal, a reasonable person might well consider the risk significant and take appropriate steps to decrease or eliminate it." Noting that significant risk can exist in the face of scientific uncertainty, the Court maintained that OSHA is "free to use conservative assumptions interpreting data with respect to carcinogenicity risking error on the side of overprotection rather than underprotection." Thus, OSHA performs quantitative risk assessments using human and/or animal data to determine if an occupational exposure poses a significant risk to workers; risks greater than 1 extra cancer death per 1000 are considered significant (12). The OSHA risk assessments and proposals for revised standards are published in the Federal Register and are open for evaluation and comment by scientists and interested parties (e.g., industry, labor groups, consumers). Informal hearings follow this process.

In contrast to OSHA, the U.S.EPA regulates excess cancer risks in the general population in the range of one per million. Though a significant risk may be clearly indicated in an occupational setting, the promulgation of a new or revised occupational standard requires demonstration that achieving such an exposure standard is both economically and technologically feasible. Hence, improving control technology will reduce worker exposures to carcinogenic agents (13).

The Toxic Substances Control Act (TSCA) created by the U.S. Congress in 1976 is administered by the U.S.EPA for the purpose of (1) regulating the production, processing, importation, and use of chemical substances that present unreasonable risk to human health or the environment; (2) requiring notification of production of new chemicals or significant new use of existing chemicals; (3) requiring toxicity testing for chemicals listed in the TSCA Inventory (generally high production volume/high exposure chemicals or chemicals that U.S.EPA believes may present an unreasonable risk to human health or the environment); and (4) requiring record keeping and reporting of any hazardous effects of any chemical to human health or the environment (11). The main source of recommendations for toxicity studies is the Interagency Testing Committee, an advisory committee that sets testing priorities for TSCA-regulatable substances.

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2.0 Carcinogen Identification
2.1 Human Studies
2.1.1 Historical Perspective In the early 1700s, Bernardino Ramazzini, the father of occupational medicine, wrote about diseases that occurred in more than 60 occupations and recommended that doctors ask their patients "What is your occupation?" This practice proved to be an extremely useful way of obtaining valuable information on associations between workplace exposures and various disease etiologies. Another early account of occupational cancer was made by a British physician, Sir Percival Pott, in the late eighteenth century when he reported that chimney sweeps developed scrotal cancer as a result of their exposure to soot (14). Subsequent research showed that agents such as soot, coal tars and coal-tar pitches, creosotes, and shale oils are carcinogenic to humans (15). Approximately a century after Pott's discovery, the German physician Rehn reported a high incidence of bladder tumors in aniline dye workers (14). Thus, the initial discovery that aromatic amines were carcinogenic was based on the detection of cancer in exposed humans; subsequent studies in laboratory animals have confirmed these findings. With the more recent advent of animal studies to evaluate the potential carcinogenicity of environmental and occupational agents, evidence of carcinogenicity for several chemicals that are now classified as known human carcinogens was first obtained in experimental animals (16). The alert clinician who recognizes an excessive number of patients who have similar tumors and traces that cluster to a particular exposure provides an enormous public health benefit that can lead to strategies to reduce risks and minimize or prevent specific occupational and environmental causes of disease. The combination of clinical, epidemiological, and experimental findings can greatly advance our understanding of mechanisms of carcinogenesis and provide data necessary to estimate risks and to reduce or eliminate occupationally induced cancers.

Several exposure–disease associations were discovered as the result of observations of high disease rates in specific populations (i.e., clusters) (17). Clusters generally appear as an unusually high occurrences of a disease in a relatively small number of people, most often occupationally or geographically based. Occupational clusters, for example, the finding of angiosarcoma of the liver in workers exposed to vinyl chloride (18) or kidney cancers in workers exposed to trichloroethylene (19), may lead to the discovery of a disease etiology because the exposures are better characterized than in an environmental cluster and there may be opportunities to confirm the association in other workplaces with similar exposure.

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3.0 Risk Assessment and the Development of Occupational Exposure Standards
3.1 General Background
Section 2.0 focused on methods to identify carcinogens and criteria used to evaluate the strength of evidence on whether an agent poses a human cancer risk. Hazard identification is the first step of the risk assessment process and is concerned with whether an agent can cause an adverse health outcome. Sources of information for this determination include epidemiological studies, animal studies, short-term assays, and evaluations of structure–activity relationships. Thus, even in the absence of epidemiological data, a potential occupational carcinogen may be identified from animal data and/or mechanistic studies.

Risk assessment provides a systematic approach for characterizing the nature and probability of adverse effects (i.e., health risks) in individuals or populations exposed to hazardous agents and often serves as the basis for risk management decisions as to whether and to what extent worker

exposure should be controlled. The National Academy of Sciences/National Research Council developed guidelines for the conduct of risk assessment in the U.S. Federal Government (80). The risk assessment paradigm developed by the NAS consists of four parts: hazard identification, dose–response assessment, exposure assessment, and risk characterization. The risk management decision-making process involves assessing and developing regulatory actions and evaluating the consequences of these actions or of alternative actions.

The evaluation of risk relies on information obtained from all relevant studies, including evidence from exposed humans, animal studies, *in vitro* studies, exposure information, and analyses of structure–activity relationships and dose–response. Uncertainties in estimating low-dose cancer risk exist because mechanisms of chemical carcinogenesis are not well enough understood and because information on the distribution of risk factors in exposed populations is generally not available. In spite of uncertainties and data gaps in the sources of information used to estimate human risk, risk management decisions can and should be made when a potentially hazardous condition is identified. To deal with uncertainties, various assumptions are made in extrapolating effects seen in animals to predictions of human risk (i.e., animals and humans are similarly susceptible to specific chemical carcinogens) and in extrapolating from the exposure range of experimental studies to a range more typical of past and present occupational exposures (i.e., low-dose effects can be estimated from observations made at higher doses). Because the estimates of risk in the low exposure range generally guide policy decisions, statistical models are needed to estimate excess risks that are not readily discernible from observational data (i.e., risks in the range of one per thousand to one per million).

The contribution of various sources of uncertainty in quantitative models of population exposure and low-dose risk can be assessed by analyzing the consequences of varying model assumptions (i.e., sensitivity analysis). A sensitivity analysis can provide information on the variability of model predictions, such as absorption or tissue dosimetry, consequent to variations in values of the model parameters. From such an analysis, the impact of uncertainty on health outcome versus containment/cleanup costs can be factored into regulatory decisions that address the consequences of human exposure to hazardous agents. Incomplete knowledge should not impede health-based decisions that would promote avoidance or reduction of human exposure to agents that are known human carcinogens or have a reasonable likelihood of causing human cancer. Specifying and characterizing uncertainties is important for enhancing the transparency and credibility of regulatory decisions and actions.

Quantitative risk assessment provides a means for incorporating basic and applied research findings into public health policy decisions. As science progresses and we gain further knowledge relevant to the extrapolation issues noted above, assumptions in risk models may be replaced with validated data. In this way, scientific knowledge can strengthen the basis for risk assessments that are used in the regulatory decision-making process. In recent years, there has been increased emphasis on shifting from default assumptions to a more science-based strategy for assessing risk. However, until the processes linking exposure to cancer outcome are better understood, much of this effort may simply reflect a shift to a new set of assumptions that are less health protective.

With respect to chemical carcinogens, the categorizations formulated by authoritative bodies (IARC, NTP, U.S. EPA) serve as the initial basis for regulatory actions. In the past, standards of permissible exposure to occupational agents were generally based on observations of acute or short-term effects in humans or toxic effects in animals. Many of the Threshold Limit Values (TLVs) set by the American Conference of Governmental Industrial Hygienists (ACGIH) (81) were based on the assumption that a threshold exposure must be exceeded before an adverse effect could occur.

Determinations of safe exposure levels have been obtained by dividing no-observed-effect levels (NOELs) or no-observed-adverse-effect levels (NOAELs) by safety factors that were intended to account for differences in susceptibility between animals and humans and variability in susceptibility among individuals. An additional safety factor would be included if the lowest dose used in the

toxicity study did not achieve a NOEL, that is, the lowest dose produced an effect that was assumed to represent the lowest-observed-effect level (LOEL). The NOAEL approach is problematic for evaluating low-dose cancer risk for several reasons. First, this approach assumes a threshold-type reponse regardless of the shape of the dose–response curve or the mechanism of disease induction. Second, the selection of "safety factors" is not based on experimental data demonstrating the validity of the selected values. Third, the dose identified as the NOAEL depends on the size of the dose groups used in the experimental study. The NOAEL is defined as the exposure level that does not produce a significant increase in an adverse effect compared to controls. Thus, if the size of the dose groups is 10, then for the following response [2 of 10 controls, 3 of 10 low dose, and 7 of the 10 high dose], the low-dose group would be labeled as a NOAEL because 3 of 10 is not statistically different from 2 of 10. However, if the group size were expanded to 1000 and the same ratio of response was observed (i.e., control: 200/1000, low dose: 300/1000, high dose 700/1000), then the low-dose group would be labeled the LOEL because 300/1000 is significantly greater than 200/1000. This point is made to demonstrate how methodological issues may impact estimations of low-dose risk.

Most of the original OSHA PELs were based on the ACGIH TLVs for specific chemicals. For example, before 1997, the OSHA 8-hour TWA occupational exposure standard for 1,3-butadiene was 1000 ppm based on early studies showing that it caused irritation to mucous membranes, skin, and eyes, or narcosis at very high concentrations (82). The carcignoenicity of 1,3-butadiene in laboratory animals at exposure concentrations less than 1000 ppm was demonstrated as early as 1984 (83, 84), and less than 7 ppm in 1990 (65); however, the reduction in the occupational exposure standard to 1 ppm was not promulgated until 13 years after the initial report on the multiple organ carcinogenicity of this chemical. There is no obvious explanation why such delays occur in enacting occupational exposure standards for carcinogenic agents. The fact that many occupational carcinogens listed in Table 4.5 lack cancer-based exposure standards indicates that much more effort is needed to protect workers from exposure to carcinogens in the workplace.

The U.S. Supreme Court's 1980 ruling on benzene (described in Section 1.2) was interpreted by OSHA to mean that the Agency must perform quantitative risk assessments, when possible, to determine whether occupational exposure to toxic or carcinogenic agents poses significant risk to workers. If a significant risk exists, then OSHA must quantify risks associated with alternative standards and determine an exposure level that poses no significant risk. Based on the benzene decision, OSHA considers a lifetime occupational risk of one extra cancer per thousand workers to be significant; this is in contrast to environmental cancer risk which is considered significant when lifetime exposure is expected to result in one or more cancer deaths per 100,000 or more than one per million in the general population. In addition, several occupational health standards are limited by economic and technological feasibility. In these cases, occupational lifetime excess cancer risks can be greater than one per thousand. For example, even after regulation the occupational lifetime excess leukemia risk for exposure to 1 ppm benzene is 10 per 1000 (1%), the excess lung cancer risk of occupational lifetime exposure to 10 mg/m^3 inorganic arsenic is 8 to 12 per 1000, and the excess lung cancer risk for occupational lifetime exposure to 5 mg/m^3 cadmium is 4 to 9 per 1000 (13). The determination of what is an accptable level of risk is made from political, social, technological, and economic considerations. Unfortunately, this can result in significant excess cancer risks for exposed workers.

Previous sections of this chapter focused on identifying cancer-causing agents, the first step of risk assessment; issues related to the other three components of the risk assessment paradigm are discussed next.

3.2 Exposure Assessment

Exposure assessment involves determining or estimating the magnitude, duration, frequency, and route(s) of human exposure to the particular carcinogenic agent(s). Thus, the exposure assessment focuses on identifying exposed populations and characterizing the routes and degrees of exposure. If exposure data are collected on an individual basis in the exposed subpopulation (e.g., workers in a specific industry), it would be possible to use that information to characterize the distribution of

exposure in relation to cancer risk. Because epidemiological studies generally lack data on exposure, especially during the time that the disease may have been initiated, retrospective estimates of exposure from incomplete data sets may introduce biases or inaccuracies in characterizing dose–response relationships. In some studies, only semiquantitative relationships between exposure and response can be determined, for example, ever/never exposed or separation into categories of relatively high, medium, or low exposure.

In some animal studies, exposures were similar to those in occupational settings. For example, 1,3-butadiene was shown to be carcinogenic in mice at exposures as low as 6.25 ppm (65), and occupational exposures to this gas ranged from less than 1 ppm to 374 ppm (85).

Model-based approaches for estimating occupational and environmental exposures need to include statistical distributions of model parameters to yield realistic estimates of exposure distribution. Otherwise, reasonable "worst-case" exposure scenatrios are estimated to reflect the upper limits of risk. This issue is particularly important for assessing occupational cancer risk because exposures in various job categories in the past compared to the present are likely to have differed substantially. A single estimate of average workplace exposure does not provide adequate information to assess risk in highly exposed individuals. Ideally, exposure assessments should be based on data from work area and personal (breathing zone) exposure monitoring; however, industrial hygiene surveys and personal monitoring have been reasonably credible only during the past 20 years. Because of changes in industrial processes and improvements in occupational health and safety practices, exposure data collected during the past two decades may have limited use in addressing previous exposures. This issue is particularly pertinent in cancer assessments because of the long latency period for the clinical manifestation of this disease. Current exposure measurements will have greatest value for future occupational epidemiological studies and prospective evaluations of the effectiveness of regulatory actions.

Most occupational exposure assessments used in evaluating human cancer risk have relied on the recall of industrial hygienists and workers and reviews of employment history. One of the most extensive characterizations of occupational exposure in relation to cancer outcome was the study by Macaluso et al. (20) of the styrene-butadiene rubber industry. The retrospective quantitative estimates of exposure included information on individual work histories, plant records relevant to exposure (e.g., industrial hygiene monitoring surveys), and interviews with plant managers, engineers, and other long-term employees to provide insight on manufacturing operations and potential exposure sources (i.e., release into the work area during sampling, loading/unloading, maintenance and cleaning, or from equipment leaks). This information was used to characterize exposure potential in work areas within each manufacturing process, while accounting for historical changes in processes that may have affected exposure, and to characterize exposure potential associated with specific tasks. Mathematical models were developed to estimate job-specific and time-period-specific average exposures. These estimates were linked with individual work histories to obtain individual cumulative exposure estimates expressed as cumulative ppm-years. Interestingly, this analysis showed that exposure to 1,3-butadiene was associated with a dose-related increase in the occurrence of leukemia among exposed workers (20).

Measurements of biomarkers (parent chemical and/or metabolites) in blood, urine, or exhaled breath can provide direct estimates of worker exposure. Other biomarkers of exposure include measurements of DNA adducts, mutations in the *hprt* gene, sister chromatid exchanges, micronuclei, and chromosomal aberrations in peripheral blood lymphocytes. The latter markers reflect interactions of the agent or its metabolite(s) with DNA and induced genotoxic effects associated with exposure.

3.3 Dose–Response Assessment

The dose response assessment for carcinogens involves the process of quantifying the dose and evaluating its relationship to the probability of tumor occurrence. Estimations of human cancer risk from exposure to chemicals identified as carcinogens in animal studies require information and methodologies for extrapolating across species (animal to human), as well as dose (experimental

exposures to workplace exposures).

3.3.1 Allometric Scaling of Animal Dose to Human Dose The first issue in the dose–response assessment, after a hazard has been identified, is defining dose. The dose received or internalized by experimental animals or exposed humans is not necessarily identical to the amount of applied agent or that encountered in the environment. The applied dose may be the concentration of the agent in water or food multiplied by the amount of food or water consumed, or the atmospheric concentration of the agent multiplied by the inhaled volume, or the amount applied to the skin, or the amount injected into the stomach (gavage). The delivered dose is the quantify of material internalized consequent to one of these exposures.

In the absence of specific information on the absorption and metabolism of the agent in animals and humans, risk assessments for airborne agents are based on the conversion of animal inhalation doses to human doses by adjusting for differences in minute volume and normalizing to body weight. If the route of animal exposure is different than that for humans, additional adjustments (e.g., differential rates of absorption from inhalation, dermal, and/or oral exposures) are made to extrapolate animal findings to humans. For example, an equivalent oral dose (EOD) from an inhalation exposure in a given species is calculated from the following equation:

$$\mathrm{EOD} = \frac{\mathrm{EC} \cdot \mathrm{ED} \cdot \mathrm{MV} \cdot \mathrm{AF} \cdot 10^{-3}}{\mathrm{BW}}$$

where

EC is the exposure concentration in air expressed as mg/L
ED is the exposure duration in minutes
MV is the minute volume expressed as mL/min
AF is the fraction of inhaled substance that is absorbed
10^{-3} is the conversion factor for L to mL
BW is body weight in kg

Power functions of 0.67 and 0.75 on body weight have been used to scale animal doses to human doses on a body surface area basis. The following example shows that a dose of 10 mg in a 300 gram (0.3 kg) rat scaled by body weight$^{0.7}$ is equivalent to a dose of 454 mg in a 70 kg human:

$$\frac{\text{rat dose (mg)}}{(\text{rat body weight})^{0.7}} = \frac{\text{human equivalent dose (mg)}}{(\text{human body weight})^{0.7}}$$

$$\text{human equivalent dose} = \text{rat dose} \cdot (\text{human body weight}/\text{rat body weight})^{0.7}$$

$$\text{human equivalent dose} = 10\,\text{mg} \cdot (70/0.3)^{0.7} = 454\,mg$$

On a body weight basis, the rat dose in this example is 33.3 mg/kg (10 mg/0.3 kg), and the human dose is 6.5 mg/kg (454 mg/70 kg). The human equivalent dose (HED) expressed as mg/kg can also be determined from the following equation:

$$\mathrm{HED} = \text{animal dose (in mg/kg)} \cdot \frac{(\text{animal body weight})^{0.3}}{(\text{human body weight})^{0.3}}$$

$$\text{HED} = 33.3\,\text{mg/kg} \cdot (0.3/70)^{0.3} = 6.5\,\text{mg/kg}$$

Several default assumptions are implicit in these calculations. Most important is the assumption that physiological and biochemical processes (e.g., absorption, metabolism) differ between laboratory animals and humans by body surface area (body weight$^{0.7}$). Although physiological processes such as ventilation rate or cardiac output may scale reasonably well with body surface area, there is no reason to assume that metabolic activities differ among species according to body surface area.

If blood or plasma time-course data for the agent are available for animals and exposed humans, then the integrated area under the plasma concentrations curve (AUC) can serve as a surrogate of internal dose for species comparisons of body burden. However, AUC data is limited to the specific exposure conditions. In addition, if the active toxic/carcinogenic agent is a metabolic intermediate, then the AUC for that metabolite would provide a better measure of potential risk.

3.3.2 Estimating Tissue Dose by Physiologically Based Toxicokinetic Modeling Tissue dosimetry becomes even more complex when multiple metabolites are involved in the carcinogenic process and their effects are interactive. A more scientifically rational approach than allometric scaling for estimating tissue dosimetry consequent to a particular exposure is to characterize the biological activities that influence the behavior of the agent in animals and in humans. Such evaluations should include determinations of the range of activities that exist in human subpopulations. Mathematical models that account for the physiological and biochemical processes that affect the absorption, distribution, metabolism, and elimination of the chemical can provide a biologically based approach for characterizing the tissue dosimetry of the parent compound and metabolites resulting from variable exposure conditions, including multiple exposure routes. Further, by using biochemical and physiological parameters that include the range of measured human values, it may be possible to address genetic variability and other factors that contribute to differential sensitivities among subpopulations. Physiologically based pharmacokinetic (PBPK) models have been developed to describe the behavior of drugs in animals and humans; similarly, physiologically based toxicokinetic (PBTK) models can characterize relationships between exposure to toxic agents and tissue concentrations of the parent compound and its metabolites.

PBTK models are designed to characterize the absorption, distribution, metabolism, and elimination of a toxic agent as a function of time. These models are being used increasingly to extrapolate animal doses to human doses because they allow consideration of species differences in physiological, biochemical, and anatomical characteristics and because they can address differences in route, frequency, and level of exposure. Kohn (86) has emphasized the importance of providing realistic representations of anatomical details in PBTK models; for example, including individual tissue capillary spaces, including an alveolar space, and separating the GI tract to allow liver perfusion via the hepatic artery (~ 20%) and via the portal vein (~ 80%) which drains the GI tract capillaries. PBTK models consist of a series of mass balance differential equations that are formulated to represent quantitatively the physiological and biochemical processes that affect the behavior of the agent in the intact animal, including the uptake of the parent compound resulting from an exposure, transport of the chemical to all tissues in the body, metabolism of the chemical, and elimination of the parent compound and metabolites. A PBTK model for 1,3-butadiene (BD) is shown in Figure 4.1 (87). In this figure, the animal is represented as divided into separate tissue compartments, including the site where the gas enters the body from inhalation exposure and the sites where it is subsequently stored or metabolized. The tissue compartments in the model are connected by arterial and venous blood flow. The kinetic behavior of the agent in an organism is determined by species–specific attributes, inlcuding physiological (ventilation rate, cardiac output, organ compartment volumes, and organ blood perfusion rates), physicochemical (tissue partition coefficients for parent compound and metabolites), and biochemical (metabolic kinetic constants) parameters. In the BD model, metabolism is represented in the liver, lung, and kidney of exposed animals. BD undergoes cytochrome P450-mediated oxidation to mutagenic epoxide intermediates, epoxybutene (EB) and diepoxybutane. Both of these epoxides are detoxified by hydrolysis via epoxide hydrolysis (EH) or

by conjugation with glutathione via glutathione-*S*-transferase (GST). By solving the equations in the model simultaneously, estimates of the tissue concentration time-courses of the parent compound and its metabolites are generated for any simulated exposure.

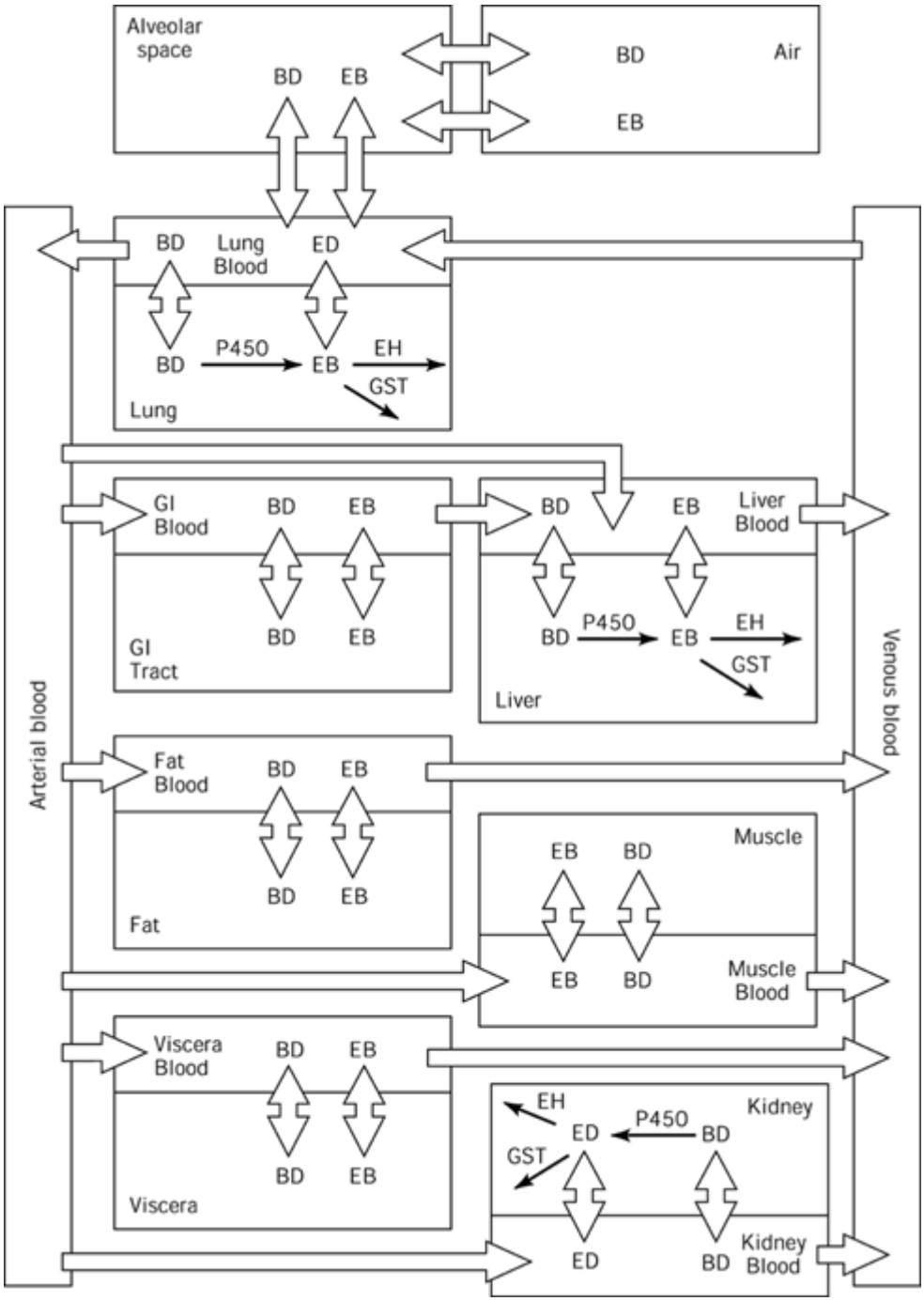

Figure 4.1. Schematic of a physiologically based toxicokinetic model for inhalation uptake, distribution, metabolism, and elimination of 1,3-butadiene (BD). The model includes cytochrome P450 mediated oxidation of BD to epoxybutene (EB), hydrolysis of EB catalyzed by epoxide hydrolase (EH), and conjugation of EB with GSH catalyzed by glutathione-*S*-transferase (GST).

Substitution of human physiological and biochemical parameters for those of laboratory animals can provide a scientifically sound basis to account for species differences in tissue dosimetry; this substitution is possible because of the high interspecies correspondence in physiological structure and function. If adequately validated, such models can serve as a powerful tool for generating biologically based estimates of tissue dose even under conditions that differ from the experimental

range (e.g., human exposure levels) and with different routes of exposure. Validation requires that the model accurately predict *in vivo* behavior of the agent in animals and humans under conditions different from those that were used to establish any adjustable parameter values. Because PBTK models can accommodate parameter values that cover the range of values in human populations, they can be used to evaluate the impact of interindividual variability on tissue dosimetry.

The utility of PBTK models depends on the extent to which testable predictions have been measured and validated. If the true carcinogenic agent arising from a particular exposure is known (parent compound or metabolite), then the model can be used to evaluate relationships between time-dependent tissue concentrations of that agent and tumor outcome. The identification of the appropriate dose surrogate derived from a PBTK model for use in a dose-response analysis is not always obvious because our understanding of the multiple mechanisms of chemical carcinogenesis is limited and because the agent may be metabolized by multiple pathways or to several intermediates that may influence the tumor response.

A validated PBTK model can be used to quantify response as a function of the dose of the toxic agent in the affected tissue site and can be used to predict the likelihood of toxic effects of the chemical at low exposures. Because PBTK models incorporate information on all of the biological processes that affect the disposition of the agent in animals and humans, they offer the opportunity to replace default assumptions associated with allometric scaling with biologically based estimates of tissue dose.

3.3.3 Dose–Response Analysis Tumor response data for the dose–response analysis may come from epidemiological studies or animals studies. Epidemiological data include the cause-specific relative risk or SMR values (the incidence of disease or cohort mortality rates in the exposed population divided by the incidence or mortality rate in the unexposed or general population) or the odds ratios (see Sectoin 2.1.2). From animal studies, the response is the tumor incidence values in the control and treated groups. As noted earlier, if survival patterns differ among dosed and control groups, then survival-adjusted incidence rates should be used in the dose–response analysis.

Several different statistical models have been applied to cancer dose–response data to characterize the shape of the dose–response curve, to identify specific doses associated with specified levels of increased cancer risk (e.g., ED10 is the estimated exposure concentration associated with an increased cancer risk of 10%), and to estimate slopes of the resultant curves. The linearized multistage (LMS) model has been the primary default dose–response model used by federal agencies to estimate human cancer potency and low-dose cancer risk. It is a statistical dose–response model used to estimate extra or additional cancer risk at a specific dose. Additional risk is the probability of a response at a particular dose, $p(d)$, minus the probability of the response at zero dose, $p(0)$. Extra risk includes an adjustment in the denominator of $1\text{-}p(0)$ for any background rate of cancer. For example, if 60 of 100 animals develop a tumor at dose d and the rate for that tumor in controls is 20 of 100, then the additional risk is $p(d)–p(0) = 40\%$ whereas the extra risk is $p(d)–p(0)/1–p(0) = 50\%$.

The LMS model can generate linear and nonlinear dose–response patterns and has been used mostly to generate a maximum likelihood estimate and an upper confidence limit on the slope of the linear low-dose term of the dose–response curve (88). It was adopted by regulatory agencies as a public health protective default approach; however, the use of this model for estimating human cancer risk has been criticized because the parameters of the model do not represent specific rates in the multistep carcinogenic process and it may overestimate the bounds of human cancer risk if the true dose–response is nonlinear.

Empirical dose–response models do not perform extrapolations from animals to humans; rather they assume that at equivalent doses the risk of developing a tumor is similar in humans and rodents. This assumption would lead to an overestimation of risk if rodents are more susceptible than humans and an underestimation of risk if humans are more susceptible than rodents. From parameter values that provide a best fit of the data to these models, estimates of the intercept, shape, and slope of the curve

can be obtained by maximum likelihood estimation. As shown in Figure 4.2, the curve shape may indicate a supralinear response (curve 1), a linear response (curve 2), a sublinear response (curve 3), a saturable reponse (curve 4), or a threshold response (curve 5). A true threshold response indicates that below a certain dose there is no increase in response compared to controls. A saturable response may arise if the metabolic pathway that produces the active intermediate becomes rate-limiting above a particular dose. The sublinear response may arise if cooperative interactions among components involved in the response promote an enhanced effect as dose is increased, or this type of response may occur if detoxification or repair pathways become saturated. The slope of the linear dose–response curve indicates that the response increases proportionally with dose. A Weibull model fit to tumor incidence data for chloroprene and 1,3-butadiene showed that the potency for induction of lung tumors in mice was the same for these two chemicals (89).

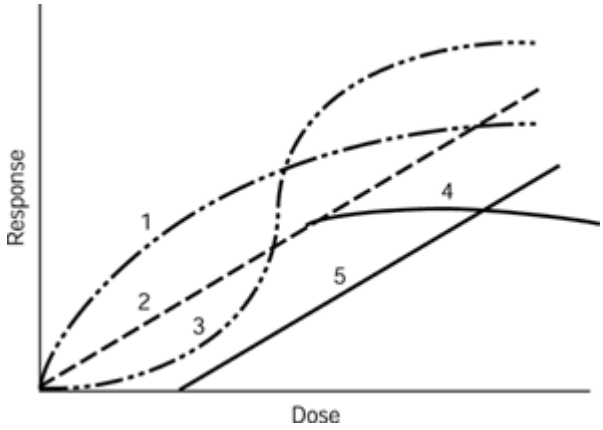

Figure 4.2. Theoretical dose–response curves. Curve 1 is a supralinear response, curve 2 is a linear response, curve 3 is a sublinear response, curve 4 is a saturable response, and curve 5 is a threshold response.

As events in the carcinogenic process become better understood and biomarkers of effect become identified, it may be possible to replace empirical dose–response models with biologically based models for estimating human risk. Mechanistic-based dose–response models link toxicokinetic activities (time course on the distribution of an agent or its metabolites in target tissues) with toxicodynamic activities (critical interactions between metabolites and target tissues). The conceptual framework for the development of such a model is shown in Figure 4.3. Dosimetry models require chemical-specific information on parameters such as tissue partitioning, metabolic activation, detoxification, protein binding, and elimination of the agent, and toxicodynamic models require information on DNA and chromosomal interactions, DNA repair, mutagenesis, altered gene expression, and effects on cell cycling. The toxicokinetic model provides the input of dose for the toxicodynamic model. Tissue time-course data and information on the elimination of parent compound, metabolites, or other biomarkers of exposure are essential for creating and validating dosimetry models, whereas measurements of DNA damage and repair, mutagenesis, mRNA levels, protooncogene activation, suppressor gene inactivation, cell replication and cell death, or other biomarkers linked to the carcinogenic process collected over a wide range of exposure are essential for creating and validating toxicodynamic models. The linking of toxicokinetic models with tissue response models through critical biochemical steps (e.g., DNA binding or receptor-based interactions) can lead to the development of biologically based dose-response models that quantify the sequence of events starting with exposure and resulting in tumor induction.

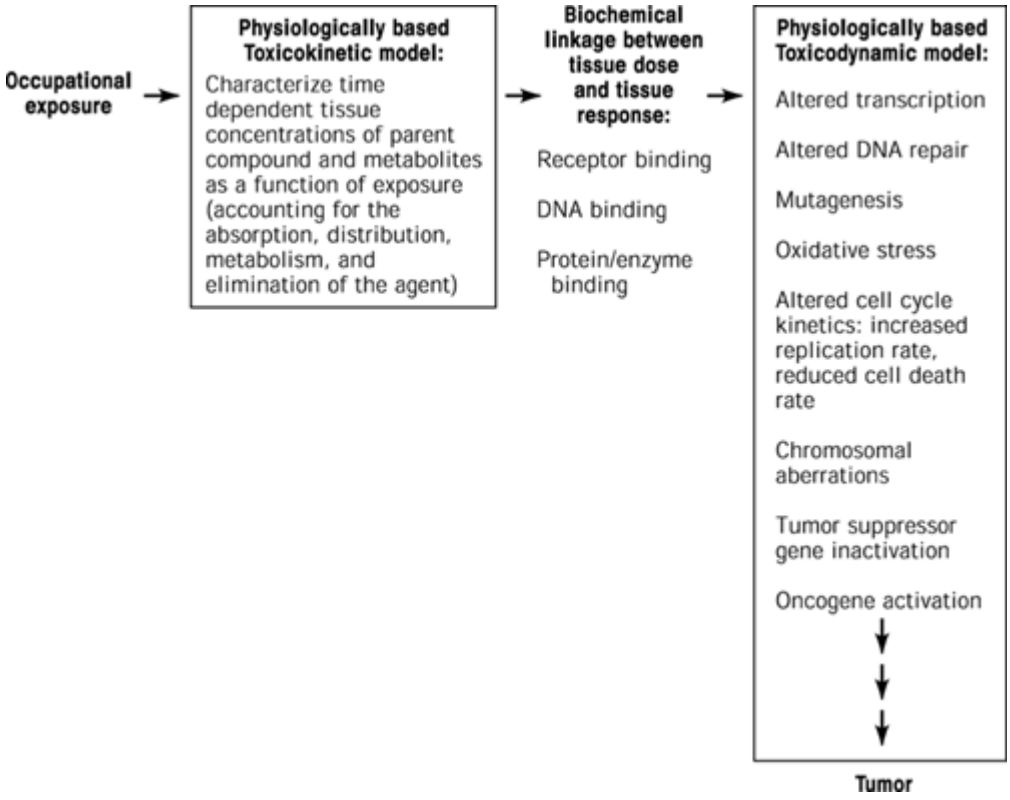

Figure 4.3. Schematic for the conceptual development of biologically based dose–response models of chemical carcinogenesis. This schematic addresses the sequence of events between exposure and tumor induction. Critical biochemical steps link tissue dose derived from the toxicokinetic model with tissue response characterized in the toxicodynamic model.

Portier and Kohn (90) developed a biologically based dose–response model for liver carcinogenesis induced by 2,3,7,8-TCDD in female arts. A PBPK model that characterized tissue dosimetry of TCDD was linked with a two-stage model of carcinogenesis. Parameter values for the carcinogenesis model (birth and death rates of intermediate cells and mutational rates of normal and intermediate cells) were obtained from estimates of changes in concentrations of biomarker proteins consequent to dosing with TCDD. Mutational effects were quantified from data on the induction of CYP1A2 (suggested to increase metabolism of estrogen to catechol estrogens, which lead to oxidative DNA damage) and birth rate/death rate effects were estimated from data on activation of the EGF-receptor. Although the model gave a reasonable fit to the experimental data and predicted a linear dose–response in the low-dose range, the authors cautioned on the use of such model for estimating low-dose risk because the mechanistic links among TCDD-mediated changes in gene expression and mutational effects and birth rate effects are not completely known.

With continued rapid growth of mechanistic information in molecular biology and carcinogenesis, especially in molecular signaling and cellular control processes, it should be possible to create scientifically credible mathematical models that accurately represent the biological processes involved in tumor induction at low doses. However, at present there is no evidence demonstrating that biologically based dose–response models are any more accurate than the LMS model for estimating low dose human risk (91).

3.4 Risk Characterization

Risk characterization provides an integrative summary of the information on the hazard identification, the exposure assessment, and the dose–response assessment that were used to estimate potential human cancer risk under various exposure circumstances. Data on the extent of human exposure to an identified cancer-causing agent are combined with the dose(exposure)–response analysis to generate estimates of potential risk (i.e., the probability or likelihood of cancer) in exposed populations and susceptible subpopulations in relation to the actual exposure circumstances.

The risk characterization should (1) evaluate the strengths and weaknesses of the data that serve as the basis for the quantitative estimates of risk, (2) explain the rationale for selecting a particular extrapolative approach to estimate low-dose risk or explain the basis for determining safe exposure levels, and (3) identify underlying assumptions and analyze uncertainties used to estimate risk. Additional issues such as the potential influence of mixed exposures and factors that contribute to individual differences in susceptibility should also be addressed. The information brought forward in risk characterization provides the basis for developing and evaluating alternative regulatory strategies. Final risk management decisions are often based on estimates of risk, as well as cost and technological feasibility.

OSHA's risk assessments are based on potential occupational lifetime exposure, i.e., working lifetime exposure is assumed to be 8 hours per day, 40 hours per week, 48 weeks per year, for 45 years. Animal inhalation cancer studies with exposure of 6 hours/day, 5 days per week, for 2 years are designed to mimic occupational exposures. Both the experimental protocol and the OSHA assessment cover approximately 15% of the expected lifetime (in hours) for humans and rodents.

Because all human carcinogens have been shown to be carcinogenic in animals when adequately tested (92, 93), most public health agencies regard animal carcinogens as potential human carcinogens. However, because many agents that have been shown to be carcinogenic in animals have not been evaluated in humans, mechanistic research in industry-sponsored laboratories has been styled to support hypotheses that suggest that animal positive findings do not reliably predict human risk. If a critical step in the carcinogenesis process occurs in animals but not in humans, then it might be appropriate to discount the animal tumor data for assessing human risk. For example, if the metabolic pathway causal for tumor induction occurs in animals but does not occur in humans, then the animal response may not be suitably informative of human risk. However, to date, no metabolic pathway causal for tumor induction has been demonstrated to be unique to the animal models used in cancer bioassays. Furthermore, other mechanisms may be operating in humans.

Differences in rates of activation or rates of detoxification between humans and animals should be accounted for in dosimetry models used to extrapolate animal findings to humans. Quantitative differences in toxicocokinetics do not indicate zero risk to humans. Furthermore, because of interindividual differences among humans, some segments of the population may be more sensitive than animals. Polymorphisms and differences in the degree of induction of inducible metabolic enzymes can result in substantial interindividual variability in risk associated with exposure to carcinogenic agents. In some instances, humans may be more susceptible to carcinogenic agents (e.g., arsenic) than animals.

Because of our limited understanding of the mechanisms of chemical carcinogenicity, the demonstration that a particular activity of a chemical is the critical step in the cancer process and that that effect or a similar effect could not occur in exposed people often relies on assumptions or unproven hypotheses (79). Although mechanistic research has increased our understanding of the carcinogenic process, it should be recognized that the exact mechanism of tumor induction has not been elucidated for any chemical that causes cancer in animals or in humans. Decisions to discount the relevance of positive animal findings for evaluations of human risk when based on acceptance of unproved hypotheses could lead to workplace exposure circumstances that pose avoidable cancer risks.

3.4.1 Extrapolation from Animals to Humans The evaluation of human risk from epidemiological data avoids uncertainties of animal to human extrapolations. However, obtaining this information requires a long follow-up period between the initial exposure and the assessment of disease incidence. The warnings from positive animal studies must be heeded to prevent disease occurrence that could have been avoided. Extrapolation models of animal findings to human risk at occupational exposures contain various inherent assumptions because mechanisms of chemical carcinogenicity are not fully understood. The advancement of scientific knowledge of critical steps involved in chemical

carcinogenesis in laboratory animals and humans may eventually obviate the need for many default assumptions used in low-dose extrapolation models, for example, the need to scale tissue dosimetry across species by allometric procedures may be replaced by models that are based on physiological and biochemical parameters specific for laboratory animals and humans.

In characterizing human risk based on tumor induction in laboratory animals, sources of uncertainty need to be identified and analyzed. Uncertainties may concern the reliability of the low-dose extrapolation model, the appropriate dose metric that is used in the tumor dose–response model (e.g., the occupational lifetime cumulative tissue dose, the time-weighted average lifetime dose, the maximum daily tissue concentration), as well as issues related to species and interindividual differences in pharmacokinetics and pharmacodynamics. Models that are validated against measured biomarkers of exposure and effect can strengthen the scientific basis for animal to human extrapolations. Pharmacokinetic issues involving estimates of internal dose or tissue dose include uncertainties in the accuracy of parameter estimates, interdependence of parameters, validity of scaling methods, variability of parameters among individuals, and effects of coexposure to other agents that may alter metabolic processes.

Additional data and models are needed to adequately account for interspecies, intraspecies, and sex differences in susceptibility. The risk characterization should address issues such as, are laboratory animals and humans similarly susceptible to the carcinogenic effects of a particular agent at equivalent doses, has the correct causative agent or intermediate(s) been specified for low-dose extrapolation, and do responses in animals reflect the range of responses that might occur in exposed workers?

Species-specific mechanistic information at the cellular and molecular levels is critical for developing biologically based dose–response models that are applicable for extrapolating animal effects to humans. Quantitative differences between species can be incorporated into mechanistic based dosimetry models used to extrapolate tumor responses observed in animals to humans. In the absence of detailed quantative information on species differences in response, it is prudent to assume that the risk of developing a tumor at equivalent doses is similar in humans and rodents. This assumptions may lead to overestimates or underestimates of human risk because of the numerous factors that can influence the disease outcome such as duration of exposure, age, race, tumor latency, exposure to other agents, route(s) of exposure, health status, lifestyle, and the multitude of hormonal and genetic factors that contribute to interspecies and intraspecies differences in susceptibility. Point estimates of risk such as the maximum likelihood estimate obtained from low-dose extrapolation models do not account for these sources of variability; upper 95% bounds on excess cancer risk address sampling variability, but not the sources of variability listed above.

3.4.2 Estimation of Low–Dose Risk Statistical models, in particular the LMS model, have been used to extrapolate animal findings to estimate risk at occupational exposures. Low-dose estimates of risk are obtained by extending the dose–response curve to the exposure level(s) of concern. However, because these extensions may go beyond the experimental exposure range, the USEPA (66) proposed using a defined value near the range of experimental data as a point of departure for estimating low-dose risk. The draft EPA guidelines for cancer risk assessment call for the use of biologically based models for low-dose extrapolations; these are defined as models in which parameter values are calculated independently of curve-fititing of tumor data. If no acceptable biologically based model is available then a statistical model is fit to the tumor dose–response data to estimate the human equivalent dose for an increased cancer risk of 10% (ED_{10}) and the lower 95% confidence limit on that dose (LED_{10}). Rather than extrapolating to low doses by the default LMS model, low-dose risk is estimated by extending a straight line from the LED_{10} to zero response for agents that indicate a linear mode of action (e.g., DNA reactive genotoxic chemicals or situations in which added human exposure is on the linear part of a dose–response curve) or for agents for which there is insufficient evidence (uncertainty) to support a nonlinear mode of action. For agents that demonstrate a nonlinear mode of action, the EPA will employ a margin of exposure analysis (i.e., the

LED_{10} divided by uncertainty or safety factors) that is intended to signify a human exposure that is considered unlikely to induce disease. By this analysis, no estimates are made of potential risk or likelihood of cancer occurrence. The uncertainty factors are intended to address interspecies and intraspecies differences in pharmacokinetics and pharmacodynamics and the adequacy of the database. The magnitude of the applied uncertainty factors must be analyzed to validate the level of protection that they are assumed to provide.

For a nonlinear dose–response, the margin of exposure approach projects that the response at low doses falls faster than that of a linear dose–response. Hence a higher level of exposure would be considered reasonably safe compared to that estimated from linear extrapolation. The margin of exposure approach is favored by those who have criticized the LMS model as overly health conservative; however, caution is needed to ensure that public and worker health is not compromised when a low-dose model with one set of assumptions is replaced with an alternative approach that is based on unproven hypotheses and less health protective assumptions.

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1 Introduction

The approach to assessing the risks of noncancer toxicity generally differs from that used to assess the potential risks of carcinogenicity. Assessment of risks of carcinogenicity most often assumes that a small number of molecular events can evoke mutagenic changes in a single cell, ultimately leading to self-replicating damage and carcinogenicity. Generally, this is considered a nonthreshold effect because presumably no level of exposure does not pose a small, but finite, probability of generating a response. In contrast, it is most often assumed that noncarcinogenic changes have a threshold, a dose level below which a response is unlikely, because homeostatic, compensating, and adaptive mechanisms in the cell protect against toxic effects. For example,

Two paracetamol [Tylenol] tablets will relieve the minor aches and pains ... Twenty-two tablets [are fatal] ... So why is not all paracetamol a danger ... ? The answer to the paracetamol puzzle is that there are two pathways down which our bodies dispose of this drug. Most is removed by converting it to a sulphate and this works fine provided there is no sudden excess that uses up our supply of sulphate enzymes. If this happens the body has another way of removing paracetamol, by oxidizing it. Unfortunately, this produces a toxic chemical that requires glutathione to detoxify it. It is only when the supply of glutathione is exhausted that the [toxin is fatal] (1).

This threshold concept is important in many regulatory contexts. The individual threshold hypothesis holds that some exposures can be tolerated by an organism that has essentially no chance of expressing a toxic effect. Further, risk management decisions frequently focus on protecting the more sensitive members of a population. In these cases efforts are made to keep exposures below the more sensitive subpopulation threshold, although it is recognized that hypersensitivity and chemical idiosyncrasy may exist at yet lower doses.

Quantitative assessment of the noncancer toxic effects of environmental exposures has traditionally been evaluated in terms of concepts such as acceptable daily intake (ADI) and margin of safety. Scientists familiar with such concepts have identified certain limits and difficulties with their use. Based on recommendations of the National Academy of Sciences (NAS) (2), scientists now are better articulating the use of experimental and epidemiological data in making and explaining risk assessment and risk management decisions. As a result, several newer quantitative procedures that augment the traditional concepts have been developed and are presented here.

The basic concepts of risk assessment are also an integral part of evaluating the health risks associated with occupational exposures. Activities such as the identification of hazards, evaluation of the supportive data for determining occupational exposure values, and conducting exposure estimates all fit well into the risk assessment paradigm described in the NAS publication (2). Although one can argue that risk assessment is common in the workplace, the application of many specific risk assessment methodologies is relatively new. Historically, occupational risk assessment decisions relied heavily on professional judgment. A more recent event is the integration of quantitative noncancer risk assessment approaches into the occupational arena. Examples of the increasing focus on the application of quantitative risk assessment are apparent from the activities of organizations that derive occupational exposure values.

Groups such as the United States Occupational Safety and Health Administration (OSHA) are increasingly relying on risk assessment tools to promulgate new or revised occupational levels such as Permissible Exposure Limits (PELs). The need to integrate risk assessment into the standard setting process was demonstrated by the court rulings in response to challenges to OSHA standards. The benzene standard and air contaminant standard were both vacated on the basis that there was an

insufficient demonstration that a significant risk existed and that adoption of the standard would reduce that risk. After addressing the risk assessment issues, OSHA promulgated its benzene standard in 1987. Importantly, in the proposed rulemaking for the update of the PELs (3–5), OSHA made clear its intention to use state-of-the-art risk assessment methods to derive new air contaminant standards. Thus it is clear that risk assessment will play an increasing role in establishing occupational health values promulgated by OSHA.

Other organizations that develop occupational exposure limits (OELs) are also moving from heavy reliance on professional judgment to consistent risk assessment approaches. The National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH), and the American Industrial Hygiene Association (AIHA) have also increased their interest and application of risk assessment techniques in the occupational setting. ACGIH has included risk assessment as an issue under study by the Chemical Substances TLV Committee (6). Similarly, AIHA recently published an issue paper on this subject (7). Documentation of risk assessment methodologies for application to occupational settings has also increased in the recent literature (8–11).

This chapter describes the general framework for noncancer risk assessment and some salient principles for evaluating the quality of data and formulating judgments about the nature and magnitude of the noncancer hazard. Highlights of noncancer risk assessment methods used by a variety of agencies and organizations, and examples of how occupational risk assessment is moving toward a more systematic use of risk assessment principles are presented.

This chapter also has several specific aims. The first is to provide scientifically supportable quantitative risk assessment procedures to meet the risk assessment goals listed following. A second aim is to provide a scientific rationale that may be used to deter-mine whether new quantitative risk assessment procedures not specifically examined in this chapter are scientifically supportable. The final aim of this chapter is to provide a basis for developing new or improved quantitative risk assessment procedures.

The quantitative risk assessment procedures described in this chapter have been developed to meet some of the risk assessment goals for various purposes. Although the protection of the public and occupational health is a common theme that runs through these separate risk assessment goals, they are sufficiently different to warrant separate and distinct procedures. Examples of such goals are

- to rank chemicals as to possible hazard
- to determine and/or estimate a level of daily exposure that is likely to be without an appreciable risk of deleterious effects during a lifetime
- to determine and/or estimate the likely human response to exposure to various levels of a particular chemical

Moreover, differing amounts of toxicity data are needed for various quantitative procedures. Thus, the amount of data available affects the choice of procedure, as shown in Table 5.1.

Table 5.1. Some Risk Assessment Goals and Required Data Availability

Goal	Amount of Data	Approach/End Result
Rank chemicals	Limited, moderate or great	Structure-activity relationships (SAR), toxicity equivalency factors (TEFs) for ranking

Get to a "safe" level	Moderate or great	Development of acceptable daily intake (ADI), reference dose (RfD), reference concentration (RfC), permissible exposure limit (PEL); use of dose–response modeling such as benchmark dose/concentration (BMD/BMC), categorical regression
Characterize the full dose–response behavior	Great	Physiologically based toxicokinetic (PBPK) model, biologically based dose–response (BBDR) model (both of which can be used in developing any of the values above)

Noncancer Risk Assessment: Principles and Practice In Environmental and Occupational Settings

Lynne T. Haber, Ph.D., Joan S. Dollarhide, MS, MTSC, JD, Andrew Maier, MS, CIH, Michael L. Dourson, Ph.D., DABT

2 Hazard Identification

Hazard identification is a necessary first step in the risk assessment of a chemical. Hazard identification involves evaluating the appropriateness, nature, quality, and relevance of scientific data on the specific chemical; the characteristics, magnitude, and relevance of the experimental routes of exposure; and the nature and significance to human health of the observed effects. Groups such as the U.S. Environmental Protection Agency (USEPA) have developed guideline documents that explain the process of hazard identification for developmental toxicity (12), reproductive toxicity (13), and neurotoxicity (14). The reader is referred to these more extensive documents for specific details.

2.1 General Principles

Many dose–response processes for noncancer toxicity depend in part on professional judgment whether an effect or collection of effects observed at any given dose of a chemical constitutes an adverse response. Such judgment may not be easily rendered and requires experts trained in the area. For example, Fig. 5.1 shows individual disability as a function of organ system impairment and the overlapping areas of adverse and nonadverse effects. Table 5.2 more clearly describes some of the terms shown in Fig. 5.1, as well as some other key terms for hazard identification.

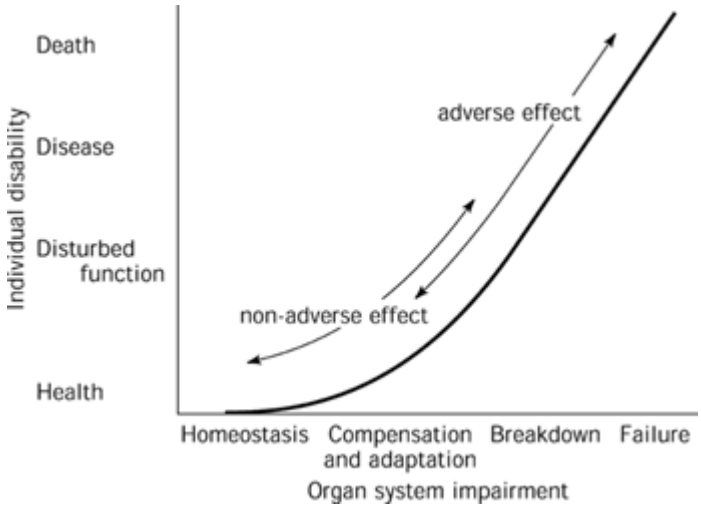

Figure 5.1. Individual disability as a function of organ system impairment.

Table 5.2. Some Key Definitions for Hazard Identification

ADAPTIVE EFFECT enhances an organism's performance as a whole and/or its ability to withstand a challenge. An increase in liver weight due to an increase in hepatic smooth endoplasmic reticulum is an example of an adaptive effect, if hepatic metabolism reduces the chemical's toxicity.
COMPENSATORY EFFECT maintains overall function without enhancement or significant cost. Increased respiration due to metabolic acidosis is an example of a compensatory effect.
CRITICAL EFFECT is the first adverse effect, or its known precursor, that occurs as dose rate or exposure level increases. One or more effects may be critical.
ADVERSE EFFECT is a biochemical change, functional impairment, or pathological lesion that impairs performance and reduces the ability of an organism to respond to additional challenge. The determination of such effects may require special tests or observation, such as preparation of slides for histological analysis.
FRANK EFFECT is an unmistakable adverse effect, such as convulsions or mortality. The determination of such effects can be done by clinical observation and normally does not require special tests.
SEVERITY connotes the toxicological significance attached to the continuum of effects, including adaptive, compensatory, critical, adverse, and frank effects, potentially associated with exposure of xenobiotics.

Although this figure and table are useful tools for showing the broad concept of adversity, the analysis of adversity for a given chemical or situation is strictly a case by case analysis by experts. For example, a chemical often elicits more than one toxic effect, even in one species or in tests of the same or different duration. After assessing the quality of each study, identifying the biological and statistical significance of observed effects (discussed later), and distinguishing between reversible and irreversible end points (discussed later), risk assessment scientists often identify the critical effect(s). The critical effect(s) is the first adverse effect(s) or its known precursor that occurs as the dose rate increases in a study. When several studies are compared, the critical effect is generally the lowest one that occurs collectively. Current dose–response methods described in this text and elsewhere use the critical effects as a basis for the dose–response assessment. The critical effects may change among toxicity studies of different durations, may be influenced by toxicity in other organs, and may differ depending on the availability of data on the shape of the dose–response curve.

Where specific guidance on hazard identification is not available, some general considerations regarding the types of toxicity evidence and adversity of effect are needed. Toward this end, risk assessment scientists look at the available data in several different ways, as outlined here. The following considerations illustrate some broad concepts of hazard identification applicable to all organ systems.

2.2 Evaluation of Human and Animal Data

In general, hazard identification should include considerations of factors affecting study quality, such as study hypothesis, design, and execution. An ideal study addresses a clearly delineated hypothesis, follows a carefully prescribed protocol, and includes sufficient subjects, observations, and statistical

analysis.

In the experience of risk assessment scientists around the world, properly conducted and ethical human studies are most useful in qualitatively establishing a link between exposure to an agent and manifestation of an adverse effect. When there is adequate information on the exposure level associated with a particular end point, controlled human exposure to levels that are not overtly toxic and/or epidemiological studies can also provide the basis for a hazard identification and dose–response assessment. The use of adequate human data to define the hazard and the dose–response relationship avoids the problem of interspecies extrapolation. Animal toxicity studies serve as supporting evidence when adequate human data are available.

Criteria for judging the adequacy of epidemiological studies are well recognized (15). They include factors such as the proper selection and characterization of exposed and control cohorts, the adequacy of duration and quality of follow-up, the proper identification and characterization of confounding factors and bias, the appropriate consideration of latent effects, the valid ascertainment of the causes of morbidity and death, the ability to detect specific effects, and the determination of exposure and/or doses. If possible, the statistical power to detect an effect should be included in the assessment. The strength of the epidemiological evidence, as judged by experts for specific health effects, depends on, among other things, the type of analysis and the magnitude and specificity of the response. For example, the weight of evidence increases rapidly with the number of adequate studies that show comparable results for populations exposed to the same agent under different conditions. As with judging the adequacy of studies, expert judgment is necessary to determine the weight of evidence for or against a specific effect.

In the absence of adequate human data, risk assessment scientists rely primarily on studies of animals for hazard identification. Adequate animal studies offer the benefit of controlled chemical exposures and definitive toxicological analysis. Experimental observations of animals are usually conducted in mammals, and the species most often studied are the rat, mouse, rabbit, guinea pig, hamster, dog, and monkey. Even when there are adequate animal studies, it is often useful to reconsider inadequate human data to evaluate whether the risk assessment based on animal data appears reasonable based on the general understanding from the human data.

Criteria for the adequacy of experimental animal studies include chemical characterization of the test compound(s), the number of individuals in the study groups and whether both sexes are used, the number of study groups, the spacing and choice of dosing levels so as to determine an adequate dose–response relationship, the types of observations and methods of analysis, the nature of pathological changes, the consideration of toxicokinetics, and whether the route and duration of exposure were relevant to environmental exposures. Criteria for the technical adequacy and evaluation of animal studies have been published (16, 17), and should be used to judge the acceptability of individual studies.

However, professional judgment regarding the adequacy of a study is not based solely on the degree to which it fits a prescribed recipe. It is also based on how well it enables one to identify potential adverse effects. Recent end-point-specific risk assessment guidelines published by the USEPA, for example, discuss such professional judgments on developmental toxicity (12) and male and female reproductive effects (13).

Supporting evidence from a wide variety of sources provides additional information for hazard identification. For example, metabolic and other toxicokinetic studies can provide insights into mechanisms of action. Comparison of the metabolism of the compound that exhibits the toxic effect in the animal with its metabolism in humans may strengthen or weaken the dose–response assessment. Toxicodynamic data may also be useful for estimating the dose to humans that would result in the same toxicity as observed in the animal study (i.e., the “equitoxic human dose”) and/or as part of the calculation of the delivered dose to the target organ or site. Evaluation of toxicokinetic differences between animals and humans has allowed the development of generalized dosimetric

adjustments of exposure levels across species (18–21). Risk assessment scientists encourage the development of comparative toxicokinetic and toxicodynamic parameters because such information increases the fundamental understanding of xenobiotic processes and reduces the uncertainties of interspecies extrapolation.

Animal and human studies that are deemed inadequate for quantitative risk assessment (e.g., due to insufficient doses, study duration, number of animals, etc.) nevertheless may provide supporting evidence regarding the target organ(s) and the critical effect. Similarly, *in vitro* studies can often provide insight, but seldom definitive conclusions, on the compound's mode of action and potential for human toxicity. However, it is possible that development of reliable and relevant *in vitro* tests may increase the usefulness of such data for assessing human risk in the future and minimize the need for live animal testing.

2.3 Route, Source, and Duration of Exposure

Because human exposure to a chemical pollutant is often route-specific (e.g., inhaled but not ingested) or source-specific (e.g., water versus food), risk assessment scientists often approach the investigation of a chemical with a particular route, source, and/or duration of exposure in mind. For example, within the oral route of exposure, the bioavailability of a chemical ingested in one source (i.e., food) may differ from that manifested when it is ingested in another source (i.e., water). Usually, the toxicity database on the compound does not provide data on all possible routes, sources, and/or durations of administration.

Toxic effects observed via one route or source of exposure are often relevant to other routes, although expert judgment should be applied in making such extrapolations. For example, if a chemical exhibits developmental effects at low doses via the oral route and it is absorbed from the respiratory tract, there is reason to suspect that it is also a developmental toxicant via the inhalation route. Consideration is given to potential differences in absorption or metabolism resulting from different routes and/or sources of exposure, such as the potential for first-pass metabolism in the case of oral exposure. Consideration is also given to the potential for portal of entry effects (e.g., gastrointestinal effects from oral exposure and respiratory effects from inhalation exposure). Whenever appropriate data are available, these factors are taken into account in the dose–response assessment. (As a specific example, the Reference Dose for hydrogen cyanide employs a fivefold modifying factor to account for the expected pharmacokinetic differences for this compound in water vs. food (2).) For example, guidance has recently been developed for extrapolating oral data to inhalation scenarios (18).

Toxic effects can also vary with magnitude, frequency, and duration of exposure. Studies differ in exposure duration (acute, subchronic, and chronic) and in dosing schedules (single, intermittent, or continuous). Information from all these studies is useful in the dose–response assessment. For example, overt neurological problems identified in a short-term, relatively high-dose study would reinforce the observation of subtle neurological changes noted in a low-dose, chronic study. Low-dose, chronic exposure, however, might also elicit effects either absent or not detected in higher dose, shorter duration exposures (and vice versa). For example, acute exposure to benzene causes central nervous system effects, whereas the critical effect for chronic exposure is hematological effects.

It is frequently necessary to extrapolate from exposures that differ in magnitude, frequency, and duration to those of interest to a specific human situation. For example, one may need to use subchronic experimental data to assess the potential hazard resulting from chronic ambient exposure. Consideration is given to potential differences in absorption or metabolism from different exposures. When appropriate data are available, the quantitative impacts of these differences on the risk assessment are delineated. The procedures outlined in this chapter are generally applicable, with proper judgment, to exposures of differing magnitude, frequency, and duration.

2.4 Evaluation of Toxicological Effects

2.4.1 Severity Defined Severity connotes the toxicological significance attached to the continuum of effects (including adaptive, compensatory, critical, adverse, and frank effects) potentially associated

with exposure to xenobiotics. In general, this continuum starts with adaptive effects, where the organism's ability to withstand a challenge is enhanced. As doses increase, compensatory effects occur and then are often seen as a way for the organism to maintain overall function without further enhancement or significant cost. At some point as dose increases, the critical effect is reached. This is the first adverse effect, or its known precursor, that occurs as dose increases. The critical effect is often the focus of the dose–response assessment based on the assumption that if the critical effect is prevented, then all subsequent adverse effects are prevented. As dose increases, the dose that causes the critical effect is exceeded, and additional adverse effects are manifested as biochemical changes, functional impairments, or pathological lesions. These progressively more severe effects generally impair the performance of the organism and/or reduce its ability to respond to additional challenges. At some point, these adverse effects become manifestly overt, and frank disease ensues.

2.4.2 Assessing the Biological Significance of Statistical Change The general approach that risk assessment scientists take in evaluating whether a change is adverse is consistent with that outlined in Ref. 22. An adverse effect is defined as a biochemical change, functional impairment, or pathological lesion that impairs performance and reduces the ability of an organism to respond to additional challenge. The presence of change alone does not necessarily indicate an adverse effect. The determination of adversity should consider the toxicological and statistical significance of the observed effect(s).

As discussed in part by Gaylor (23), the toxicological and statistical significance of an observed effect must not be equated and in fact toxicological and statistical considerations are often regarded sequentially. The determination of adversity should, instead, involve careful toxicological evaluation where statistics are used only as a tool for clarifying the implications of the data. The actual decision whether an effect is adverse should be based solely on biological grounds. Any animal that is in a state of physiological compromise should be judged as exhibiting an adverse effect. If difficulties exist in interpreting the importance of the effects, these difficulties are often related to whether the effect was statistically significant.

Apparent conflicts between statistics and toxicology can arise when toxicologically insignificant effects are statistically significant or vice versa. For example, the observation in a chronic study of a 5% decrease in net body weight in an experimental group compared to the control group may be statistically significant but may not be considered toxicologically important if both groups are fed ad libitum because such a decrease is often associated with increased longevity. Instead of a real conflict, however, the statistical significance suggests that the effect is real, but the biological reasoning indicates that the effect is not adverse. A special case in this situation is where the toxicological relevance of the statistically significant effect is uncertain. In this case, it is incumbent upon the professionals to judge whether the effect is toxicologically significant.

Evaluating changes that are not statistically significant is more difficult because the observed effects are then only weakly linked to the exposure. The problem is compounded when statistical methods are inappropriately applied. For example, consider the case when the exposed group shows a rare type of lesion. If the observed frequency in the exposed group is small, then the effect is unlikely to be statistically significant, compared with the experimental control group. The risk assessment scientist, however, often evaluates the nature and frequency of the observation in the context of previous experience or data in historical controls (i.e., knowledge of the spontaneous occurrence of the observation in the species) and concludes that the effect is worth further study. Again, this does not imply a conflict but instead illustrates the different types of data analysis that may be performed. If the statistical analysis also included historical controls, the same conclusion might have been reached. Similarly, an effect may exhibit a clear dose–response relationship, but not be statistically significant in pairwise comparisons. In this case, a trend test, or a NOSTASOT test (a method for determining a no observed adverse effect level by doing successive trend tests and removing the highest dose) may support a toxicologist's conclusion that an adverse effect is occurring.

The evaluation of rare effects is not as confusing when the goal is to estimate a dose–response curve,

rather than to determine whether a particular dose level leads to toxicologically significant changes. In the former case, the rarity of the lesion would be used as part of the dose–response relationship.

2.4.3 Assessing the Toxicological Significance of Observed Effects In some instances, the risk assessor must evaluate the toxicological significance of the observed effects, for example when the effect is reversible. A reversible change is often an adaptive or compensatory response to stress or may be an overt adverse response that the body can repair. Reversible changes return to normal or within normal limits either during the course of or following exposure. An irreversible change persists or may progress even after exposure ceases (22). It must be recognized that although a change may be reversible when exposure is terminated, it still may be adverse to an organism. In fact, depending upon the changes observed at the various dose levels tested, a potentially reversible change may well be selected as the critical effect in the dose-response assessment because reversibility often depends on the magnitude of the dose and the duration of exposure. The longer the test species receives the chemical exposure and/or the larger the amount of chemical administered, the greater is the likelihood that the reversible change in the early stages will progress to a permanent irreversible state. For example, the early stages of alcohol intoxication result in fatty infiltration of the liver, which is most often reversible upon cessation of exposure. However, when the exposure becomes chronic and the dose administered is sufficiently high, a permanent cirrhotic condition develops. Both effects are adverse, because the fatty changes, although reversible, result from functional impairment and are a precursor state that can progress to irreversible toxicity; however, liver cirrhosis is considered more serious in nature because reversibility is no longer possible (24).

Certain effects are irreversible (e.g., certain chronic neurological diseases, liver cirrhosis, and emphysema). The description of such effects has a useful role in the hazard evaluation of the chemical in conjunction with more subtle end points because the chemical's full dose–response behavior is described. However, the descriptions of irreversible effects by themselves are seldom considered useful in dose–response assessment because such effects often appear well above the experimental threshold range.

When identifying a hazard, irreversible effects can usually be distinguished from less serious but still adverse changes. However, difficulty arises when trying to determine the toxicological significance of more subtle and/or reversible changes. For example, transient hypertrophy or hyperplasia can be an adaptive change resulting from exposure to a xenobiotic or can be a precursor effect to the production of more severe toxicity, such as the disruption of normal organ function. The toxicological significance of such manifestations is established by carefully analyzing the biochemical, morphological, and physiological changes that occur at other doses and available supporting data and by combining the data analysis with professional scientific judgment to reach an overall determination.

In some cases, it must be ascertained whether an adverse effect that is observed is truly treatment related. For example, if a respiratory tract infection is present in the animal colony, this may predispose the exposed animals to the development of adverse respiratory effects in response to chemical exposure, whereas such effects may not occur in healthy animals. However, if the effects noted demonstrate a clear concentration–response relationship, despite the presence of infection, then the effect may be considered treatment related. For example, mild irritant effects induced by chemical exposure may allow mycoplasma to become established in the extrathoracic region, leading to pneumonia. In this case, the incidence of pneumonia may not be a direct effect of chemical exposure but is secondary to irritation induced by exposure to the chemical and therefore can be considered treatment related.

2.5 Essential Elements and Bioavailability

Special consideration is required for developing oral risk values, such as RfDs, for essential elements, primarily metals. In such cases, particular attention is paid to the available human data for both toxicity and essentiality. Where available, World Health Organization (WHO) and U.S. National Academy of Sciences (NAS) values for minimal requirements and the recommended dietary allowance (RDA) or the estimated safe and adequate daily dietary intake (ESADDI) are

carefully considered in the development of an RfD. For example, consideration of uncertainty factors used in deriving an RfD should take into account that the RfD should generally not be lower than the ESADDI or RDA. Conversely, a risk manager may need to take into account normal dietary exposure to the chemical of interest in calculating acceptable environmental exposure levels. These issues were taken into account, for example, in the RfD for manganese (25).

It is also important to take bioavailability into account in developing risk values, such as PELs and RfDs. The absorption of some chemicals, particularly metals, may depend on the route and form of administration. For example, the inhalation absorption, bioavailability, and subsequent toxicity of nickel compounds is thought to vary by nickel species (6, 26). Gastrointestinal uptake of nickel also varies depending on whether it is in water or in food: human subjects who fasted absorbed 27% of a dose of soluble nickel salts when administered in water but 0.7% when administered in food (27). To account in part for potential differences in the bioavailability of manganese in food compared to water and soil, the USEPA adopted a modifying factor of 3 for the manganese RfD when exposure is via drinking water or soil.

A full consensus has not been reached on accounting for essentiality and differences in bioavailability. An alternative to using a modifying factor is to specify that the risk value is for the dose above that normally ingested in food. Another, more complex approach is to note the degree of absorption via different routes and for risk assessors to take that into account when calculating the total dose. Recent work in this area includes the effort by the National Academy of Sciences to determine the upper intake level for nutrients as part of its overall effort to establish dietary reference intakes (28).

2.6 Weight of the Overall Evidence

Evaluation of the overall weight of evidence is a key step in identifying the critical effect for a noncancer assessment. Evaluation of the overall weight of evidence includes characterization of (1) the quality of the evidence from human studies, (2) the quality of evidence from animal studies, and (3) other supportive information, which is assessed to determine whether the overall weight of evidence should be modified. The other supportive information can be used in evaluating the relevance to humans of the experimental animal model or the observed effect and in identifying the appropriate gas category for conducting dosimetric adjustments (see Section 3.1.2). Hill (15) provided criteria for evaluating whether a causal relationship has been established in an epidemiological study and in the overall epidemiological database. As noted by the USEPA (18), these same criteria apply in evaluating the weight of evidence for the entire database (Table 5.3).

Table 5.3. Criteria for Establishing Causal Significance

The strength of the association is enhanced when
▪ Consistent results are obtained by different investigators under a variety of circumstances.
▪ The association is stronger (larger relative risk or odds ratio).
▪ The association is specific, the exposure is associated with a specific effect, and that effect is specific to the exposure.
▪ Exposure occurs prior to the development of the effect (temporality).
▪ The association is consistent with what is known about the chemical's effects and mechanism based on clinical or animal studies (coherence and biological plausibility).
▪ A dose–response relationship is observed.

Similar criteria apply in evaluating animal data. Ideally, the database should include studies of several species in which a variety of end points are evaluated. For noncancer assessments, this

evaluation should include systemic toxicity following acute, intermediate, or chronic exposure by several routes of exposure, as well as developmental and reproductive effects. If these general tests or analogy to other chemicals suggests a concern, it may also be necessary to conduct specialized testing, such as evaluations of immunotoxicity or neurotoxicity. These studies are used to characterize the chemical's spectrum of potential human toxicity by identifying target organs and the dose ranges associated with adverse effects in animals. *In vitro* data can be used to elucidate potential mechanisms of biological activity, to evaluate the relevance of the end point to humans, and to improve the extrapolation from animals to humans, or to characterize within-human variability. The assessment of the animal database should include an evaluation of the reliability of the experimental design and toxicological interpretation of the results, as described before. In addition, consideration should be given to studies designed to evaluate the metabolism and toxicokinetics of the chemical and to data from other studies that may elucidate its mechanism(s) of action.

Once the data have been critically reviewed, all of the results from the various studies should be examined collectively to determine if a causal relationship exists between chemical exposure and the observed effects. In addition to the general criteria described in Table 5.3, the strength of the overall evidence is enhanced if (1) similar effects are observed in structurally similar compounds and (2) there is some evidence that the chemical also causes the particular effects in humans.

Species-specific differences in sensitivity to a chemical should also be considered. These differences may result from differences in metabolizing the chemical, from other physiological differences such as differences in the anatomy of the respiratory system, or from differences in the sensitivity of the target tissue. These differences can result in apparently inconsistent data that can be explained by considering the chemical's dosimetry, toxicokinetics, and toxicodynamics. Thus, evaluation of toxicokinetics and toxicodynamics can play an important role in evaluating the weight of evidence. For inhalation studies, consideration of particle size is an important part of evaluating the weight of evidence and may explain apparently conflicting results among studies. It is also important to distinguish differences that result from study limitations and experimental design from those that are related to species-specific differences in respiratory function.

Noncancer Risk Assessment: Principles and Practice In Environmental and Occupational Settings

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3 Dose–Response Assessment

Dose–response assessment is generally the next step in the risk assessment process. It uses the results of the hazard identification as a starting point for determining the likely quantitative outcome in humans. The results of the dose–response assessment generally follow the methods described in Table 5.1. Additional details on the “safe” dose model and improvements to this model follow here.

3.1 General Principles

“Safe” or subthreshold doses are defined by a number of health agencies worldwide. Different names are used for these values, such as Health Canada's Tolerable Daily Intake or Concentration (TDI or TDC) (29); International Programme on Chemical Safety's Tolerable Intake (TI) (30); U.S. Agency for Toxic Substances and Disease Registry's (ATSDR's) Minimal Risk Level (MRL) (31); USEPA's Reference Dose (RfD) (32, 33) or Reference Concentration (RfC) (18, 20); or the World Health Organization's Acceptable Daily Intake (ADI) (34, 35). Many of the underlying assumptions, judgments of critical effect, and choices of uncertainty factors (or safety factors) are similar among health agencies in estimating these subthreshold doses. Approaches used to derive these different subthreshold doses are addressed in more detail in Section 3.3.

We describe here the method for estimating “safe” doses of the USEPA as a way of showcasing some general principles about this scientific area.

3.1.1 USEPA's Method for Developing Reference Doses (RfDs) and Reference Concentrations (RfCs) USEPA defines the RfD (or RfC) as “an estimate (uncertainty spans perhaps an order of magnitude) of a daily (or continuous) exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime” (18, 32). The RfD/RfC is composed of the no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL) or NOAEL surrogate, such as a benchmark dose/concentration (BMD/BMC) for the critical effect, divided by the composite uncertainty factor (UF) and modifying factor (MF). The following equation is used:

$$\text{RfD/RfC} = (\text{NOAEL, LOAEL or BMD/BMC})(\text{UF} \times \text{MF}).$$

The phrase “with uncertainty spanning perhaps an order of magnitude” is intended to reflect the overall precision of the estimate, generally an order of magnitude $\log_{10}$. This does not preclude less precise estimates, however, or the occasional estimate that may be precise to one arithmetic digit. The phrase “including sensitive subgroups” suggests that the estimate is intended for sensitive individuals, leading to the common interpretation that the RfD/RfC is a NOAEL for sensitive individuals. An additional implication of this phrase is that the average individual can be safely exposed to doses somewhat higher than the RfD/RfC. However, the estimate is not intended to protect hypersusceptible individuals, if they exist for particular chemicals. Thus, for example, the RfD/RfC is intended to protect against sensitization (see the RfC for beryllium and compounds, Ref. 25). Once an individual is sensitized, however, that individual may react to exposures much lower than those that caused sensitization, and the RfD/RfC may not protect against such a reaction. The phrase “likely to be without an appreciable risk” means that the estimate is thought to be without the risk of adverse effects for most, if not all chemicals, based on the available toxicity data and the use of uncertainty factors to account for data gaps. The complete absence of risk cannot, however, be guaranteed, in the light of the (small) potential for data gaps that have not been taken into account and the known variability in response among individuals.

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4 Risk Characterization

Risk characterization, the final step in the risk assessment process, integrates the results of the hazard identification and dose–response assessment (toxicity assessment) and the exposure assessment. In essence, risk characterization is the “product” of risk assessment because it evaluates and synthesizes the data collected and the decisions made in the risk assessment. The outcome of risk characterization is a summary of the risks posed to individuals and populations, as well as the strengths and weaknesses of the risk assessment. Risk characterization is also a communication tool that provides the risk manager with sufficient information to make effective risk management policies. According to the USEPA (130), an effective risk characterization must have the following qualities:

- Transparency. The risk characterization must clearly describe where scientific data were used and where science policy judgments were used in the risk assessment. Default assumptions should also be clearly explained. Transparency ensures clear separation between science and policy decisions, allows for an assessment of the applicability of the risk estimate by the risk manager, and

facilitates the comparison of different risk estimates.

- Clarity. The risk characterization should present a summary of the key issues and conclusions from each section of the risk assessment, and it should discuss the overall strengths and weaknesses of the assessment.
- Consistency. All risk characterizations should be consistent in general format, while accounting for the unique nature of each specific risk assessment.
- Reasonableness. For the risk assessment to be credible and therefore a useful tool for the risk manager, the risk characterization must be accurate and well balanced. Appropriate conclusions should be drawn without overstretching the data; alternative conclusions should be presented.

The USEPA (130) recommends that each risk characterization include three components: a qualitative summary of each section of the risk assessment, a numerical risk estimate, and a description of uncertainties. This section describes each of these components separately and then discusses how these apply to risk assessment in the occupational setting.

4.1 Developing a Qualitative Summary

In evaluating the use of risk assessment in the federal government, the Commission on Risk Assessment and Risk Management (131) noted that risk characterizations that rely primarily on quantitative estimates "often convey an unwarranted source of precision while failing to convey the range of scientific opinion." As a result of this finding, the Commission recommended that risk assessments should include qualitative information on the nature of the adverse effects and on the risk assessment itself, so that risk managers have information on the range of scientific views and the evidence to support them.

A full discussion of the uncertainty within each analysis and that related to the overall assessment is critical to a complete risk characterization. Uncertainty discussions are important because they form the basis for the overall judgment as to the adequacy of the data and conclusions drawn from it. In addition, highlighting of uncertainties can identify areas where the collection of additional data may reduce the uncertainty and strengthen the risk assessment. An uncertainty discussion includes the quality and quantity of available data (toxicity and exposure), identification of data gaps, the use of default assumptions and parameter values, and the uncertainties in the models used.

The USEPA (130) has prepared an excellent guide for risk assessors to follow when developing the qualitative summary for a risk characterization. The guide is presented in two parts. By asking a series of questions, the guide first directs risk assessors to bring together the major conclusions of the risk assessment and then provides an outline for drawing together all of the information to characterize risk. A summary of the USEPA (130) guidance is presented in Table 5.7.

Table 5.7. Summary of EPA (130) Guidelines on Risk Characterization

Characterize Hazard
▪ Describe key studies, studies that support the key studies, and other valid studies with conflicting results.
▪ Describe what is known about the mechanism of chemical action.
▪ Comment on nonpositive data and whether these data were considered in the hazard characterization.
▪ Summarize the hazard identification including the confidence in the conclusions, alternative conclusions, significant data gaps, highlights of major assumptions.
Characterize Dose
▪ Describe the data used to develop the dose–response curve.
▪ Describe the model used to develop the dose–response curve.

- Discuss the route and level of exposure compared to expected human exposure.

Characterize Exposure

- Discuss significant sources of exposure.
- Describe the populations exposed.
- Describe any modeling used to generate exposure estimates.
- Describe the key descriptors of exposure.
- Evaluate cumulative or multiple exposures.
- Summarize the exposure assessment conclusions, including results of different approaches, limitations of approaches, range of exposure values, confidence in the results.

Risk Conclusions

- Overall picture of risk.
- Major conclusions and strengths.
- Major limitations.
- Science policy options and defaults used.
- Reasons for choices made.

Although application of the principles described in the USEPA risk characterization guidance represents good industrial hygiene practice, there are no specific guidelines for risk characterization in the occupational setting. Typically the "risk characterization document" resulting from an occupational survey is in the form of a survey report. Such a survey report typically describes the rationale for the survey (hazard recognition), the exposure assessment strategies used, the results of the exposure analysis, comparison of the results to occupational standards (hazard evaluation), and recommendations for control of any hazards (hazard control). An important difference in the qualitative description of the risk assessment is the lesser emphasis on the strengths and weaknesses of the reference level and greater emphasis on the exposure estimates. Another major difference is the overlap between risk characterization and risk management. The risk manager for the occupational risk characterization is often not trained in the appropriate evaluation of exposure control options. For this reason, the recommended hierarchy of controls is commonly outlined in the occupational risk characterization document.

4.2 Presenting the Risk Estimate

Once the risk characterization has summarized the qualitative aspects of the risk assessment, it should then present the quantitative aspects of the risk assessment, including calculating risk estimates and discussing the risk in context of other similar risks. For noncancer risk assessment, developing a quantitative risk estimate involves comparing the measure of exposure to a criterion level that has been determined from the toxicity estimate. Based on the traditional approach, the result allows determining whether the exposure (dose) exceeds the allowable dose level. For cancer assessment, a probabilistic measure of risk (e.g. 1:1000 likelihood of excess cancer) is calculated and compared with some risk management standard of "acceptable risk." By contrast, for noncancer risk assessment, the exposure is described only as being larger than, equal to, or less than the RfD, RfC, or other risk value. For example, the exposure may be divided by the RfD or RfC (resulting in the hazard quotient) in an analysis of a Superfund site, the oral intake of a pesticide may be compared to the RfD, or a worker's TWA exposure may be compared to an occupational exposure limit.

In both the environmental and occupational evaluations of risk, it often necessary to evaluate risk in response to a combination of exposures or to exposures through multiple routes. One approach that is used in assessing risk from multiple substances at Superfund sites is determining the hazard index. This involves summing the hazard quotient for each of the substances of concern. In the occupational setting, similar approaches have been adopted by OSHA (5) and ACGIH (6). In the case of the

ACGIH, for exposure to multiple substances with similar effects, the summation of the individual exposure/TLV ratios are compared to a value of 1. If the substances have differing effects, however, then each exposure/TLV ratio is compared to a value of 1 independently.

The approaches for assessing the risk from multiple routes of exposure differ substantially between environmental and occupational settings. In the Superfund paradigm, the total dose can be calculated for the combined inhalation, dermal, and oral exposure before comparison to the appropriate criterion level. In the occupational setting, exposure though inhalation is typically measured as the predominant exposure route. Methods are available to measure dermal exposure; however, this is not often done. As a result, for substances that are absorbed through the skin, comparison of the air concentration to the exposure threshold may not adequately estimate potential risk. To address this problem qualitatively, many organizations that establish occupational exposure limits (OELs) add a notation for substances for which dermal absorption can contribute meaningfully to the total dose. Another approach in occupational assessment to account for the contribution of multiple exposure routes is the use of biological markers of exposure. Several OSHA substance-specific standards include requirements for biological measures of exposure. In addition, biological exposure indices (BEIs) are published by the ACGIH (6).

A single risk estimate is not sufficient to provide risk managers with a clear understanding of risks. Rather, the USEPA (130) suggests that a range of risk descriptors be used to "allow managers to identify populations at greater and lesser risk and to shape regulatory decisions accordingly." The risk descriptors suggested by the USEPA (130) include

- individual risk at both the "central tendency" (50^{th} percentile) and "high end" ($90–95^{th}$ percentile) of the risk distribution.
- population risk: For noncancer risk assessment, this is an estimate of the portion of the population whose exposure exceeds the reference level.
- risk to important subgroups of the population.

It is important to note that, because risk is estimated as a function of exposure, the characteristics that distinguish these different risk descriptors will be related primarily to differing exposure. In addition, the Commission on Risk Assessment and Risk Management (131) suggests comparing the distribution of a population's exposure to the reference level, so that the relationship between exposure and the potential for harmful effects is clearer.

In the occupational setting, the presentation of the variability in the exposure estimates often receives more weight than the uncertainty surrounding the derivation of the OEL. Issues surrounding exposure variability in occupational settings differ from those in environmental risk assessment, in that the exposure estimate is often based directly on measured exposures. The presentation of the data depends on the underlying purpose for the measurements, but it is common for compliance purposes to measure workers expected to have the greatest exposure for a representative exposure group. Thus, an upper bound estimate of exposure is compared to the appropriate occupational exposure limit, whereas comparison of the distribution of the exposures to the OEL would be less common.

Once the range of potential risks has been estimated, it is important that the risk characterization place the risk into the context of other similar risks. Issues to address in completing this part of the risk characterization include evaluating alternatives to the hazard and making risk comparisons. The Commission on Risk Assessment and Risk Management (131) recommends that the following risk comparisons are useful in placing risk in context:

- risks associated with chemically-related agents
- risks with the same agent from different exposure sources

• risks with different agents from the same exposure pathway
• risks of different agents that produce similar effects

4.3 Evaluating the Uncertainty Associated with the Risk Estimates

Another component in risk characterization is the discussion of the sources of both variability and uncertainty in the risk assessment and the evaluation of uncertainty associated with the risk assessment. The USEPA distinguishes between variability and uncertainty in its risk characterization guidance (130). Variability describes interindividual, spatial, or temporal differences within an animal or human population or within monitoring data. It reflects the inherent heterogeneity of the population and cannot be reduced by gathering additional data. Uncertainty, on the other hand, reflects areas for which data are unknown. By contrast, uncertainty can be reduced by eliminating data gaps. Uncertainties are associated with both dose–response models and with fate and transport models; an uncertainty analysis would evaluate the basis for and validation of the model. There are also uncertainties associated with dose–response evaluation that do not use mathematical models. As described in Section 3.3, a number of organizations use uncertainty factors to address such data gaps. Uncertainty is also inherent in estimating the best choice of uncertainty factor.

The field of risk assessment is increasingly utilizing uncertainty and sensitivity analyses to better quantify uncertainty in evaluating risks to human health. Probabilistic methods, such as Monte Carlo modeling, can be used to quantitatively describe uncertainty and parameter sensitivity. In this approach, each of the parameters in a model or calculation is represented by a distribution of possible values. The probability distribution for each parameter is randomly sampled, and the model is run using the chosen set of parameter values. This process is repeated a large number of times until the probability distribution for the desired model output is determined. Using this approach, a "high-end" value (e.g., 95^{th}or 99^{th} percentile) for the overall model can be estimated more accurately than by simply using the "high-end" estimates for each of the inputs. Monte Carlo methods have been used in evaluating exposure for site assessments and for characterizing uncertainty in PBPK models. Such approaches can also be used for quantitative sensitivity analyses by determining how the overall model output varies as one parameter is varied.

An analysis of the uncertainty in noncancer risk values is one area that has received little attention to date. Noncancer risk assessment has traditionally calculated reference values to be protective of human health, rather than predictive of actual toxicity. Each reference value is based on numerous assumptions and uncertainties, which contribute to the lack of precision in these values.

Noncancer risk values are not precise. USEPA's definition for RfDs and RfCs addresses this lack of precision, as " ... an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily or continuous exposure ... " (18, 32) Similarly, IPCS defines Tolerable Intakes (TIs) as "an estimate of the intake of a substance over a lifetime that is considered to be without appreciable health risk" (30). Such lack of precision is specifically mentioned in IPCS (30), which indicates that the precision of the tolerable intake depends upon the validity and reliability of the data and also on the magnitude of the uncertainty factor. The precision of a RfD or TI is to one significant figure at best, and an order of magnitude is the most usual case. As the uncertainty factor increases beyond 1,000, however, the precision becomes even less.

However, as discussed more fully by Felter and Dourson (36), the concept that risk estimates are inherently imprecise seems to have been lost somewhere between calculating risk values and making risk management decisions. There may be several reasons for this, including the desire by risk managers and the public to know with certainty what the risks to public health might be, or alternatively, what dose is safe. The underlying science can seldom determine such "bright lines." Making decisions with imprecise and uncertain data is much more difficult.

Unlike EPA's RfDs and RfCs, which have a stated uncertainty spanning an order of magnitude, explicit quantitative estimates of the range of uncertainty in occupational exposure values are less

clearly outlined. The OSHA PEL does not state the underlying uncertainty associated with its use, and it is enforced so that a single 8-hour TWA above the PEL on any day would be viewed as noncompliance (5). In contrast, the ACGIH TLV-TWA is "an exposure level to which it is " ... believed that nearly all workers may be repeatedly exposed, day after day, without adverse effect." The TLV documentation addresses the underlying uncertainty by indicating that the database used in deriving the value varies from substance to substance, and thus the precision of the estimated TLV is subject to variation. Furthermore, the TLV is not to be considered a fine line between safe and dangerous concentrations.

Even when the lack of precision is acknowledged in the definition of the RfD/RfC, the lack of scientific data upon which the order of magnitude definition is based has led to widely varying interpretations of the inherent range. A recent informal survey of risk assessors and managers at the USEPA found that there were several interpretations of the "order of magnitude" in the definition of the RfD (36). As described in that publication, these interpretations can be described as

"range = x to 10x (where the point estimate of RfD = x). This view is supported by those who believe that the risk assessment process is so inherently conservative that the RfD should be considered the lowest estimate and the range of imprecision all rests above this point estimate.
range = 0.3x to 3x. This is the view held by many of USEPA's former RfD/RfC Work Group members, wherein the RfD is associated with uncertainty on either side. The order of magnitude is divided into half-logs.
range = 0.1x to x. This is the view held by many risk managers, that is, regulatory decisions (e.g., setting of standards or cleanup levels) are based on the assumption that we are "OK" as long as we do not exceed the level of the RfD.
range = 0.1x to 10x. This range could be envisioned if one were to assume that the order of magnitude range could be on either side of the point estimate x."

As discussed by Felter and Dourson (36), even if there were agreement among risk assessors how this "order of magnitude" uncertainty should be interpreted, it may not be appropriate to apply this range of precision equally to all risk values. A number of factors contribute to the precision in a given noncancer risk value. These include the dose spacing, the quality of the study, the degree to which the experimental animal species predicts effects in humans, the severity of the critical effect and the slope of the dose–response curve (both of which are related to the precision with which the threshold is estimated), and the size of the composite uncertainty factor. Thus, the "true" range of the resulting risk value is specific to a given chemical and database. To some degree, the statements that the USEPA includes about the confidence in the study, database, and overall confidence in the RfD/RfC are meant to address the precision in the resulting value, but risk managers may find it difficult to quantitatively apply such qualitative statements. A more formal description of uncertainty in risk assessments can help risk managers move beyond "bright line" values and incorporate uncertainty in risk management decisions.

Felter and Dourson (36) suggested that the expression of risk values as a range has several advantages. Expressing these values as a range makes explicit to risk managers that these values are not "bright lines." Presentation of a range may help with prioritizing hazards and resulting decisions (for example, if two chemicals have similar hazard quotients, but differ in the associated precision.) International harmonization efforts may be assisted by making the range explicit, as risk managers are made aware that the values for a given chemical from different organizations might differ somewhat, but may still fall within the same range. The establishment of ranges, however, would necessitate the development of consistent guidance for interpreting and using these ranges.

A recent invited commentary was held on the imprecision of risk numbers (132). Papers from Health Canada, IPCS, Toxicology Excellence for Risk Assessment (TERA), and the USEPA, USFDA, and

USATSDR set forth various views on this subject. One conclusion from this effort was that risk assessors should be careful to convey a measure of confidence in their results and quantify this when possible. Allowing risk managers and the public to believe that risk estimates are more precise than appropriate may lead to inappropriate risk management decisions and less trust in the science and practice of risk assessment.

4.4 Margin of Safety and Margin of Exposure Approach

Margin of safety (MOS) has traditionally been used in the field of toxicology as a tool to compare dose–response data between a drug's desirable effective dose (ED) and its lethal dose (LD) or minimum toxic dose. For example, the ED_{99} can be divided by the LD_{01} to calculate the margin of safety, or therapeutic index, as it is sometimes called. The larger the MOS, the greater the presumed safety in using the drug.

The MOS concept is useful and has also been carried over to the field of environmental health. In this case, a NOAEL from a toxicity study is divided by a measured exposure to the human population to calculate a MOS. Again, the larger the MOS, the greater the presumed safety. MOS addresses both dose/response (NOAEL) and exposure and therefore, falls within risk characterization as defined by the NAS (2). The MOS must be interpreted by experts depending, in part, on the completeness of the toxicity database from which the NOAEL of the critical effect is derived (129). An analogous term, the margin of exposure (MOE), is also used, as discussed in Barnes and Dourson (32).

The MOS method, as practiced by the EU (129, 133) begins with the same evaluation of toxicity data to determine the NOAEL or LOAEL in the hazard identification step of the risk assessment process. It is after the hazard identification step that the MOS/MOE approach diverges from the estimation of a “safe” dose. The MOS compares this NOAEL or LOAEL to the exposure estimate(s) for the exposed human population(s), whereas in the “safe” dose approaches, uncertainty factors are used to estimate a “safe” dose. If it is not possible to derive a N(L)OAEL/exposure ratio, a qualitative comparison of effects with exposure data should be made. Where it is not possible to determine a N(L)OAEL (e.g. irritation, corrosivity, sometimes sensitization, mutagenicity, genotoxic carcinogenicity), the likelihood that the effect will occur is evaluated on the basis of exposure information. The comparison is in the form of a dimensionless ratio where the NOAEL or LOAEL is in the numerator, the measured or estimated exposure is in the denominator, and both are in the same units. Exposure estimates higher than or equal to the NOAEL or LOAEL indicate concern. Those exposures lower than the NOAEL or LOAEL are evaluated on the basis of expert judgment of the uncertainties related to the following parameters, as outlined in Ref. 129:

- the uncertainty arising, among other factors, from the variability in the experimental data and intra- and interspecies variation;
- the nature and severity of the effect;
- the human population to which the quantitative and/or qualitative information on exposure applies;
- the differences in exposure (route, duration, frequency and pattern);
- the dose–response relationship observed; and,
- the overall confidence in the database.

These assessment factors are similar to those covered by the uncertainty factors of the tolerable intake approach. However, in contrast to the TI approach where expert judgments about the appropriate factors are considered in determining a “safe” dose, which is then used to estimate a guidance value, the MOS approach relies on expert judgments to reach conclusions about given exposures on a case by case basis.

Because the MOS/MOE is a risk characterization technique (i.e., it combines both dose–response and exposure assessment), the results should be compared to other established risk characterization techniques, such as the development of criteria or guideline values. (A good discussion of the

development of guideline values can be found in Ref. 30). One advantage of deriving a guidance value from a TI when compared to the MOS is that exposures at or less than the guidance value can generally be interpreted as without risk. However, when exposures exceed the guidance value, then expert judgment is needed to interpret the significance in health terms of the exceedence. One advantage of the MOS when compared to the guidance values (from a TI) is that not all toxicity databases are strong enough to develop a TI, yet generally these databases can be used to determine a MOS. However, additional care is needed in interpreting of this MOS because the database is correspondingly weaker.

Overlap often exists between the derivation of a guidance value (from a TI) and MOS. This is not unexpected nor necessarily undesirable. However, in such situations, an analysis of these techniques in relationship to each other should be conducted.

Although this type of approach has been used for a number of years in noncancer risk assessment, its use in cancer risk assessment is also becoming more prevalent. Some of the issues and concerns raised with these approaches are pertinent to noncancer risk assessment as well. For example, Health Canada utilizes an Exposure/Potency Index (EPI) (29) to characterize risk from "nonthreshold toxicants" and provide guidance for determining further action under the Canadian Environmental Protection Act. The EPI approach compares quantitative estimates of carcinogenic and mutagenic potency to the estimated daily intake of the substance by the general population (or high-exposure subgroups) or to concentrations in specific media. A margin of exposure (MOE) analysis is recommended by the USEPA in its proposed cancer guidelines (134) as the default approach when there is no evidence for linearity and there is sufficient evidence to support an assumption of nonlinearity.

Each of these approaches (i.e., MOS, MOE, or EPI) is similar in that they compare an experimental dose or potency to an exposure to determine the ratio; the larger the ratio, the "safer" the presumed exposure. Although the ratios may be based on scientific data, the interpretation of these ratios is more of a management judgment. Health Canada (29) clearly identifies the EPI as a tool to characterize risk and provide guidance in setting priorities. Under the CEPA mandate, this is the extent of decision making that needs to be addressed, and guidance is provided as to what ranges of EPIs would indicate priority for further action. USEPA (134) discusses MOE in the dose–response section of cancer assessments, even though it is clearly a risk characterization concept, because it compares dose–response information and exposure data. The proposed USEPA cancer guidelines include a general discussion of some factors that may be considered guidance for the risk manager in determining the appropriate MOE. These are based upon the traditional uncertainty factors utilized in the tolerable intake approaches. However, no definitive suggestions are made for applying these or other factors.

Although developing a MOS, MOE, or EPI is useful in evaluating safety, alternatives exist to characterize the risk when a predetermined exposure level does not exist. One approach is to develop a guidance value, or criterion. How should the estimate of these guidance values fit with approaches such as the MOE or EPI? Specifically, for the MOE, the risk manager must determine a priori which factors need to be included in extrapolating from, for example, an LED_{10} from animal bioassay data to a "safe" intake level for humans. This is best handled by the using uncertainty factors, in a manner similar to that currently used in the tolerable intake approaches for noncarcinogens and the subsequent development of guidance values. Because not all LED_{10}s are created equally—some will be based on increased incidences of severe lesions; others will be based on precursor lesions with no immediate health impact—a comparable strategy of uncertainty factors based on scientific data is needed.

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5 Summary
The field of noncancer risk assessment is changing. Improvements based on research and analysis during the last 20 years have yielded newer, more quantitative methods for determining health risks associated with chemical exposures—whether such exposures are from the workplace or the environment. These methods can answer more questions asked of the existing data and allow better risk management decisions. These methods also have broader use and may integrate this area of risk assessment with those that focus more on cancer toxicity and chemical mixtures.

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Interactions

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Environmental Exposures

We live in a chemical world, and exposure to xenobiotics is a fact of life. Humans are exposed daily to a variety of chemicals including but not limited to large categories of pesticides, pharmaceuticals, household products, and food additives. Chemical exposures can be intentional or unintentional, to a single chemical or to a mixture of chemicals. Exposures to environmental chemicals occur in populations living in inner cities near chemical manufacturing plants (1, 2) hazardous waste sites, and in the near field runoffs from fields and fertilizers (3). An overturned cargo train or transportation truck can spill chemicals in a pristine environment and become a source of pollution, contamination, and exposure, and eventually lead to an emergency response event. Exposures to environmental chemicals can affect humans, animals, and plants. Thus people of various interests and backgrounds are concerned about environmental exposures. Everyone carries a body burden of chemicals that range from primary elements and radioactive materials to synthetic, persistent chemicals such as dioxins, polychlorinated biphenyls (PCBs), and certain chlorinated pesticides. The major issue is not whether we are being exposed to mixtures of chemicals, but whether these exposure levels exceed the body's ability to detoxify, adapt, or otherwise compensate.

Following a chemical exposure, the body exhibits a spectrum of biologic responses (Fig. 6.1) (1). For many chemicals, low-level human exposures do not produce observable health effects. Physiologically, the body adjusts to the presence of chemicals at this level through adaptive mechanisms. As chemical exposure increases, effects such as enzyme induction and certain biochemical and subcellular changes of uncertain significance may result. The body may have compensatory mechanisms at this level of chemical exposure (3). However, as chemical exposures continue to increase, observable adverse effects may ensue as the body exhausts its adaptive and compensatory mechanisms. Such adverse effects could lead to biochemical, pathophysiologic, histopathologic changes resulting in organ dysfunction. Exposure to higher levels of pollutants could lead to morbidity and mortality. Exposures from multiple sources or pathways may lower the threshold for adverse health effects along this continuum. Considering that humans generally lack homogeneity in biochemical characteristics, some groups within the population will be more susceptible to chemical exposures than others.

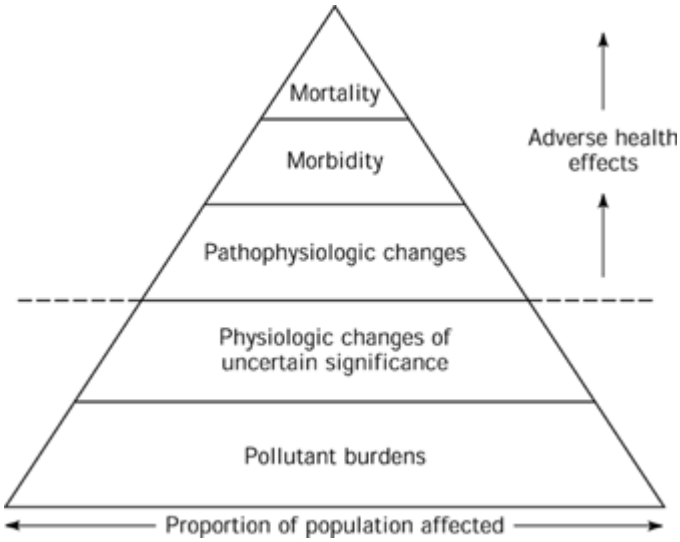

Figure 6.1. Spectrum of biological response to environmental pollutant exposure.

Thus it is important that exposure to environmental chemicals be viewed in the context of overall chemical exposures. Concurrent exposures to chemicals such as welding fumes, indoor air pollutants, tobacco smoke, alcohol, and prescription and nonprescription drugs complicate the health risk assessment of low-level, involuntary, environmental exposure such as may occur at hazardous waste sites. Voluntary exposures to some chemicals frequently entail exposures to relatively high chemical concentrations and are usually well defined and quantifiable, whereas involuntary exposures from waste sites may be at low concentrations and difficult to characterize and quantify. Individual control over exposure varies across personal, occupational, and environmental chemical exposure pathways (Fig. 6.2). Personal exposures such as firsthand tobacco smoke or alcohol are voluntary. Occupational exposure is voluntary, but the individual generally has less control over these exposures. On the other hand, individuals usually have few options for controlling environmental exposures under ordinary circumstances. In most cases, other than relocation, there are no clear options for individual control over hazardous waste exposures. Often an individual may not even be aware of the site, the exposure pathways, or the nature of the exposure. In terms of concentrations, for general populations, personal exposures are usually at higher levels than hazardous waste exposures. Such combined exposures may produce obvious adverse health effects or compromise physiologic defenses that are necessary for maintaining homeostasis.

Figure 6.2. Human exposures to chemicals in the environment.

The potential for combined chemical exposures to compromise physiologic systems may be greater in susceptible populations that include children, elderly persons, women of childbearing age, fetuses, persons with certain genetic disorders, and persons with preexisting infirmities (3). In such populations, pollutant burdens can initiate pathophysiologic changes at lower levels in comparison to the general population. For example, human infants and children differ from adults in size, immaturity of biochemical and physiologic functions in major body systems, and body composition

in terms of proportions of water, fat, protein, mineral mass, and chemical constituents (4, 5). During the first 2 months of life, rapid development occurs in the brain (cell migration, neuron myelination, and creation of neuron synapses), lungs (developing alveoli), and bones (rapid growth). Development of the brain and lungs continues until age 12, at which time gonad maturation, ova and sperm maturations, and breast development occur (6). Depending on the chemical, the stage of growth and development may be a critical factor in determining toxicity (7). Finally, the contribution of hazardous waste to exposures of populations living near hazardous waste sites may constitute a significant contribution to overall body burdens when concurrent with occupational and personal exposures.

Historically, health concerns from exposure to single chemicals drive criteria derivation procedures. Usually, the target chemical, or group of chemicals, is identified by a government agency, international organization, or an advisory body based on legislative mandate, evidence or potential for human risk, or community concerns. For each chemical, exposure and health effects data are reviewed, and a single route-specific index of "acceptable" exposure is derived for the chemical. This approach is taken by several organizations such as the American Conference of Governmental Industrial Hygienists (ACGIH), the Agency for Toxic Substances and Disease Registry (ATSDR), the National Institute for Occupational Safety and Health (NIOSH), the U.S. Environmental Protection Agency (EPA), and the World Health Organization (WHO) (Table 6.1). However, most exposures are not to single chemicals, but to complex mixtures of chemicals that can affect public health through multiple routes of exposure. The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, or Superfund) of 1980, the Clean Air Act of 1990, and the Food Quality and Protection Act of 1996 all mandate organizations and agencies to consider multiple chemical exposures, sequentially or simultaneously, while setting the criteria to protect public health from potential health effects of chemicals. Thus one has to consider comprehensive risk to populations that are exposed not only to a specific mixture but also to additional environmental agents and naturally occurring compounds that may enhance, inhibit, or contribute to the health risks posed by that mixture. In very few cases, the available information on a mixture and its components is reviewed and a criteria for the mixture are derived. The purpose of this chapter is to highlight issues relevant to the joint toxicity assessment of chemical mixtures through the use of representative published studies, to present the alternative experimental testing approaches for mixtures, and to promote the use of innovative techniques to advance joint toxicity assessment methods.

Table 6.1. Examples of Agencies and Their Derived Criteria

Agency or Organization	Acronym	Criteria Derived
American Conference of Governmental Industrial Hygienists	ACGIH	Threshold limit value (TLV)
Agency for Toxic Substances and Disease Registry	ATSDR	Minimal risk level (MRL)
National Institute for Occupational Safety and Health	NIOSH	Recommended exposure level (REL)
Occupational Safety and Health Administration	OSHA	Permissible exposure level (PEL)
U.S. Environmental Protection Agency	U.S. EPA	Reference dose (RfD); reference concentration (RfC)
U.S. Food and Drug Administration	U.S. FDA	Acceptable daily intake (ADI)
World Health Organization	WHO	Environmental health criteria

(EHC)

Types of Mixtures

Simple Mixtures Human populations are exposed to a range of chemical mixtures that can be simple or complex, partially or completely characterized, and of stable or varying composition. This can be illustrated through a continuum of mixtures as illustrated in Table 6.2. In the field of anesthesiology, combinations of well-defined anesthetics under completely controlled exposure regimens have been used for a long time. For example, morphine in combination with other epidural anesthetics has been used effectively to provide improved overall pain relief following surgery (8). This is an example of a simple mixture that is completely characterized, and the route and duration of exposure are completely controlled.

Table 6.2. Continuum of Chemical Mixtures to Which Humans Can Be Potentially Exposed

	Mogensen et al. (8)	Institute of Medicine (9)
Exposure and conditions	Well-defined, controlled	III-defined, uncontrolled
Causative agents	Bupivacaine, morphine, and Clonidine	Unknown chemical/biological petroleum combustion products
Route of exposure	Inhalation and epidural	Mixed; inhalation, oral or dermal
Monitoring data	Complete	Very limited
Hypothesis testing	Yes	No

Complex Mixtures At the opposite end of the spectrum is exposure to complex mixtures, which can be intentional or unintentional. During the Gulf War, military personnel were intentionally exposed to vaccines and preventive agents including anthrax vaccine and the chemical warfare antidote pyridostigmines (9). Unintentional exposures included chemical/biologic agents and smoke and petroleum combustion products. Potential exposures could have been through a combination of inhalation, oral, and dermal routes. Such mixed exposures were associated with symptoms such as fatigue, abdominal pain, diarrhea, headache, memory loss, skin rashes, and hair loss. Also, the exposure occurred under varying environmental conditions of temperature, humidity, and high winds. These types of complex mixture exposures pose a formidable challenge for health risk assessors. In general, the availability of information on chemical mixtures encountered in the real world varies greatly between simple and completely characterized, and the highly complex and poorly characterized mixtures.

NIOSH estimates that more than one-half of the U.S. workforce is employed indoors, and that this trend will continue to expand (10). This trend is paralleled by the increase in reports of symptoms and signs related to indoor air environments. These effects range from nonspecific symptoms of headaches and eye irritations to signs of allergic and infectious diseases. Although the majority of health problems reported in indoor workers cannot be attributed to specific exposures, evidence suggests that multiple factors are involved including microbiologic, chemical, physical, and

psychologic/social stressors. In addition, voluntary exposures to tobacco, prescription and nonprescription drugs, alcohol, herbal remedies, vitamins, and cosmetics add to the complexity.

Some of the most complex and hard to characterize mixtures are those found at hazardous waste sites because hundreds of chemicals have been identified at such sites (11–13). Attempts have been made to rank them singly (14–16) and in combination (15, 17) based on the threat they pose to the environment and to public health. Parameters influencing exposure, such as transportation of chemicals from waste sites to receptor populations, have also been examined (18, 19). Environmental laws such as CERCLA (or Superfund) section 104, as amended by the Superfund Amendments and Reauthorization Act (SARA) (USC 9604) [i][2]), have helped to focus efforts on the fundamental issue of assessing the impact of chemicals and chemical mixtures. Through this legislation, ATSDR has been specifically mandated to identify individual substances and combinations of substances that pose the greatest public health hazard at hazardous waste sites. The information thus obtained allows the agency to pursue activities such as developing toxicological profiles, identifying substance-specific data needs, and establishing research agendas.

Until recently, basic and critical information necessary for identifying the mixtures most commonly found at hazardous waste sites was not available. ATSDR's Hazardous Substance Release/Health Effects Database (HazDat) is a searchable database that captures pertinent information from public health assessments performed by the agency for hazardous waste sites on the National Priorities List (NPL). HazDat contains environmental contamination and other data from more than 3500 hazardous waste sites or events for which ATSDR has conducted public health assessments, prepared consultations, or provided responses to emergencies involving releases of substances into community environments (20). Using HazDat, the agency produced a list of the top 275 single substances of public health concern at U.S. hazardous waste sites (12). The algorithm used to rank these single chemicals is driven by empirical data and consists of three components: frequency of occurrence, inherent toxicity, and potential for human exposure. Scores from each of the three components are added, and the chemicals ranked according to their overall score. This single-substance list is unparalleled in the public health arena since it is based on the most comprehensive data readily available regarding contaminants at hazardous waste sites. A trend analysis was performed, employing HazDat, to identify the substances and mixtures that occur most frequently in three environmental media: water, soil, and air. This analysis revealed that water, soil, and air were contaminated at 1067 (90%), 894 (75%), and 222 (19%) sites, respectively. Within these subsets of sites, 965 (90%) 770 (86%), and 139 (62%), respectively, exhibited two or more contaminants. The results for the highest occurring single substances and binary and trinary combinations are given for the three media in Table 6.3.

Table 6.3. Priority Substances Found in the Environment: Frequencies of Occurrences of Sir Substances and Their Combinations at 1188 Hazardous Waste Sites[a]

No.	% of Sites	Single Substance	% of Sites	Binary Pairs		% of Sites	Trinary (Tertiary) Combinati		
					Water				
1	42.4	TCE	23.5	TCE	Perc	11.6	1,1,1-TCA	TCE	Perc
2	38.4	Lead	18.9	Lead	Chromium	10.6	Benzene	TCE	Perc
3	27.3	Perc	17.9	1,1,1-TCA	TCE	10.6	Lead	Cadmium	Chro
4	25.8	Benzene	17.3	TCE	Lead	9.8	1,1,1-TCA	1,1-DCA	TCE
5	25.8	Chromium	17.2	Lead	Cadmium	9.7	Lead	Arsenic	Cadn
6	23.9	Arsenic	17.0	benzene	TCE	9.7	TCE	Perc	Lead

7	20.8	1,1,1-TCA	16.3	Lead	Arsenic	9.6	Lead	Arsenic	Chro
8	20.3	Toluene	14.5	TCE	Trans-1,2-DCE	9.4	Benzene	TCE	Tolue
9	19.8	Cadmium	13.6	TCE	Toluene	9.3	TCE	Perc	*Trans* DCE
10	17.7	MeCl	13.5	Benzene	Lead	9.1	TCE	Lead	Chro
					Soil				
1	37.7	Lead	20.5	Lead	Chromium	12.0	Lead	Cadmium	Chro
2	25.3	Chromium	17.8	Lead	Arsenic	11.6	Lead	Arsenic	Chro
3	23.0	Arsenic	17.6	Lead	Cadmium	10.9	Lead	Arsenic	Cadn
4	19.7	Cadmium	13.3	Arsenic	Chromium	8.4	Arsenic	Cadmium	Chro
5	19.1	TCE	12.9	Cadmium	Chromium	8.1	Lead	Nickel	Chro
6	16.0	Toluene	11.6	Arsenic	Cadmium	7.9	Lead	Chromium	Zinc
7	14.8	Perc	10.9	TCE	Perc	7.7	Lead	Copper	Zinc
8	13.6	PCBs	10.9	Lead	Zinc	7.6	Toluene	Lead	Chro
9	13.0	Xylenes	10.4	Ethylbenzene	Toluene	7.5	Ethlybenzene	Toluene	Xyle
10	12.8	Ethylbenzene	10.4	Lead	Nickel	7.5	Lead	Nickel	Cadn
					Air				
1	6.0	Benzene	3.5	Benzene	Toluene	2.2	Benzene	TCE	Perc
2	4.7	Toluene	2.7	Benzene	TCE	1.9	Benzene	Ethylbenzene	Tolue
3	3.8	TCE	2.6	Benzene	Perc	1.8	Benzene	Toluene	Perc
4	3.4	Perc	2.6	TCE	Perc	1.8	Benzene	TCE	Tolue
5	3.1	1,1,1-TCA	2.3	Toluene	Perc	1.8	TCE	Toluene	Perc
6	2.6	Lead	2.1	Ethylbenzene	Toluene	1.4	1,1,1-TCA	Toluene	Perc
7	2.5	Ethylbenzene	2.1	TCE	Toluene	1.4	1,1,1-TCA	TCE	Perc
8	2.4	MeCl[a]	1.9	1,1,1-TCA	TCE	1.3	Benzene	1,1,1-TCA	Perc
9	2.4	Xylenes	1.9	Toluene	Xylenes	1.3	Benzene	Toluene	Xyle
10	1.8	Chloroform	1.9	1,1,1-TCA	Perc	1.3	1,1,1-TCA	TCE	Tolue

[a] MeCl = methylene chloride, PCBs = polychlorinated biphenyls, Perc=perchloroethylene (tetrachloroethylene), 1,1,1-TCA = 1,1,1-trichloroethane, TCE = trichloroethylene, *trans*-1,2-DCE = *trans*-1,2-Dichloroethylene.

Completed Exposure Pathways

The mere presence of single chemicals or chemical mixtures in the environment does not indicate that a health threat exists. A four-step process is proposed to identify the chemicals that present an actual risk to human health or wildlife (Fig. 6.3). This process allows chemicals and chemical mixtures of concern at waste sites to be identified in a systematic manner by combining the hazard assessment and exposure assessment information of the chemicals (19). In the first step, an all-inclusive list of chemicals is identified. Second, a list is prepared of those chemicals found off-site in environmental media. This takes into account the uneven movement of the chemicals through various environmental pathways from the source of disposal to other areas in the vicinity of the site. The third step involves compiling a list of chemicals with completed exposure pathways. This is a list of chemicals for which all data are available to establish the link between the source of contamination, the mechanism of transport through environmental media, routes of exposure, and a receptor population. Populations have been exposed to such chemicals in the past, are being exposed at present, or will be exposed in the future unless remedial actions are taken. Finally, the chemicals of actual public health concern are selected by comparing the concentrations found with medium-specific, health-based comparison values (and indicating those chemicals) that exceed the established

safe levels. If the concentration of a chemical in a given medium exceeds the appropriate comparison value, the chemical is retained as a contaminant of concern for further evaluation. The most often used comparison values are: environmental media evaluation guides (EMEGs), reference doses (RfDs), cancer slope factors, health advisories (HAs), water quality criteria (WQCs), and permissible exposure limits (PELs).

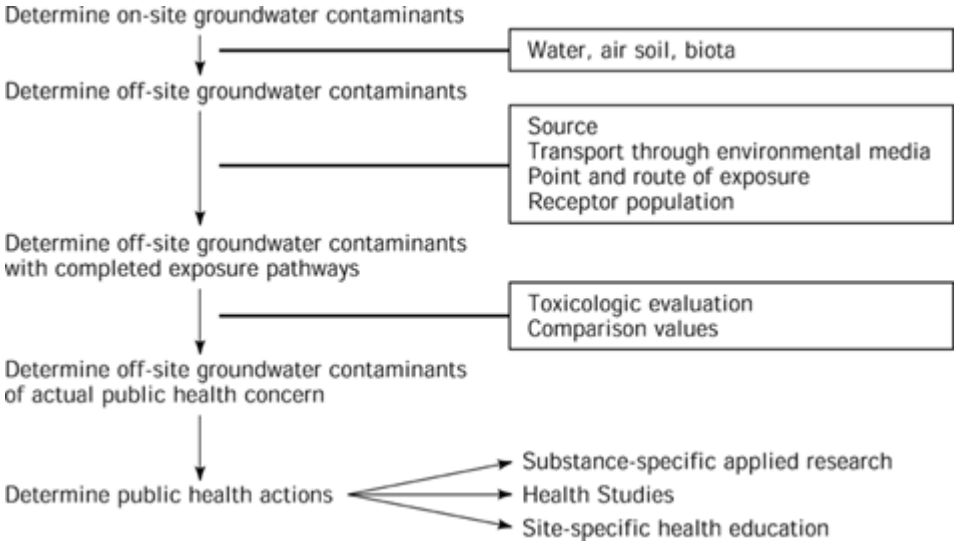

Figure 6.3. The identification of chemicals/chemical mixtures found in completed exposure pathways.

Thus environmental chemical mixtures are characterized through the identification of individual chemical components in completed exposure pathways and joint toxicity assessments are carried out on such mixtures that pose a potential threat to human health and/or the environment.

Interactions

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Approaches for Assessment of Joint Toxic Action

Historical Background

Toxicity assessments for chemical mixtures are based on the following major concepts of "joint action" as defined by Bliss (21).

Similar joint action: The chemicals produce identical effects but have different potencies, so that one component can be substituted for a constant proportion of the other. The toxicity of a mixture is predictable directly from that of the constituents if their relative proportions are known. Thus components of a mixture behave as concentrations or dilutions of one another, differing only in their potencies. This type of joint action is commonly referred to as *dose addition*.

Independent joint action: The chemicals act independently and have different modes of toxic action; that is, the toxicity of the first component may or may not be correlated with the toxicity of a second component. Thus the toxicity of the mixture can be predicted from the dosage–mortality curve for each constituent applied alone and based on the correlation in toxicity between the two chemicals. The observed toxicity can be computed on this basis irrespective of their relative proportions. This type of joint action is commonly referred to as *response addition*.

The mixture of concern, similar mixture, and component-based approaches are used to perform joint

toxicity evaluations of chemical mixtures (22, 23). These three approaches parallel the differences in the categories of chemical mixtures that are encountered in day-to-day life. These categories are based, for the most part, on the nature and number of components in the mixture. The health risk assessors utilize all the plausible approaches that can be applied, compare the results, and decide to use the approach that best suits a given exposure scenario. The results of such multiple analyses may be useful in describing the uncertainty in the joint toxicity assessment. In practice, the use of all three approaches may not be possible for every mixture because of lack of data, time, and other resources.

The "mixture of concern" approach is the most direct and simple method and entails the fewest uncertainties. Hence, it can be called the preferred approach. This approach, however, is the one that can be least frequently applied because it requires that toxicity data be available on the specific mixture of concern and that these data be adequate for deriving an integrated allowable level, such as a minimal risk level (MRL), for the mixture. An MRL is defined as an estimate of daily human exposure to a mixture that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. In real life, mixtures with adequate toxicity data are very few. An MRL was derived for fuel oils, a mixture that may vary to a small degree in its composition, but is reasonably consistent from sample to sample. The study used in the MRL derivation represented the actual controlled exposure to a well-defined mixture (24). Often it is not possible to derive a single assessment value that can be used directly in every exposure scenario because some mixtures, such as gasoline, are generally substantially variable in composition depending on the source of the crude oil or differences in the fractionation process. Furthermore, limitations of the mixture of concern approach include uncertainties regarding the extent to which the mixture from the exposure assessment matches the mixture that is the basis for the MRL, due to changes in its composition with time and distance from the release, and/or differences in the original mixture.

Interactions

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Approaches for Experimental Studies of Mixtures

Many approaches can be used for experimental studies of mixtures, depending on the desired goals (31). Problem definition and the formulation of specific questions are important steps that need to be addressed before selecting a specific approach. If toxic effects and risks posed by a mixture are to be determined, then the toxicologic evaluation of the mixture is carried out by testing the whole mixture through the tier or screening approach. If a causative agent(s) is to be determined to mitigate exposures to the active ingredient of a mixture or to identify the source of pollution, bioassay-directed fractionation is carried out. Finally, if the tools for predictive values are being developed, then toxicologic evaluation of individual components, in various combinations, is carried out to gain toxicologic knowledge about the mechanism and mode of action as well as mechanisms of interactions between the components and within the mixture.

Ideally, all the components of the mixture need to be identified, and their toxicity experimentally determined or obtained from the literature. Several testing protocols can be used to obtain appropriate information, but the actual experimental design depends on the number of chemical components of the mixture and if it is desirable to assess possible existing interactions between chemicals in a mixture. The mixture should be tested both at high effective concentrations and at low realistic concentrations.

Once the data are generated, it is necessary to analyze and interpret them. Many descriptive terms and mathematical, graphical, and statistical models have been used to evaluate the joint toxicity of mixtures. Interactive effects of compounds in mixtures with more than three compounds can be best ascertained with the help of statistical designs such as (fractionated) factorial designs or ray design.

In view of the importance of joint toxicity assessment of human exposure to multiple toxicants, appropriate experimental designs and methods of analysis must be used to support conclusions of additivity, synergy, and antagonism.

Whole Mixtures

Whole mixture studies involve exposing test systems to the intact mixture and conducting exposure–response studies to evaluate the nature and magnitude of the hazard associated with exposure. The design of these studies is usually chosen to reflect the net effect of all compounds in the mixture. This approach is applied to study real-life mixtures, such as tobacco smoke, jet fuels, or specially designed mixtures (88).

JP-5 is U.S. Navy's primary jet fuel. It is made up of a collection of hydrocarbons such as paraffins, monocycloparaffins, bicycloparaffins, olefins, alkylbenzenes, and others. The whole mixture of jet fuel JP-5 was administered to groups of 37–50 female C57BL/6 mice at 0, 150, or 750 mg/m^3 by inhalation continuously for 90 d (89). The endpoints evaluated were clinical signs, hematology, blood chemistry, body weight, and histopathological examination of major tissues. No effect on body weight gain was noted. The only remarkable finding in mice was hepatocellular fatty changes and vacuolization at 150 and 750 mg/m^3. This study was used to derive an MRL value of 3 mg/kg/d (25).

The whole mixture approach is recommended for situations where the mixtures are not well characterized and for mixtures with reasonably stable concentrations. In many cases, a whole mixture approach is advised because it can provide a real-life situation exposure scenario. However, caution should be exercised since in many cases these mixtures do vary in composition from time to time and from one exposure to the next. Without knowledge of the individual effects of each of the components to the response given by the whole mixture, no unique single estimate for risk to exposed populations can be estimated.

Formulated Mixtures

A systemic toxicity testing of n components in a chemical mixture would involve 2^n-1 experiments to address all possible combinations at one dose level for each component. To include several doses, one must use a more focused design such as a full-factorial design, which involves k^n experiments when a range of k doses is applied for each of the n components. In most cases, such mechanistically oriented experiments involve separating the mixture into several components that are studied together in formulated mixtures.

A classical design in the statistical literature for studying toxicologic interaction is a factorial design where each of the chemicals in the mixture is studied at all levels of the other chemicals. Generally, the levels of each factor are evenly spaced so as to cover systematically the dose region of interest. The logic of a factorial design is to support efficiently the estimation of a response surface that includes interaction model parameters (90).

A 5 × 5 × 5 factorial design was utilized to identify nonadditive effects on developmental toxicity in Fischer 344 rats caused by combinations of trichloroethylene (TCE), di(2-ethylhexyl)phthalate (DEHP), and heptachlor (HEPT) (78). The 5 × 5 × 5 full-factorial design was selected to detect binary and tertiary interactions among the chemicals in the mixture. The chemicals were administered by gavage to Fischer 344 rats on gestation days 6–15. Dose levels were 0, 10.1, 32, 101, and 320 mg/kg/d for TCE; 0, 24.7, 78, 247, and 780 mg/kg/d for DEHP; and 0, 0.25, 0.8, 2.5, and 8 mg/kg/d for HEPT. The dams were allowed to deliver, and their pups were weighed and examined postnatally. Of the nine endpoints that were analyzed statistically, six had significant binary interactions. Both synergistic and antagonistic interactions were detected among the three components. Maternal death showed no main effects, but DEHP and HEPT were synergistic. For maternal weight gain on gestation days 6–8, main effects for all three agents were observed, as well as TCE–HEPT synergism and DEHP–HEPT antagonism. Maternal weight gain on gestational days 6–20, adjusted for litter weight, showed main effects for TCE and HEPT, but no interactions. Main effects for all three chemicals were evident for full-litter resorptions and prenatal loss. For full-litter

loss, the TCE–HEPT and DEHP–HEPT interactions were antagonistic. Postnatal loss showed DEHP and HEPT main effects but no interactions. Analysis of pup weights on day 1 revealed TCE and DEHP main effects and DEHP–HEPT antagonism; on day 6, DEHP and HEPT main effects, DEHP–HEPT antagonism, and TCE–DEHP synergism were evident. Microphthalmia and anophthalmia incidences revealed TCE and DEHP main effects but no interactions. This extensive examination of a full-factorial design elucidates the complexities of studying and interpreting mixture toxicity. Although the Narotsky study illustrates the utility of full-factorial design to investigate binary and tertiary interaction, the study also used the large number of 2000 pregnant rats experimentally.

The feasibility of carrying a full-factorial design with many chemicals rapidly decreases (90). To overcome the usually costly full-factorial designs, statistically less-than-full designs are used. These designs are referred to as fractionated factorial designs. A fractionated two-level factorial study was designed for a combination of nine chemicals in a subacute rat study (91). In the study, an efficient fractionated design for 16 different groups was used as a subset of the full design, which would have required 2^9 (512) experiments. The combination experiments (satellite part) were composed of a fraction of 1/32 subsets (of the full 512 experiments). The study was intended to find out whether simultaneous administration of nine chemicals at a concentration equal to the "no-observed-adverse-effect level" for each of the chemicals would result in a NOAEL for the combination. A 4-wk oral/inhalation study in male Wistar rats was performed in which the toxicity (clinical chemistry, hematology, biochemistry, and pathology) of combinations of nine chemicals was examined. The study consisted of 20 groups, 4 groups in the main part (n = 8) and 16 groups in the satellite part (n = 5). In the main study, the rats were simultaneously exposed to various combinations of all nine chemicals (dichloromethane, formaldehyde, aspirin, di-(2-ethylhexyl)phthalate, cadmium chloride, stannous chloride, butyl hydroxyanisol, loperamide, and spermine) at concentrations equal to "minimum-observed adverse-effect level" (MOAEL), NOAEL, or $\frac{1}{3}$NOAEL. In the satellite study, the rats were simultaneously exposed to combinations of maximally nine factors (= 9 chemicals) in 16 experimental groups (1/32 fraction of a complete study). In the main part, many effects on hematology and clinical chemistry were observed at the MOAEL. In addition, rats of the MOAEL group showed hyperplasia of the transitional epithelium and/or squamous metaplasia of the respiratory epithelium in the nose. Only very few adverse effects were observed in the NOAEL group. For most of the endpoints chosen, the factorial design revealed main effects of the individual compounds and interactions (cases of nonadditivity) between the compounds.

Other fractionated designs include ray designs in which mixtures of chemicals under study are evaluated along rays of fixed ratios. In a ray design, for example, for a mixture of three chemicals with fixed ratios, represented by chemicals A, B, and C, a 1:0:0 ratio represents a ray of chemical A alone, while a 1:1:1 ratio represents a ray of equal levels of the three chemicals. A ray design for a small number of chemicals and many mixture rays can support the estimation of a response surface. However, the advantage of a ray design is that it can also be used with a mixture of many chemicals and a few mixture rays (90). The ray design was employed to estimate a response surface of developmental toxicity in rats using data from an earlier study in which a full-factorial design was used (78, 90). Similar to the ray designs, other fractional procedures such as the central composite and Box–Behnken designs use specific regions of the dose–response surface to optimize combinational experimental procedures.

Mathematical/Statistical Procedures

Once the data are generated, they need to be analyzed and interpreted. Many descriptive terms and mathematical, graphical, and statistical models have been used to evaluate the joint toxicity of mixtures. In general terms, the purpose of these models is to help interpret data for the entire range of the dose–response surface based on a mathematical/statistical description of the interaction criteria. Thus validated models can also be used to extrapolate from one region to other regions of the dose–response space. The models can also be used for the development of efficient experimental design by considering the cycle of model-experiment procedures to optimize the use of resources and time. The following discussions explain three mathematical and statistical procedures frequently used by scientists interested in combinational toxicology.

Isobolographic Methods An isobole is a contour line that represents equal effects of two agents or more in a mixture. Thus, when the joint effects of various dosages of two agents are plotted, each point of equal response (e.g., ED_{50}, percent lethality, ... , etc.) corresponding to varying doses of both chemicals form the isobole. Isoboles can be used to characterize the nature of the toxicologic interaction. This is done by comparing the isoboles to the line of additivity as shown in Fig. 6.9. The graphical representation of the interactions criteria can also be depicted mathematically as follows: For additivity:

$$\frac{A_c}{A_e} + \frac{B_c}{B_e} + \cdots + \frac{N_c}{N_e} = 1 \tag{7}$$

For synergism:

[TEXnical Error] (8)

For antagonism:

[TEXnical Error] (9)

where A_e, B_e, and N_e are the doses of chemical components A, B, and N that produce the measured response of each chemical as if it were the only component of the mixture. A_c, B_c, and N_c are the doses of each chemical that produce a similar response when the chemicals are all combined together.

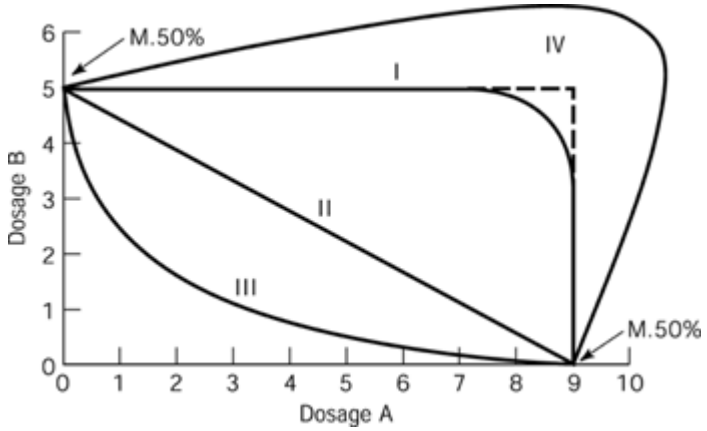

Figure 6.9. Four types of isoboles for a binary mixture of chemical A and B. Curve I describes no-interaction effect, curve II is the line of additivity, and curves III and IV depict synergism and antagonism effects, respectively. M.50% is the dose at which 50% of the tested animals died.

The preceding equations represent the criteria for assessing interaction modes among the different agents in a mixture (92). However, for these equations to be used, individual chemicals in the mixture should have a nonzero response at the given doses (i.e., $A_e \neq 0$, $B_e \neq 0$, ... , $N_e \neq 0$). The major disadvantage of the isobolographic methods is the requirement for a large number of experiments to produce the individual isoboles. For example, one can start with doses of chemicals A and B for a binary mixture, if the response is not equal to the one chosen for the isobole, then doses of A and/or B have to change up or down until the fixed response is obtained. This highly iterative procedure is very resources extensive. With a conventional experimental approach, the isobolographic method is tedious and requires extremely large data sets. For instance, 2000–3000 animals were used to generate an isobole to study the interaction between ethanol and chloral

hydrate effect on the righting reflex of mice (93). Furthermore, the isobolographic methods can only be applied to chemicals that share similar mechanisms and induce the same endpoint of toxicity.

For chemicals that do not share similar mechanisms, a more general mathematical procedure than isobolographic methods is employed. One such procedure is the median-effect principle (MEP). This method is based on the assumption that dose–response relationships of many physical, chemical, and biological processes, specifically related to ligand–enzyme receptor-site interactions, can be described by a general formula:

$$\frac{f_a}{f_u} = \left(\frac{D}{D_m}\right)^h \tag{10}$$

where f_a and f_u are the fractions of the system affected and unaffected, respectively, by the dose (D). D_m is the dose required to produce the median effect (similar to the more familiar ED_{50}), and h is a Hill-type coefficient signifying the sigmoidicity of the dose–response curve. Expansions of this equation to include criteria for the different modes of toxicologic interactions have been published (94).

The MEP method was used for the analyzing of the interactions effect of combined administration of immunosuppressive drugs with cyclosporine (95). Cyclosporine is widely used in organ transplantation. However, its renal, hepatic, and nervous system toxicities limit its therapeutic potential. This problem was addressed using MEP to find other immunosuppressive drugs that can interact synergistically with lower (non-toxic) concentrations of cyclosporine.

Response Surface Methodology The response surface methodology (RSM) allows the study of the mathematical relationship (model) that exists between the chemicals in the mixture and the endpoint of toxicity. RSM was successfully applied to study the interaction between trichloroethylene, carbon tetrachloride, and chloroform using the levels of plasma enzyme activities of ALT, AST, and SDH as endpoints of toxicity in rats (96). This application of RSM showed that carbon tetrachloride/chloroform and carbon tetrachloride/trichloroethylene both displayed a synergistic response for each plasma enzyme activity.

The application of the method relies on statistical regression methods efficiently to design experiments that yield adequate and reliable measurements of the response of interest. The mathematical model is then developed that best fits the collected data. This is accomplished by conducting appropriate statistical tests of hypotheses regarding the model parameters.

Isobolographic, median-effect principle, and response surface methods can quantitatively characterize interaction among components of a chemical mixture. However, these methods cannot provide mechanistic information for the presence of interactions because they are not based on biological mechanisms. This shortcoming can be avoided by employing more mechanistically oriented models such as physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models.

Physiologically Based Pharmacokinetic/Pharmacodynamic Models PBPK/PD models mathematically describe the processes of absorption, distribution, storage, metabolism, and excretion; the pharmacodynamic aspects cover the toxic response of the chemical at the target tissue. Fig. 6.10 is a schematic of a compartmental PBPK model.

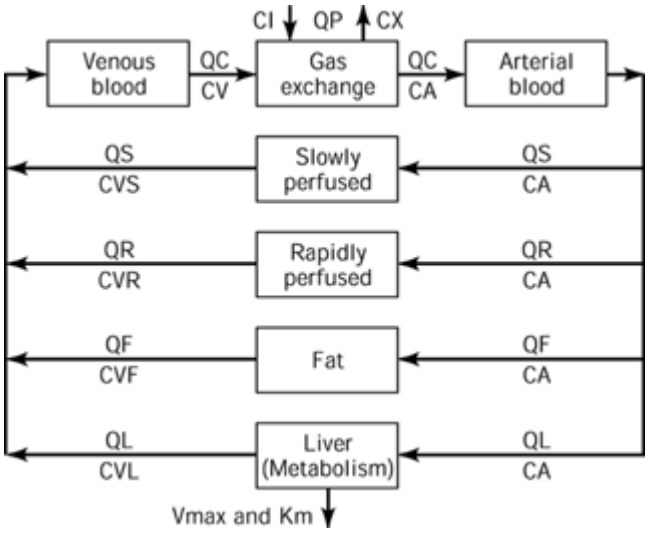

Figure 6.10. Compartments of a typical inhalation exposure PBPK model. Each compartment is characterized by physiological and biochemical parameters. In this specific example, the chemical under study is highly lipophilic, which causes its disposition to be blood flow limited. Thus tissues are selected based on their blood perfusion rates (slowly and rapidly perfused), the chemical's affinity to the tissues (fat), and metabolism sites (liver). The Qs are blood flows into each compartment. CVS, CVR, CVF and CVL, are the venous blood concentration of the chemical leaving the slowly perfused, rapidly perfused, fat, and liver compartments, respectively. CI is the inhaled concentration, CX is the exhaled concentration, and CA is the arterial concentration of the chemical in question.

Pharmacokinetic interaction mechanics can be introduced into PBPK models and verified experimentally. A PBPK model was used to quantitatively distinguish between different types of enzyme inhibition (competitive, uncompetitive, and noncompetitive) (97). A validated PBPK model can also be used to investigate the interaction presence at varying levels of exposure to the different components in a mixture. The PBPK model for the interaction between trichloroethylene and 1,1-dichloroethylene was expanded to include description of the chemicals interactions at the available enzyme sites (98). The investigators' efforts showed the presence of an interaction threshold, absence of interaction, at levels of 100 ppm or less for both chemicals. Expansion of PBPK interaction modeling to investigate a ternary mixture of alkyl benzene in rats and humans was accomplished (99). Few examples in the literature illustrate the application of pharmacodynamic models for analyzing toxicologic interactions. One study was able to investigate quantitatively the interaction mechanism between Kepone and carbon tetrachloride by the use of PBPD models that described the rates of injury and death of hepatocytes as they are affected by this highly synergistic interaction (100). The PBPK/PD model was coupled with Monte Carlo simulations to estimate mortality results for any given combination of the chemicals. To predict the response surface, mortality results are applied to the following logistic regression equation:

$$y = \beta_0 + \beta_1(kep - \overline{\text{kep}}) + \beta_2(CCl_4 - \overline{\text{CCl}_4}) + \beta_3(kep - \overline{\text{kep}})(CCl_4 - \overline{\text{CCl}_4}) \qquad (11)$$

where b_0 is the background rate of lethality rate, b_1 is the slope of the dose–response relationship for Kepone (kep) alone, b_2 is the slope of the dose–response relationship for carbon tetrachloride (CCl_4) alone, and b_3 is the interaction parameter between Kepone and carbon tetrachloride. The overlined kep and CCl_4 are the average estimates of the range of simulated or applied doses of each chemical. The outcome of Eq. (11) can then be introduced into the following equation to calculate the lethality percentage:

$$\% \text{ lethality} = \left(\frac{e^{y}}{e^{y}+1}\right) \times 100 \qquad (12)$$

Subsequently, the model simulations are compared to the experimentally determined lethalities to estimate the values for all the bs; specifically, b_3 was significantly different from zero at a value of 0.01 for the interaction between carbon tetrachloride and Kepone. This positive value is indicative of a synergistic interaction. The regression equations with the model-estimated parameters were then used to derive the isoboles for the interaction between Kepone and carbon tetrachloride at different responses (Fig. 6.11) (101).

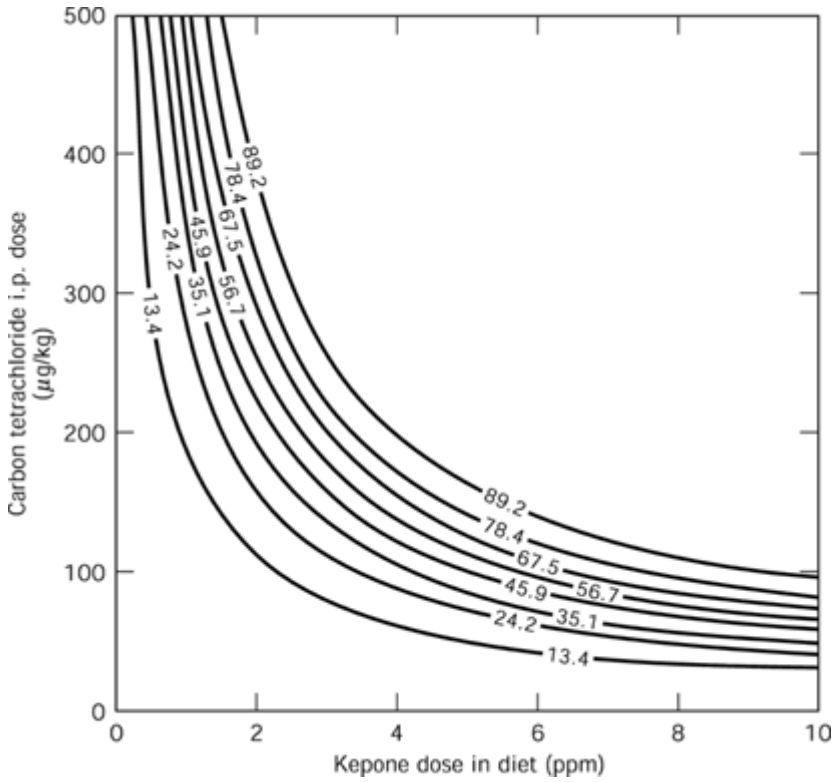

Figure 6.11. An illustration of the contour lines (isoboles) of percent lethality of rats exposed to varying concentrations of Kepone in diet (*x* axis) and intraperitoneal (IP) injections of $CC1_4$ (*y* axis). The lines were generated by PBPK/PD model simulations and a regression equation.

In addition to the complexity of the problem of aggregate toxicity, several problems impair the proper selection, implementation, and application of these approaches to risk assessment. Because of this, for example, the occupational hygienist or toxicologist shopping for an appropriate experimental approach is frequently confounded by the lack of direct comparisons between approaches. Fundamentally, the characterization of chemical interactions consists of the rejection or acceptance of a single model or the selection of a particular model from among competing models. These decisions are based on statistical and/or graphical information involving regression equations, each with underlying implicit and explicit mathematical, statistical, and data structure assumptions (102). It is no easy task to distinguish clearly the intrinsic differences, distinctions, and limitations of these models when applied to characterizing the potential interactive toxicities in the workplace. Adverse health effects are diverse and include parametric and nonparametric responses for cancers, and signs and symptoms of organ dysfunction. As such, the choice of model, criteria for goodness of fit, data transformation, and method of parameter estimation are important to support a mathematically and biologically sound decision.

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Future Directions and Conclusions
Given the different types of mixtures for which joint toxicity assessment are performed as well as the many factors that effect the overall toxicity of such mixtures, no single approach is suitable to conduct such assessment for every exposure scenario. However, developing joint toxicity assessment procedures and models is a complex data-intensive task because paucity of data is frequently the bottleneck. For these reasons it is imperative that research to develop appropriate methods continue.

Data gaps can be filled through experimental research to generate key data needed to elucidate toxicologic mechanisms and decipher the mechanisms of interaction so as to incorporate the principles of molecular toxicology in predictable mechanistic models. With reference to chemical mixtures, from the outset, such research should identify elements that could contribute to the joint toxic action of chemicals such as (1) determination of internal doses through toxicokinetics (absorption, distribution, metabolism, receptor binding, and elimination), (2) evaluation of mechanisms of interactions and their significance, (3) identification of multiple target organs that are affected, and (4) assessment of biomarkers, adducts, and metabolites that can be used to biomonitor exposures.

This type of integrated systematic research is possible only when the laboratory investigators, the model developers, and the health assessors work in a collaborative relationship to ensure parallel research in various areas of this multidiscipline research. Special attention is needed to ensure that the animals or test system, doses and dosing regimen, and other variables of the experimental procedure have been selected based on existing data and efficient experimental design to address existing data gaps in the interlinked areas of research. This type of balanced and pragmatic approach has been recommended to meet short-term and long-term needs for screening, prioritizing, and predicting the health effects of chemical mixtures by international panels of scientists educators and administrators (103, 104).

The limitations of available resources make it unlikely that experimental toxicology will yield direct information about all the possible mixtures to which humans or other species may be exposed. Indeed, the information needed to assess hazards from individual chemical exposures may never be obtained. In the current environment of austere resource allocations and heightened awareness of animal use in toxicologic research, more pragmatic experimental testing methods must be used without compromising the sensitivity or specificity obtained through classical methods. Efforts should take into consideration all options available, including recently developed innovative techniques. Several innovative approaches can be implemented for the assessment of joint toxic action of chemicals. To this extent significant advances have been made in alternative toxicologic testing methods, such as *in vitro* testing, PBPK modeling, and biologically based dose–response modeling. Also, correlations have been established between *in vitro* and *in vivo* potencies of chemicals. Hence, several *in vitro* assays validated with *in vivo* studies are available to conduct toxicant interaction studies. Even though most of these tests are still in various investigatory phases, they have been studied enough to obtain initial estimates of dose–response relationships for mixtures of chemicals. Using these types of assays, for specific endpoints, it may be feasible to develop a screen of tests to study interactions. The underlying assumption in such screens is that if biologic activity in these tests is well correlated with *in vivo* toxic potency, interaction coefficients measured using such screening tests may be similarly correlated. The plausibility of such theoretical assumptions must be further established by highly focused *in vivo* studies.

An example of such studies is collaborative research between ATSDR and TNO Nutrition and Food Research Institute to evaluate the role of chemical interactions in the expression of toxicity from low-level exposure to combinations of chemicals (105). The goal of this project was to compare the

estimated toxicity with experimentally determined toxicity of the mixtures so as to determine the accuracy and the predictive capability of the assessment method. The procedure used for the joint toxicity estimates was adopted from the detailed published WOE method (74). Briefly, in the first step, qualitative weight-of-evidence statements for binary pairs of chemicals were prepared for various combinations of chemicals such as (1) the effect of butylhydroxyanisole (BHA) on di(2-ethylhexyl)phthalate (DEHP), (2) the effect of stannous chloride ($SnCl_2$) on cadmium chloride ($CdCl_2$), and (3) the effect of cadmium chloride ($CdCl_2$) on loperamide (Lop). In the second step, these qualitative evaluations were converted to numerical scores, which were then combined to obtain the estimate of toxicity of the four-component mixture. The estimations were made through integration of the component chemical dose–response assessment with computative algorithms that incorporate potential chemical interactions. The estimates thus obtained were compared with results from experimental animal studies using the dose addition, the response addition, and the WOE models. These comparisons indicate that the WOE approach can be used to estimate qualitatively the joint toxicity of these mixtures. Additionally, the results from the WOE method provided the best fit to the experimental results of the mixture of similarly acting nephrotoxicants—namely, trichloroethylene, tetrachloroethylene, hexachloro-1,3-butadiene (HCBD), and 1,1,2-trichloro-3,3,3-trifloropropene (TCTFP). However, this was not true for the mixture of dissimilarly acting nephrotoxicants—namely, mercuric chloride, lysinolalanine, *d*-limonene, and HCBD. This could have been anticipated because the WOE method is based on the concept of dose additivity, which in turn is practiced only when the mechanisms are similar. Thus these results indicated that the WOE-approach evaluations, based on consideration of common mechanisms, can lead to better estimates of joint toxic action than the default assumption of dose additivity. These results also confirmed earlier suggestions (74) that the WOE evaluations should be effect and target-organ specific because none of the models tested could approximate the observed responses in organs other than the target organs. Thus, to verify the role of chemical interactions and the overall toxicity of a mixture, these kinds of specially designed focused experimental studies need to be conducted to help advance the methods for the toxicity assessments of chemical mixtures.

Screening a selection of mixtures in *in vitro* assays can identify a broal range of interaction relationships that could be beneficial to the ultimate goal of predicting interactions. Consequently, *in vivo* measurements could be made to confirm the previously determined *in vitro* relationships covering comparable concentrations. The linkage between the *in vitro* and *in vivo* assay correlations needs to be strengthened by testing chemical mixtures for various effects such as nephrotoxicity, neurotoxicity, and hepatotoxicity in target-organ-specific assays.

An experimental parallelogram design has been used to conduct such carefully planned and goal-oriented research (Fig. 6.12). This design allows multispecies comparisons as well as extrapolation to humans. As a first step, *in vitro* rodent species bioassays (rats, mice, or hamsters) are conducted to test the toxic effects of chemicals. Results from such studies are validated in *in vivo* rodent studies. These studies are then followed with *in vitro* studies with human systems (e.g., human cell lines) to evaluate the findings of the animal studies. Thus the *in vitro* rodent studies are used to confirm the initial *in vivo* rodent findings, and these results are subsequently confirmed *in vitro* in human systems. The information thus generated is used to extrapolate the potential effects of the chemicals to humans. With this design, humans and rats have been shown to have comparable metabolism of 1,3-butadiene which differed from metabolism in mice (106). These comparative data suggested that because the concentration of butadiene epoxide, the active moiety, will be low in humans, the human cancer risk following exposure to butadiene will be similarly low. However, if this assessment was based only on mouse data, the risk would have been incorrectly estimated. This experimental design can be employed for the study of toxicity of chemical mixtures. Eventually, the transformation of *in vitro* findings to *in vivo* observations can be met using computational tools such as PBPK modeling and biologically based dose–response modeling.

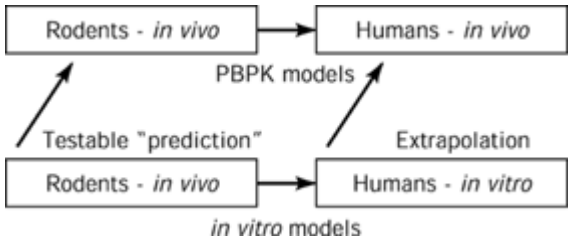

Figure 6.12. *In vitro–in vivo* extrapolation between animals and humans.

In general, computational methodologies provide insights and focus for strategic research. Such methods have to be used to formulate specific hypotheses, based on available data. Then appropriate hypotheses that support public health assessments have to be subjected to experimental testing through collaborative research with partners using *in vitro* or limited *in vivo* studies. The results of such investigations may lead to further testing, revisions in hypotheses, and/or the formulation of new hypotheses. When verified, such hypotheses would allow the development of generalizable rules that can be applied to mixtures of interest that have not been subjected to testing, cannot be subjected to testing, or cannot be used until testing data become available. ATSDR has established a computational toxicology laboratory with capabilities to conduct PBPK extrapolations and quantitative structure–activity relationship (QSAR) studies that allow extrapolations of toxicity within and across chemical classes. Such studies are being supported through collaboration among governmental bodies, the private sector, and academic institutions.

Through cooperative agreements with research institutions, alternative mixtures toxicity testing methods are being developed. Cell culture systems and *in vivo* animal studies are being employed to generate mechanistic and pharmacokinetic information. Following is a brief description of some studies that are ongoing:

1. Human keratinocytes have been used to test the departure from additivity in chemical mixtures of frequently co-occurring metals using cytotoxicity as an index (107). When individual dose–response curves of arsenic, cadmium, chromium, and lead were used in conjunction with the mixtures of these four metals at seven different concentrations, six of these concentrations were found to follow additivity while one of these concentrations showed a highly significant antagonistic effect. In a series of *in vivo* animal studies, the role of individual chemicals in producing liver foci by a mixture containing arsenic, 1,2-dichloroethane, trichloroethylene, and vinyl chloride was studied. Preliminary results show that arsenic is the main component responsible for the antagonistic interactions observed for this mixture.
2. Cultured Rhesus monkey renal cortical cells have been used to investigate the interactions between cadmium and mercury (108). The release of lactate dehydrogenase (LDH) was measured for selected concentrations of 0–50 mM $HgCl_2$, $CdCl_2$, or binary mixtures of both metals in varying ratios of 20:1, 10:1, 5:1, or 2:1. To characterize the interaction, the data were analyzed graphically and mathematically using statistical isobologram, linear, and nonlinear models. The isobolographic and response surface analysis suggested antagonism, while nonlinear models concluded no interaction. Most models supported an overall synergistic interaction when data from all mixing ratios were modeled together. However, individual data set analyses revealed that as the ratio decreased from 20:1 to 2:1, the nature of the interaction gradually changed from synergism to additivity. The relationship was consistent among all the models used, but was most clearly revealed by the linear models.
3. With a goal to develop a PBPK/PD model to integrate tissue injury and repair, an *in vivo* study has been designed to evaluate the toxicologic interactions between trichloroethylene, thioacetamide, allyl alcohol, and chloroform. Liver injury was measured by monitoring plasma enzymes, ALT and SDH, and histopathology. The tissue generation was measured by [H^3]-thymidine incorporation into hepatic nuclear DNA. Preliminary results indicate that the mixture of four hepatotoxicants caused

additive toxicity. The model will be used to quantify liver injury, repair, and the overall joint toxic action as a function of mixture dose.

4. Polycyclic aromatic hydrocarbons (PAHs) and halogenated aromatic hydrocarbons (HAHs) were tested utilizing a battery of cell culture assays (genotoxicity, immunotoxicity, etc.) to investigate the toxicity of several classes of environmentally important chemical mixtures. Results from a genotoxicity assay using binary and tertiary mixtures of PAHs revealed a dose–response gradient with B(*a*)P–chrysene mixture, suggesting an interaction. Similar studies with complex mixtures and isolated fractions indicate that the B(*a*)P content of the PAH mixture cannot be used to predict the genotoxicity. The results from assays of an extract of a manufactured gas plant residue separated into four fractions revealed that genotoxicity varied from fraction to fraction (109). Analyses are being performed to determine the role of high-molecular-weight PAHs or possibly alkyl-substituted PAHs.

The above examples of collaborative research investigations were based on HazDat analyses and observations that several simple mixtures could be identified that would lend themselves to the design of experiments and a systematic way to obtain data. They follow the general hypothesis that research conducted on a small group of chemicals or simple chemical mixtures could benefit communities being exposed to multiple chemicals, such as those living in the vicinity of hazardous waste sites. Additionally, the insights attained from such experimental and computational studies develop professional judgment as a substitute until generalizable rules for joint toxic actions are formulated.

Parallel progress in experimentation, quantitative modeling, and assessment are important to devising generalizable rules through in-depth analysis of data (Fig. 6.13). In the meantime, continued focused experimental/computational research is needed for conducting joint toxicity assessments to ensure adequate public health protection. This assessment process will benefit by using a team approach wherein experimental scientists, model developers, and health risk assessors work to develop consensus on those issues key to protecting the public's health.

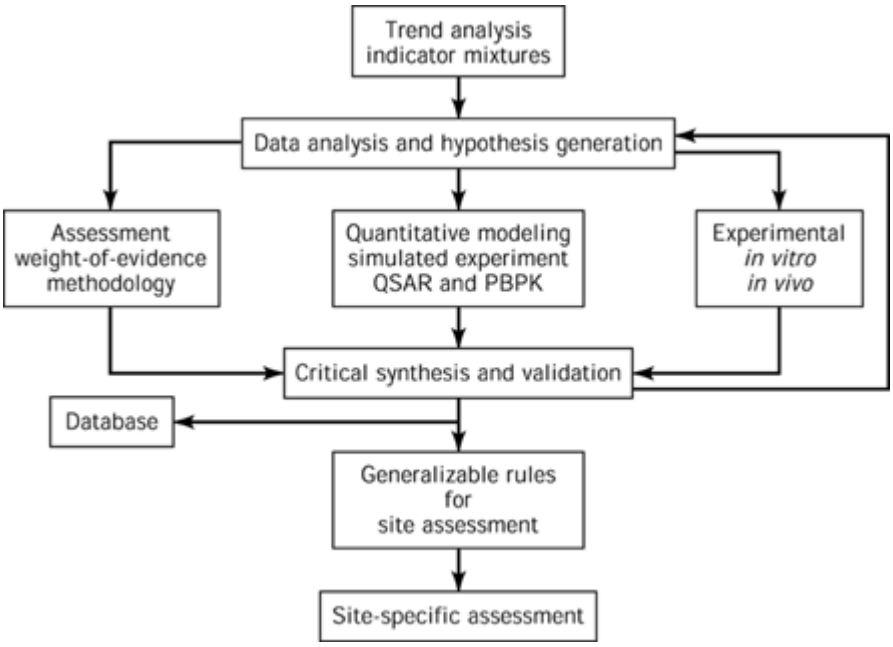

Figure 6.13. A strategic mixtures research program that allows parallel progress between experimental assessment, and computational techniques.

In conclusion, the carcinogenic and noncarcinogenic toxicities associated with chemicals found in the environment do not necessarily translate into actual adverse human health or environmental

effects. One must ascertain the extent of actual exposure experienced by populations at risk and the susceptibility of members of such populations (13). Thus the risk-assessment process must be considered as one component of risk analysis, which also includes biomedical judgment and peer review as recommended by the NRC (110) as well as risk communication and risk management (111). Fig. 6.14 is an illustration of the multiple components of the overall decision-making process of risk analysis. Importantly, this process should reflect a rigorous identification of attendant uncertainties associated with the components of risk assessment as part of risk analysis (112). This procedure would allow the types and the extent of uncertainties to be highlighted, thus promoting the appropriate interpretation of numerical risk estimates in decision making. Although the utility of numerical risk estimates in risk analysis is recognized, these estimates should be considered in the context of the variables and assumptions involved in their derivation and in the broader context of biomedical opinion, host factors, and actual exposure conditions. Thus the actual parameters of environmental exposures must be given careful consideration in evaluating the assumptions and variables relating to both toxicity and exposure.

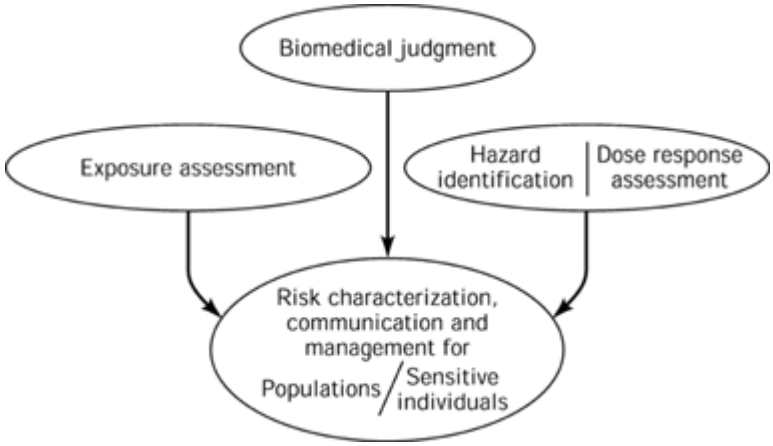

Figure 6.14. The elements of risk analysis with emphasis on biomedical judgment, including molecular epidemiology.

Lack of knowledge and understanding of data make it virtually impossible at this time to determine whether current approaches to protecting public health from the adverse effects of chemical mixtures are adequate. However, from the perspective of protecting public health a high priority needs to be given to identify and conduct research on specific mixtures. Through advances in focused experimental and computational methods it is possible to develop simulation programs that allow modeling of chemical mixtures behavior in biological systems and predict their toxicologic response. Hence, it is important to continue developing suitable new methods and improving old ones for mixture-related research. These types of efforts will help us understand the characteristics of hazard/risk (113) and allow us better to identify, quantify, and express uncertainties in mixture-related risk assessments (103).

Interactions
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Interactions

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Ecogenetics: The Study of Gene–Environment Interactions
Daniel W. Nebert, Amy L. Roe, Ph.D

1 Introduction

What is "an environmental disease?" Why are some individuals and some families affected more easily than others? Indeed, even within families, why are some members affected whereas others are not? When taking the same dose of a prescribed medication, why do some patients—but not others—experience side effects? Why do only 7 out of every 100 cigarette smokers die of lung cancer? The answer to each of these questions involves *interindividual genetic variation* and *the environment*.

We begin this chapter with brief descriptions of the reasons for environmental illnesses. Next, genetic terminology and a definition of "susceptibility genes" are covered—followed by our current understanding of the drug-metabolizing enzymes (DMEs) and the receptors that regulate DME genes. Subsequently, we provide a number of examples and brief summaries of the present-day knowledge of many of these polymorphisms. Last, we speculate as to why these human polymorphisms might exist in the first place. Many of the references cited include reviews in which the reader will find numerous additional studies cited and details described.

Ecogenetics: The Study of Gene–Environment Interactions
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2 Exposure and Genetic Predisposition

What is "an environmental disease?" Table 7.1 is not intended to be inclusive, but lists more than a dozen examples of environmentally caused diseases. As will become clear, the two most important determinants in one's risk of developing an environmental disease are (*1*) exposure and (*2*) one's unique genetic makeup.

Table 7.1. Examples of Environmentally Caused Diseases

Bronchogenic carcinoma in cigarette smokers
Chronic bronchitis, emphysema, and heavy wrinkles in cigarette smokers
Liver fibrosis and cirrhosis in alcoholics
Drug-related lupus syndrome in patients taking procainamide
Dangerously lowered blood pressure in patients taking debrisoquine or sparteine
Lung cancer in people exposed to radon
Malignant melanoma, other skin cancers, heat stroke, sunburn in persons exposed to excessive sunlight
Lung cancer in uranium mine workers
Chloracne, porphyria cutanea tarda in workers exposed to dioxin and other halogenated hydrocarbons
Ataxia, lowered mentality in persons exposed to high levels of lead
Increased risk of chronic myelogenous leukemia in workers exposed to benzene, and of urinary bladder cancer in chemical dye workers
Asthma in children and adults exposed to indoor or outdoor air pollution

The first six examples in Table 7.1 represent large doses of an environmental agent that can be quite easily documented by a good medical history [e.g., pack-years of smoking (number of cigarette packs smoked per year multiplied by number of years that the person has smoked), quantity of alcohol consumed, length of time and the dose of drug taken, length of time living in a radon-exposed house]. The next three examples represent exposures to sun and the outdoors and to chemicals in the workplace; quantitation in these cases is generally more difficult than the first six examples (e.g., "What is the actual number of days worked? Was the exposure identical for all these days? Are we dealing with a single chemical or a mixture of multiple chemicals?"). The last four examples in Table 7.1 depict even fuzzier cases in which a cause–effect correlation can be inferred only by an epidemiological study of large human populations, but such a correlation in a particular individual is often difficult to prove—medically, or in a court of law (e.g., ataxia might occur in one patient whose blood Pb^{2+} level is more than 3 times lower than that of another who is asymptomatic. "Is the malignancy diagnosed in a worker caused by his/her occupational exposure, or was he/she going to develop it, anyway?" "Is this particular bout of asthma caused by urban pollution, or is it caused by house dust or cockroach dander in the home?").

Not listed in Table 7.1 are the even more ambiguous situations. For example, how often can an environmental disease be caused by minuscule and intermittent exposures—over decades or a lifetime—to "everyday" chemicals (e.g., eating fruit that had been treated with a fungicide, playing on a golf course that had been sprayed with insecticides or herbicides, ingesting canned food having "detectable" amounts of an endocrine disruptor). Toxicity or cancer occurring in individuals with these kinds of exposure are the most problematic for scientists to quantitate and interpret.

In addition to the *exposure* component, why is it increasingly difficult for a scientist or clinician to be certain of the cause of environmental disease, as one moves down the list in Table 7.1? The answer to this question resides in our *genes*. It is now clear that, just as we each have a distinctive set of fingerprints, each of us has a novel combination of genes that enable us to be resistant or sensitive to various types of chemical and physical insults. This leads to our own unique underlying genetic predisposition to toxicity or cancer. This field of study was termed *ecogenetics* by Brewer in the mid-1970s, and a subset of this field (interaction between genes and response to drugs) had been named *pharmacogenetics* in 1959 by Vogel (1–4). Before examining "gene–environment interactions" in more detail, we will review briefly the essentials of genetics and the fundamentals of exposure and risk estimation.

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3 Introduction to Genetics
Healthy humans have 23 pairs of chromosomes, 22 autosomal pairs plus the sex chromosomal pair (XX or XY). A gene denotes a location (stretch of DNA) on each of a chromosome pair that encodes a gene product (enzyme, or other protein). A *locus* indicates the location of a stretch of DNA on each of a pair of chromosomes that need not necessarily code for a gene product. *Diploid* refers to a eukaryote having chromosome pairs; *haploid* refers to one active chromosome of each pair (e.g., as found in the sperm and egg). Each gene is made up of two *alleles*, one from the father and one from the mother; the combination of these two alleles, as well as one's genetic makeup, is called the *genotype*. An allele can transmit a dominantly inherited trait (e.g., pigmented skin) or a recessive trait (e.g., blue eyes). Another term for "trait" is *phenotype*. *Homozygotes* are individuals having two

identical alleles; *heterozygotes* are individuals having two different alleles.

3.1 Simple Mendelian Traits

Consider a *single-gene trait* such as the alleles *colored* (*C*) and *noncolored* (*c*) in Mendel's original studies of the garden pea. Allele *C* (red phenotype) is dominant to allele *c* (white phenotype). The Hardy–Weinberg distribution [$(p + q)^2 = p^2 + 2pq + q^2$] states that, if the *allelic frequencies* of *C* (= *p*) and *c* (= *q*) in the population are 0.4 and 0.6, respectively, this would mean that 36% of the population would have the white trait, that is, homozygous for the *cc* genotype (Fig. 7.1). Crossing two *Cc* heterozygotes (which have the red phenotype) would give a 1 : 2 : 1 ratio of the *CC* : *Cc* : *cc* genotypes and a 3 : 1 ratio of the red and white *phenotypes*.

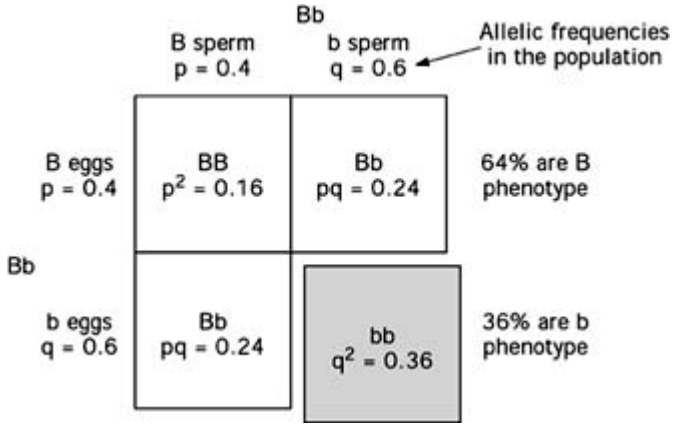

Figure 7.1. Diagram of the Hardy–Weinberg distribution ($p^2 + 2pq + q^2$), showing genotype frequency as a function of allelic frequency.

3.2 Polygenic Traits

A phenotype that is dependent on two or more genes is called *polygenic*, *multifactorial*, or a *multiplex phenotype* (e.g., blood pressure, height, weight). The 1 : 2 : 1 ratio (Fig. 7.2) is the most complicated that a (Mendelian) single-gene, two-allele trait can exhibit. If one considers a trait expressed by two alleles from each of two genes, or from each of three genes (Fig. 7.2), we can readily appreciate how quickly and complex the genotypes and corresponding phenotypes will become. Obviously, the outliers, or individuals at the extreme ends of the spectrum of phenotype, are the most valuable patients to scientists for dissecting the genes involved in producing the phenotype. Virtually 100% of all diseases, including environmental diseases, should be regarded as multiplex phenotypes—usually caused by two or more major genes and perhaps several dozen modifier genes. For example, an abnormal *BRCA1* "tumor suppressor gene" can be regarded as a *major* gene for increasing risk of breast cancer, in probably at least 5% of women, and being homozygous for *NAT2* slow acetylator alleles can be regarded as a *modifier* for enhancing one's risk of breast cancer (see discussion below).

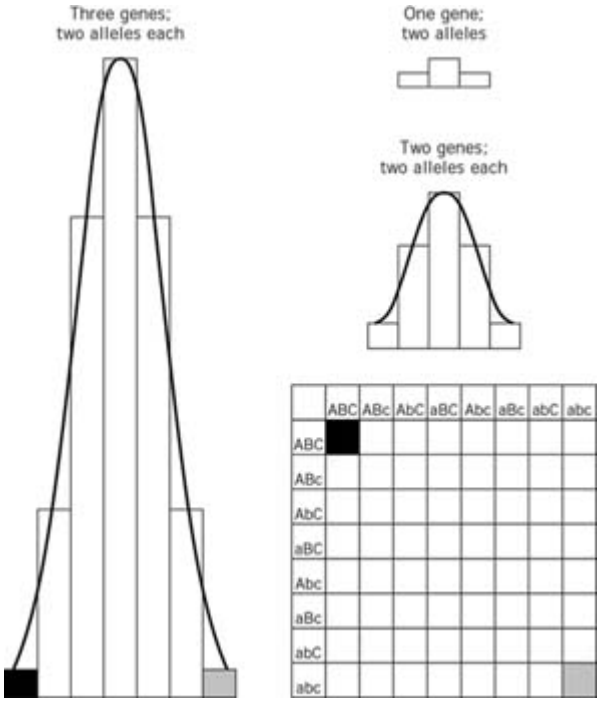

Figure 7.2. Illustration of the distribution of phenotypes, or genetic variation, for one, two or three genes (but having only two alleles each).

3.3 Polymorphism

In a population, there are always more than two alleles for any given gene. Dozens of alleles at a single locus give rise, for example, to the highly variable phenotypes of wing color in butterflies, moths, and ladybugs. A genetic polymorphism exists when a subset (second allele, locus or phenotype) is found in a population. Typically, the allelic frequency is considered by epidemiologists to be "zero," or negligible, or insignificant in its effects on the population structure, if less than 1% of homozygous individuals are affected. However, this is a completely arbitrary choice, and "a polymorphism" exists ipso facto—even if only one case is seen in an entire population.

Others commonly regard a polymorphism as any time a particular phenotype in a population occurs at frequencies of 1 in 1000 or 1 in 10,000. *Mutations* are defined as one or more altered bases (adenine, thymine, cytosine, guanine) in the DNA; mutations require one round of new DNA synthesis to become "fixed." For every one fixed mutation, there are between 1000 and 10,000 "oxidative hits" or other forms of DNA damage that get repaired without turning into a mutation. *Spontaneous* mutation rates (e.g., by background ionizing radiation) occur at frequencies between 1 in 10^6 and 1 in 10^8. Geneticists therefore regard any allele that persists in a population at a frequency of <1 in 10^6 as "having a reason for existing in that population that we might not yet understand." Possible mechanisms for why a particular allelic variant would persist at greater than spontaneous frequencies in a population might include (*1*) *balanced polymorphisms* (in which presence of the mutant allele confers some advantage to the heterozygote; e.g., sickle cell anemia), (*2*) genetic *bottlenecks* (enhanced interbreeding due to low numbers of individuals available, or due to geography), and (*3*) *founder effects* (spread of a mutant allele, originally by one reproductively vigorous individual). We will return to this topic at the end of this chapter.

3.4 Biomarkers

Because of confusion in the field of epidemiology, we believe that the term *biomarkers* needs to be clarified. A *biomarker* refers to some type of evidence that environmental agents have altered cellular macromolecules. Environmental exposure might be *genotoxic* (causing DNA damage) or *nongenotoxic* (disrupting endogenous signal transduction pathways independent of DNA damage) in the cell or organism. Thus, biomarkers would include damaged, or chemically altered, DNA bases or

protein (e.g., oxidized guanine, aflatoxin B_1-DNA adducts, aniline–hemoglobin adducts) or elevated components in the cell or organism (e.g., a-fetoprotein, metallothionein)—as the result of the metabolism of endogenous or exogenous substrates, and/or oxidative stress. Biomarkers are often used as an assessment of exposure to a particular chemical, especially in occupational medicine. The activation of a protooncogene (e.g., *RAS*, *TRP53*), or the inactivation of a tumor suppressor gene (e.g., *RB1*, *WT1*)—leading to cancer—can be the result of mutations caused by abnormally toxic levels of endogenous or foreign chemical metabolites (e.g., benzo[*a*]pyrene, aflatoxin B_1); as such, these mutations represent biomarkers. On the other hand, "variant, or mutant, alleles" (i.e., one's genetic predisposition, inherited from one's parents) have sometimes been regarded by epidemiologists as "biomarkers"; this terminology is strongly discouraged.

3.5 The Human Genome Project

The human genome is estimated to contain approximately 120,000 ± 20,000 genes distributed within the 3.5 billion base pairs of DNA, which constitute the haploid genome. About 5% of the genome represents genes, and the rest represents intergenic spacer regions. Current predictions are that all genes will be identified (but most not yet characterized) by the end of 2001. Currently, McKusick's catalogue (OMIM, "On-line database of Mendelian Inheritance in Man," August 1999) lists more than 10,000 loci, of which about 75% are associated with a disease phenotype. These data would suggest that at least 80,000 genes might have mutant alleles that adversely affect human health and/or cause human disease. It is also possible that mutations in *every* gene, under the right conditions, might contribute to human disease.

3.6 Reverse Genetics

The "candidate gene approach" means that, if gene *XYZ* had already been cloned and characterized and was known to encode, for example, an enzyme that metabolizes a particular environmental chemical to an ultimate toxic or carcinogenic intermediate, one might ask whether *XYZ* allelic differences can be shown statistically to be significantly correlated to the toxicity or cancer phenotype caused by that particular environmental chemical. Hence, *reverse genetics* is the methodology of going from the gene to epidemiological studies in an attempt to explain the etiology of an environmental disease.

3.7 Forward Genetics

As mentioned above, virtually all environmental diseases are now believed to reflect multiplex phenotypes. For example, toxicity caused by a particular environmental chemical (or chemical mixture) might be manifested by the actions of five genes contributing, say, 40, 30, 15, 10, and 5% to the phenotype; three "modifier" genes might influence the action of two "major" genes. How can such complexity be dissected and understood? The recent advances in the genetic dissection of complex traits via forward genetics (or, the "positional cloning approach") promise to be very exciting indeed during the next few years—not only in human genetics—but particularly in environmental genetics.

The challenge of genetic dissection of complex traits has become highly successful through four major approaches: linkage analysis, allele sharing (nonparametric) methods, association studies, and polygenic dissection of experimental laboratory animal crosses. The key breakthrough was the recognition in the mid 1980s (5) that naturally occurring DNA sequence variation provides a virtually unlimited supply of *genetic markers* (as opposed to *biomarkers*).

The first "useful" genetic marker, described in the late 1970s, was *restriction fragment length polymorphisms* (RFLPs)—due to restriction endonuclease "sites" in the DNA usually 4–8 bases in length. A second class of RFLPs, in which the restriction fragment length variability is caused by a *variable number of tandem repeats* (VNTRs, also called *minisatellites*), was described in the mid-1980s. A more useful subclass of VNTR polymorphisms, in which the repeat unit consists of only two base pairs (called dinucleotide repeats, or microsatellites), was discovered in the late-1980s and shown to be easily scored by the *polymerase chain reaction* (PCR). These microsatellites show a large variability in length per DNA locus, are distributed randomly throughout the genome, and are present as several thousand copies per genome. During the 'nineties, DNA microsatellite marker methodology was the most common and most successfully used technique for linkage analysis. This

technology is being rapidly replaced by *single-nucleotide polymorphisms* (SNPs) methodologies. There are an estimated 6–30 million SNPs throughout the 3.5 billion bases in the human genome; this means the possibility of genetic markers every 200 to 1,000 base pairs (bp) throughout the human (or mouse) genome. Within the next 2 years, it is anticipated that informative SNPs every 10 kb (kilo–base pairs) to every 50 kb throughout the entire 3.5 billion base pairs of the human genome will be identified.

With the availability of so many useful SNPs as markers throughout the entire genome, a new type of analysis is rapidly emerging as perhaps the most exciting advance in the field of genetics since our understanding of mendelian inheritance in the mid nineteenth century. This type of approach has been called *quantitative trait loci* (QTL) analysis, which is the method for determining the chromosomal locations of two or more unlinked genes that contribute to a multiplex phenotype (Fig. 7.3). Interestingly, the method of genetic mapping, by which one compares the inheritance patterns of chromosomal regions, allows one to find where a gene is located without knowing what the gene is. Hence, this positional cloning approach (forward genetics) is just the opposite of the above-described candidate gene approach (reverse genetics), which has been the predominantly used method during the past two decades.

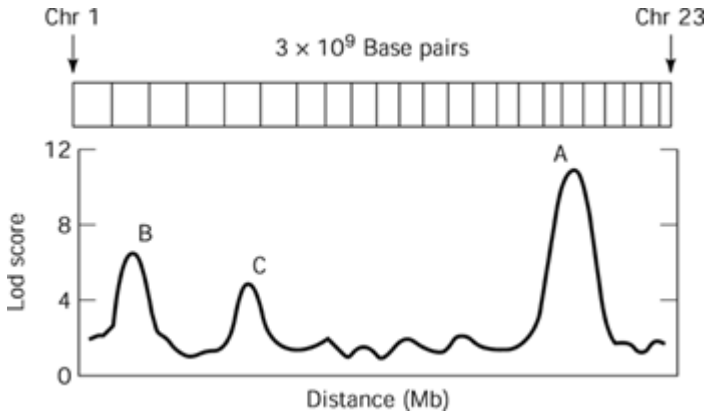

Figure 7.3. How to correlate phenotype with genotype by QTL mapping analysis. Human (or any other species) chromosomes are placed end to end, making the 3.5 billion bases (of human DNA) as if it were a straight line. Following a "genomic screen," lod scores of a trait (phenotype) are computed as a function of points along this straight line (genotype). In this imaginary example, primary gene A has a lod score of about 11, secondary gene B about 6, and secondary gene C about 4 (localized to chromosomes 18, 3, and 7, respectively) [Chr, chromosome; Mb, megabases (linear distance of 1 million base pairs of DNA)].

3.8 Lod Scores

Linkage analysis is a means of correlating phenotype with genotype (Fig. 7.3) via lod scores (6). Screening a human population for a correlation between a trait (e.g., red hair) and each of (e.g.) 2600 DNA markers, we can ask "What is the likelihood that the trait will correctly match one or more DNA markers, versus the likelihood of a random match by chance alone?" This is what is computed in a "log odds" (*lod*) score, which can establish whether a randomly chosen DNA marker is actually linked to that particular trait. The likelihood of two (or more) loci remaining together when chromosomes are recombined (following union of the sperm and ovum) is represented by the recombination fraction, q; this is written $L(q)$. The closer the two loci are to one another, the smaller q is. The likelihood ratio, $L(q)/L$ (½) measures whether the recombination fraction is equal to q (< ½ denotes linkage), as opposed to being equal to ½ (i.e., no linkage). Hence, the equation

$$\text{Lod score} = \log_{10} \frac{L(\theta)L}{L(\frac{1}{2})} = \frac{\text{likelihood of "true" linkage}}{\text{likelihood of chance alone}}$$

If the likelihood of true linkage is 1000 times greater than that by chance alone, the $\log_{10}$ of the ratio

1000 is 3.0, and this is considered in human genetics as a “significant” lod score. Numerous software programs are now available to compute lod scores, “set” the baseline, and suggest the chromosomal locations of many “significant” major and modifier genes that might be found correlated with a phenotype (Fig. 7.3).

It should be emphasized, however, that having a significant lod score with a particular gene does not necessarily implicate a correlation between phenotype and genotype; in other words, ultimately experiments that carry out *functional genomics* are absolutely mandatory. The true gene responsible for the trait might be tens of thousands of base pairs away in linkage disequilibrium (i.e., two loci segregating together from one generation to the next, due to being closely linked on a chromosome and therefore unlikely to be separated via recombination events during meiosis). It is only after *functional studies* are completed (e.g., demonstrating that an amino acid change leads to alteration in function of the gene product in the mutant allele but not wild-type allele) that one has proven an association between phenotype and genotype.

Experimental proof of a lowered enzyme activity or greater receptor affinity are examples of functional studies. A recent example of an erroneous relationship was the molecular epidemiological report on a purported association between risk of prostate cancer and the vitamin D_3 receptor (VD3R) gene (7). After the cDNA-expressed VD3R protein was demonstrated to have no alterations in function [i.e., no differences in receptor affinity (7), it was concluded that another gene—in linkage disequilibrium—must be responsible for the increased risk in prostate cancer. The same appears to be the case for nonfunctional mutations in the coding region (I462V), or Msp I site 3'-ward of the last exon, of the human *CYP1A1* structural gene and its association with increased risk of lung cancer in Japanese populations (3, 4).

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4 Environmental Genetics
Genes that encode the DMEs involved in metabolism of environmental chemicals, and genes that code for the DME receptors with which environmental chemicals or physical agents interact as either agonists or antagonists, might influence a toxic or carcinogenic outcome (Fig. 7.4). There continues to be an increasing understanding of the mechanisms by which differences in these genes or loci (*genotype*) and the degree of resistance or sensitivity to a toxic or carcinogenic chemical (*phenotype*) lead to environmental disease in some individuals but not others. Foreign chemicals and physical agents (e.g., exposure or dosage), as well as the effects by other modifier genes, are all able to influence one's genotype—leading ultimately to the toxic effect or malignancy (phenotype) (Fig. 7.4).

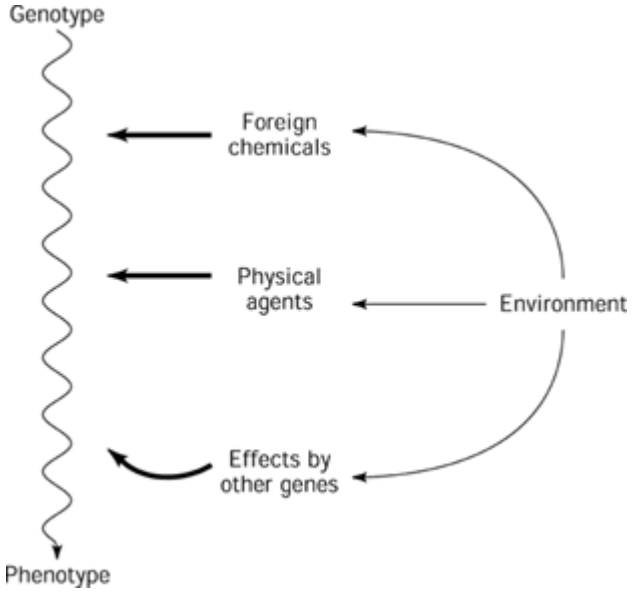

Figure 7.4. Illustration of the effects of the environment on an organism's genotype, by which the phenotype can be changed.

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5 Susceptibility Genes
Of the 120,000 genes in the human genome, what genes might be involved in causing environmental toxicity and cancer? As described earlier in this chapter, it is likely that at least 75% of these 120,000 genes might contribute to human diseases including environmental diseases. The 120,000 genes can be divided roughly into three broad categories: metabolism genes, the signal transduction genes, and the infrastructure genes.

Metabolism genes code for enzymes. Enzymes "act as a catalyst to induce chemical changes, altering a substrate to form an intermediate or product." Benzo[*a*]pyrene hydroxylase, mediated by CYP1A1, is an example of an enzyme characterized because of its capacity to metabolize the environmental agent benzo[*a*]pyrene; although the enzyme must have an endogenous substrate for evolutionary reasons, and is known (e.g.) to metabolize arachidonic acid metabolites, the true endogenous substrate has not yet been established. Adenine deaminase is generally regarded as an endogenous enzyme, metabolizing the known endogenous substrate adenine; however, any adenine analog used as a chemotherapeutic agent would be regarded as a drug, or environmental agent—thus demonstrating that virtually any "housekeeping gene" encoding an enzyme critical to endogenous pathways in the cell still might contribute to environmental disease under a particular circumstance. Any allelic differences in the genes (e.g., low enzymatic activity), encoding either benzo[*a*]pyrene hydroxylase or adenine deaminase, combined with the proper environmental exposure (or dose of drug), could therefore be responsible for interindividual susceptibility to environmental toxicity or cancer. The genes and enzymes involved in metabolism of virtually all endogenous as well as environmental chemicals have also been termed *drug-metabolizing enzymes* and *DME genes*, respectively, and the receptors that up- and down-regulate many of these enzymes have been called *DME receptors* (4, 8). DME genes (e.g., *CYP1A2*, *CYP26*, *GSTP1*, *ALDH2*, *UGT1A6*, *NQO1*, *HYL1*, *SULT1*, *FMO3*) represent the majority of the metabolism genes.

Signal transduction genes encode proteins (including kinases, phosphatases, transcription factors, cell-surface receptors, DME receptors, drug transporters, binding proteins, tumor suppressors) that participate in signal transduction cascades (e.g., *TP53*, *RB1*, *APC*, *WT1*, *BRCA1*, *PMS2*, *MSH6*, *PPA2*, *MDM2*, *AHR*, *RAR*, *RXR*, *PPARA*). Genes encoding proteins involved in the nuclear matrix, histones, chromatin, or nucleosomes (anything involved in the transcriptional response to endogenous or exogenous signaling) are also included in this category.

Infrastructure genes code for proteins involved in the assembly of all cellular and subcellular structures (e.g., spindle formation, kinesins, adhesion proteins, Golgi apparatus, ribosomes, peroxisomes, nucleolar membranes).

A *susceptibility gene* is defined as any gene that encodes a *gene product* (enzyme, or other protein) that an environmental agent might interfere with (either as an agonist or an antagonist), causing perturbation of normal cellular functions and critical life processes of the cell—leading ultimately to toxicity or malignancy. Susceptibility genes presumably constitute subsets of metabolism genes, signal transduction genes, and infrastructure genes. Allelic differences in any susceptibility gene would therefore produce differences in risk of environmental toxicity or cancer. It seems feasible that allelic variants in metabolism genes would be less likely lethal, compared with that in signal transduction genes or infrastructure genes; studies with "knockout" mouse lines have repeatedly demonstrated, however, that disruption of a gene considered to be "essential" did not lead to morbidity or mortality in the mouse line. It is therefore increasingly appreciated that signal transduction cascades exhibit a great deal of redundancy; hence, we anticipate that human allelic variants in such signal transduction genes will exist at rates similar to that in metabolism genes.

Interindividual differences in DME activities have been shown to be particularly substantial (e.g., 10 to >40-fold), whereas differences in receptor affinity and other signal transduction function are seldom so striking (2- to perhaps 20-fold). Such dramatic increases or decreases in DME activity can lead to large differences in toxicity or cancer risk—in response to the same amount of exposure to an environmental pollutant (or chemical mixture) or to a physical agent such as sunlight or ionizing radiation.

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6 Drug-Metabolizing Enzymes
Around 1930–1970, DMEs were considered as a "liver detoxification system" responsible for breaking down drugs and other hydrophobic environmental chemicals for excretion. It is now clear that (*1*) at least some of these DMEs are located in every eukaryotic cell, (*2*) almost all DMEs have endogenous compounds as their natural substrates, and (*3*) many of these DMEs have existed in evolution prior to the divergence of bacteria from eukaryotes, indicating that these DMEs have been responsible for critical life functions long before animal–plant divergence (8, 9).

Since the late 1940s, it has been taught that drug and carcinogen metabolism is carried out by phase I (functionalization) and phase II (conjugation) reactions (Fig. 7.5). Originally, these two coupled reactions were regarded simply as a "liver detoxification system." In the 1960s, some of these activities were then discovered in nonhepatic tissues such as lung, kidney, and gastrointestinal tract—indicating that the activities were not confined only to liver. Then, by the late 1960s, it was realized that some inert chemicals can actually be activated, or metabolically potentiated, to the toxic or carcinogenic intermediate (10). Phase I DMEs, many of which are in the cytochrome P450 superfamily, introduce a functional group, usually a hydroxyl, into their endogenous and exogenous substrates. Thus, a procarcinogen such as benzo[*a*]pyrene, found in cigarette smoke, becomes

metabolically activated to reactive intermediates such as benzo[*a*]pyrene 7,8-oxide and 4,5-oxide. There are >1000 other polycyclic aromatic hydrocarbons in cigarette smoke. Phase II DMEs—such as glutathione transferases, UDP glucuronosyltransferases and *N*-acetyltransferases—take the P450-mediated oxygenated product (or any other endogenous or exogenous compound already having functional groups) and use the functional group for conjugation with such moieties as glutathione, glucuronic acid, sulfate, cysteine, or acetate—yielding a very hydrophilic product that can easily be excreted. Table 7.2 lists many of the prototypic phase I and phase II enzymes.

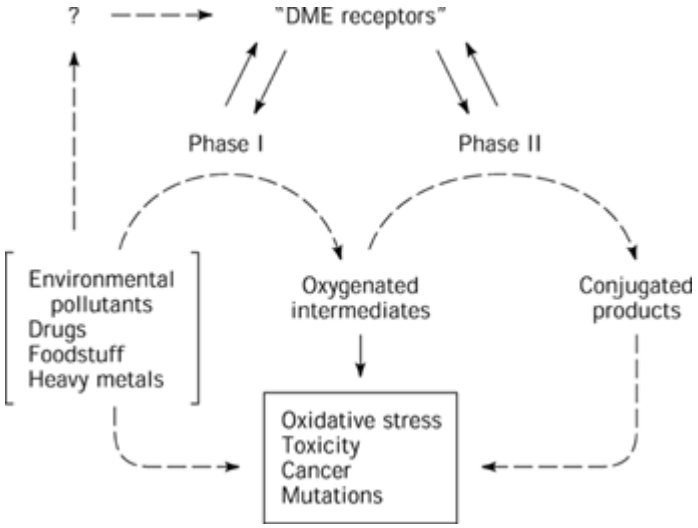

Figure 7.5. Diagram of the fate of drugs (R) entering the cell. The fate of other environmental chemicals is essentially the same. Chemicals can enter the cell by either passive diffusion or active transporters. Either the parent nonmetabolized drug or metabolite reaches its clinical target (efficacy), or the foreign chemical or metabolite can cause toxicity via perturbation of the cell cycle or covalent binding. Reception mechanisms are able to detect the environmental chemical as a "signal" and sometimes can up- or down-regulate phase I and phase II DMEs (9). Transporter proteins can also assist in moving the parent foreign chemical and metabolites out of the cell. Reproduced with permission from Nebert et al. (4).

Table 7.2. List of Enzymes that are Often Included as Drug-metabolizing Enzymes

Phase I
P450s, flavin-containing monooxygenases (FMOs), hydroxylases, lipoxygenases, cyclooxygenases, peroxidases, oxidases, monoamine oxidases (MAOs), dioxygenases, reductases, quinone reductases, aldoketoreductases, carboxylesterases, NAD- and NADP-dependent alcohol (and steroid) dehydrogenases
Phase II
UDP glucuronosyl-, glutathione-, and sulfotransferases
Transaminases, acetyltransferases, methyltransferases, acyltransferases
Glycosylases, glucuronidases, various hydrolases and esterases

These phase I and phase II reactions can be very complex (11). For example, it is possible for benzo[*a*]pyrene to be metabolized to more than 700 intermediates and products, if one counts all the stereoisomers. Benzo[*a*]pyrene 7,8-oxide can be converted (by epoxide hydrolase) to the *trans*-7,8-

dihydrodiol, which can then be activated by a phase I P450 to the ultimate carcinogen benzo[*a*] pyrene *trans*-7,8-dihydrodiol-9,10-epoxide (BPDE). Although the combined effect of phase I and phase II DME activities is usually the detoxification of the drug or environmental chemical, metabolic intermediates, (e.g., BPDE) readily form protein and DNA adducts and are strong toxicants, mutagens and carcinogens, by virtue of their highly reactive electrophilic groups. BPDE is genotoxic because it produces DNA damage. Moreover, it is worth noting that incoming chemicals can be toxic and carcinogenic without requiring metabolism. Also, so-called detoxified conjugated products can even be cleaved to form toxic, mutagenic or carcinogenic intermediates (Fig. 7.5). Reduced glutathione (GSH) conjugation can also enhance toxicity or malignancy. Incoming chemicals, their metabolites, and their conjugated products can all be moved in or out of the cell by drug transporters. Hence, allelic mutants in any of these DME genes or DME receptor or drug transporter genes can play an important role in determining interindividual risk of environmental toxicity or cancer.

It therefore follows that exposure to environmental agents in a "high phase I–low phase II" metabolism individual might lead to more toxicity or cancer than that in a "low phase I–high phase II" individual (Fig. 7.6). An example of this concept has been demonstrated in epidemiologic studies in Japan, showing an increased risk of cigarette smoking-induced bronchogenic carcinoma associated with particular alleles of the *CYP1A1* and *GSTM1* genes (*see below*). DME receptors that up- and down-regulate the levels of the DME enzymes might also be responsible for contributing to this toxicity or cancer. The remainder of this Chapter is a series of brief summaries of some of the more extensively studied human polymorphisms. Lastly, drug transporters are likely to contribute to interindividual differences in toxicity in cancer; allelic variants in transporter genes have only begun to be studied.

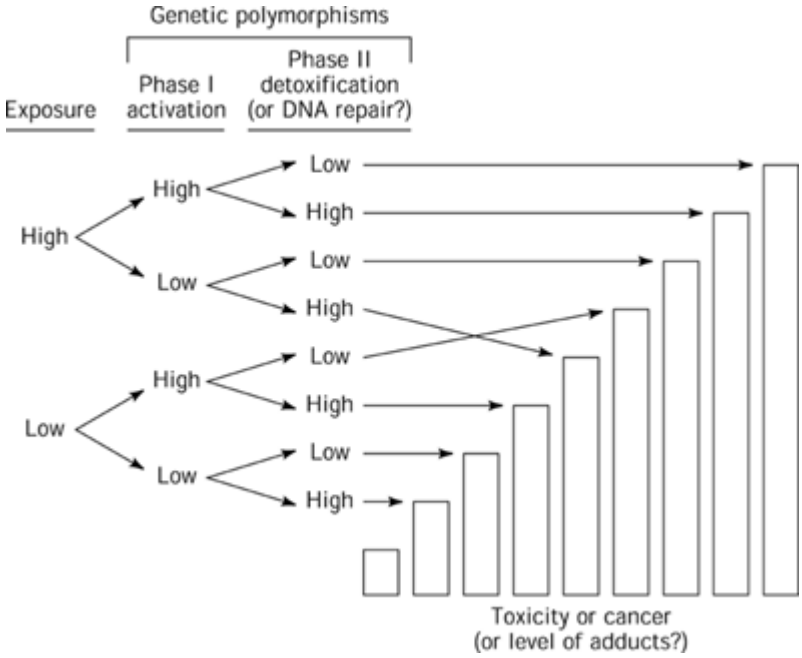

Figure 7.6. The possible combined effects of environmental or occupational exposure and genetic polymorphisms in the phase I and phase II DMEs in causing toxicity or cancer. Reproduced with permission from Nebert and Carvan 1997.

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7 Classification of Ecogenetic Differences

Various colleagues have differing opinions as to what might be included as an "ecogenetics difference," because some of these are commonly considered as "inborn errors of metabolism." Table 7.3 lists the classification we will use here, based on categories of less enzyme or defective protein, increased resistance (usually a receptor-mediated mechanism), altered response due to differences in enzyme induction, abnormal metal distribution, and "other" disorders of unknown etiology. The examples that are detailed below are selected from Table 7.3, and in the order in which they appear on this list. (For further discussion on many of these other ecogenetic differences, the reader is referred to Refs. 3, 4, 8, and 11–24).

Table 7.3. One Possible Classification of Human Ecogenetic Differences[a]

Less enzyme/defective protein
N-acetylation polymorphisms (*NAT2*, *NAT1*)
Increased susceptibility to chemical-induced hemolysis (G6PD deficiency) (*G6PD*)
a_1-Antitrypsin [protease inhibitor (*PI*)], defective alleles associated with increased toxicity by cigarette smoke
a_1-Antichymotrypsin (*AACT*), mutant alleles also associated with more toxicity by cigarette smoke?
Hereditary methemoglobinemias
P450 monooxygenase polymorphisms (oxidation deficiencies) debrisoquine (*CYP2D6*), phenytoin (*CYP2C9*, *CYP2C19*), nifedipine (*CYP3A4*), coumarin and nicotine (*CYP2A6*), acetaminophen (*CYP2E1*, *CYP1A2*)
Null mutants of glutathione transferase, m class (*GSTM1*), or q class (*GSTT1*)
Thiopurine methyltransferase (*TPMT*)
Paraoxonase deficiency, sarinase (*PON1*, *PON2*, *PON3*)
UDP glucuronosyltransferase (*UGT1A1*, *UGT2B7*)
NAD(P)H:quinone oxidoreductase (*NQO1*)
Epoxide hydrolase (*HYL1*)
Atypical alcohol dehydrogenase (*ADH*)
Atypical/lack of aldehyde dehydrogenase (*ALDH2*)
Increased resistance to chemicals
Inability to taste phenylthiourea
Coumarin resistance
Increased metabolism—atypical liver alcohol dehydrogenase (*ADH*)
Defective receptor—malignant hyperthermia / general anesthesia (Ca^{2+}-release channel ryanodine receptor) (*RYR1*, *MHS1*)
Defective drug transporters, *e.g. MDR1*, resistance to chemotherapeutic agents
Change in response due to enzyme induction
Porphyrias (esp. cutanea tarda)
Aryl hydrocarbon receptor (*AHR*) polymorphism (inducibility of *CYP1A1*,

CYP1A2) dioxin-caused chloracne, porphyria cutanea tarda, cancer, immunosuppression, (?) birth defects, (?) eye, (?) ovary

Abnormal metal distribution

Iron [hemochromatosis (*HFE*)], copper (Wilson's disease, Menkes's disease), (?) lead, (?) cadmium, (?) other metals

Disorders of unknown etiology (clinically observed to run in families)

Corticosteroid (eyedrops)-induced glaucoma

Halothane-induced hepatitis

Chloramphenicol-induced aplastic anemia

[a] From Nebert (Ref. 4a).

Note that the term *ecogenetic differences*, rather than *disorders*, is being used here. This is because a low enzymatic activity need not necessarily be associated with an adverse reaction or unwanted outcome. For example, an NAT2 slow acetylator who smokes cigarettes has an increased risk of urinary bladder cancer when working in the chemical dye industry, or increased risk of breast cancer, but has a reduced risk of colorectal cancer (4, 18).

7.1 N-Acetylation (NAT2) Polymorphism

Originally called the *isoniazid acetylation polymorphism*, this polymorphism was first identified in the late 1940s in tuberculosis patients treated with isoniazid. Individuals can be phenotyped as "slow" or "rapid" acetylators. Slow acetylators are homozygous for any one of dozens of slow acetylator (*r*) alleles, whereas rapid acetylators are either heterozygous or homozygous for the rapid (*R*) (wild-type) alleles. Therefore, the slow phenotype is inherited as an autosomal recessive trait. The frequency of the *r* alleles is about 0.72 in the United States, meaning that about one in every two individuals [according to the Hardy–Weinberg equation, *viz.*, $(p+q)^2 = p^2+2pq+q^2$, $q^2 = 0.72 \times 0.72 = 0.5184$, i.e., 52% of population] is homozygous for *r/r* and exhibits the slow acetylator phenotype. The frequency of the slow acetylator trait ranges worldwide (Table 7.4) from approximately 10% in Japanese populations to more than 90% in some Mediterranean peoples (24).

Table 7.4. Frequency of the Slow *N*-Acetylator *NAT2* Alleles (q) in Different Ethnic Populations[a]

Population	Number of Studies	Mean
Eskimo	4	0.23
South Pacific Islands	5	0.35
Korean/Chinese/Japanese	14	0.37
North and South American Indian	10	0.50
African (excluding Kung, 0.18)	19	0.71
Central and west Asian	22	0.74
European	50	0.75
Egyptian	2	0.96

[a] Data modified and condensed from Price-Evans 1992.

Two *N*-acetyltransferase functional genes (*NAT1*, *NAT2*) and one pseudogene (*NATP*) have been cloned and localized to the same region on human chromosome 8pter-q11. The rapid and slow acetylator phenotype was found to reflect principally the *NAT2* gene, encoding the NAT2 enzyme, which has a 10 times lower K_m (Michaelis constant) value for aromatic amines than does NAT1.

Three major slow acetylator alleles (two common in Caucasians, one common in Asians), each identifiable at a restriction endonuclease site, have independently been identified in several human populations (Fig. 7.7). The number of minor, rare *NAT2* alleles is now greater than 30 (25–27).

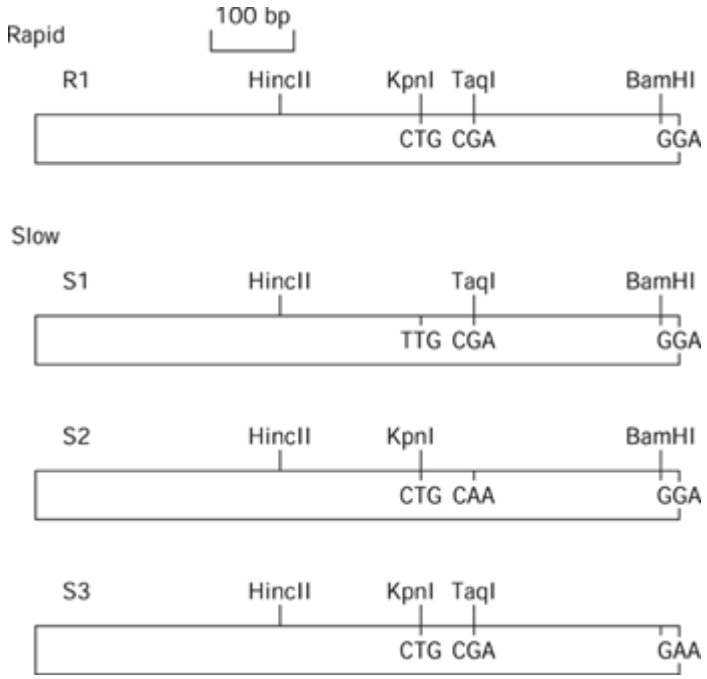

Figure 7.7. Diagram of the wild-type (R1, rapid) and three mutant (slow) alleles of the *NAT2* gene. The gene has only two exons, and these three variants can all be detected by changes in the patterns of restriction enzyme fragments: there is loss of a KpnI site in S1, loss of a Taq I site in S2, and loss of a Bam HI site in S3. The S1 and S2 alleles are the two most common among Caucasians, and the S3 allele is most common among Asians. There is now recommended nomenclature for all *NAT2* and *NAT1* alleles. Reproduced with permission from Nebert and Carvan 1997.

There are distinct associations between acetylation phenotypes and cancer or toxicity. For example, the slow acetylator phenotype shows a lower incidence of colorectal carcinoma but a higher incidence (odds ratio of 16.7) of bladder cancer (2). Both occupational exposure to arylamines and cigarette smoking are required, in conjunction with the slow acetylator phenotype, for development of bladder cancer, and no relationship was found between acetylator phenotype and smoking-related bladder cancer in the absence of exposure to arylamines. These findings have been independently confirmed by many laboratories. The slow acetylator phenotype has also been associated with enhanced plasma levels of drugs that are NAT2 substrates. Treatment of patients with certain drugs has resulted in the development of antinuclear antibodies and systemic lupus erythematosis at a much greater frequency among slow acetylators than among rapid acetylators (26).

7.2 Glucose-6-phosphate Dehydrogenase (G6PD)

G6PD is an enzyme in the hexose monophosphate shunt, one of the principal sources of NADPH generation in the normal red cell and many other tissues. Thiazolsulfone was the first arylamine sulfa drug shown to cause hemolytic anemia, and a bimodal distribution was seen in the treated population due to G6PD differences. The enzyme G6PD has perhaps more human variants than any other protein. Approximately 10% of the world population has one or another of the more than 350 different G6PD variants. Ethnic differences can be striking (e.g., >100-fold between Ashkenazic and Sephardic Jews). The *G6PD* gene has been cloned and is located on the X chromosome, which is consistent with the transmission of G6PD deficiency as an X-linked recessive trait; this means that a "carrier" mother and a healthy father will have children displaying one of four possibilities: a healthy female, a carrier female, a healthy male, and an afflicted male (16, 24).

Ecogenetics: The Study of Gene–Environment Interactions
Daniel W. Nebert, Amy L. Roe, Ph.D

8 Synergy between two Pharmacogenetic LOCI
A toxic response to an environmental agent can be greatly exaggerated by the combination of two ecogenetic differences in the same individual. For example, individuals with both the slow acetylator phenotype and G6PD deficiency can be affected quite dramatically by specific environmental agents (Table 7.5). Aniline-hemoglobin adducts among workers exposed to aniline were found to be ~50 times higher in G6PD-deficient slow acetylators than in G6PD-normal rapid acetylators. Thus, although individuals might be exposed to the same level of an environmental chemical or mixture—whether at a toxic waste site, in the form of a pesticide/herbicide, polluted urban air, or in the workplace—the risk of an adverse health effect may vary by two or more orders of magnitude, due to synergism caused by two or more ecogenetic differences. Furthermore, biomarker measurements—presumed to determine the amount of exposure in the workplace—may vary greatly because of underlying interindividual ecogenetic differences rather than actual occupational exposure. This point has very important implications to those who work in the biomonitoring field.

Table 7.5. Hemoglobin (Hgb) Adducts in Chemical Dye Workers Exposed to Aniline[a]

Acetylator Status		G6PD Deficiency		
Fast	**Slow**	**No**	**Yes**	**Aniline-Hgb Adducts**
+		+		2
+			+	30
	+	+		20
	+		+	100

[a] Modified and condensed from Lewalter and Korallus (1985).

Ecogenetics: The Study of Gene–Environment Interactions
Daniel W. Nebert, Amy L. Roe, Ph.D

9 Polymorphism and Other forms of Gene–Environment Adaptation
9.1 a_1-Antitrypsin Polymorphism (a_1-AT)
a_1-AT is a protease inhibitor (PI), the deficiency of which is associated with emphysema and liver disease. This secretory glycoprotein is formed primarily in liver cells for the purpose of inhibiting proteolytic enzymes produced by neutrophils; these enzymes include elastase, cathepsin G, and proteinase-3. a_1-AT deficiency is one of the most common lethal hereditary disorders in Caucasians of European descent. The disease is an autosomal recessive disorder characterized by reduced serum

a_1-AT levels. Serum a_1-AT concentrations of 20–53 mM are considered normal in humans (28). Individuals with serum levels of <20 mM are considered "deficient" in a_1-AT. Deficiencies in a_1-AT are caused by defects in the protease inhibitor (*PI*) gene, located at 14q31-31.2 (29). More than 70 different phenotypes for the *PI* gene (a_1-AT gene) have been identified as of this writing (30). The most common (wild-type) *M* in human populations represents at least six alleles, resulting in normal serum a_1-AT levels. a_1-AT deficiency is associated with the *Z* and *S* alleles. The prevalence in the Caucasian population of the *M/M*, *M/S*, and *M/Z* genotypes is 86, 9, and 3%, respectively (30). Individuals homozygous for the *Z* allele (i.e., *Z/Z*) display a severe deficiency in serum a_1-AT levels, and have a high risk for developing emphysema and liver disease, as well as an increased risk for chronic obstructive pulmonary disease (COPD) (28, 30). The *S/S* genotype occurs in ~ 0.1% of the Caucasian population. *S/Z* heterozygotes are also at risk for developing COPD, but only at mild risk for developing emphysema (28, 30, 31). A summary of the relative risk for emphysema based on serum a_1-AT levels and the risk of COPD as a function of phenotype is found in Table 7.6.

Table 7.6. Relative Risk for Emphysema Based on Seruma a_1-AT Levels and Risk of Chronic Obstructive Pulmonary Disease (COPD) as a Function of Phenotype[a]

Phenotype	Serum a_1-AT Levels (mM)	Emphysema Risk Compared to General Population	Risk of COPD Based on Phenotype
MM	20–53	No increase	None
MZ	12–35	No increase	None
SS	15–33	No increase	None
SZ	8–19	Mild increased risk	Yes
ZZ	2.5–7	High risk	Yes
Null–null[b]	0	High risk	*(?)

[a] Modified from Crystal (28). COPD data taken from Sandford et al. 30.
[b] Null–null individuals have not yet been studied for risk of COPD.

Several studies have examined the combined effects of deficient levels of a_1-AT and various environmental and occupational exposures. Environmental exposures—such as cigarette smoke, air pollution, and passive smoke—and occupational exposures to dust and fumes appear to predispose the a_1-AT-deficient individual to the development of respiratory diseases including COPD and emphysema (31–33).

9.2 a_1-Antichymotrypsin (AACT)

AACT is a plasma protease inhibitor, synthesized in the liver, belonging to the class of serine protease inhibitors. The normal AACT serum levels are about one-tenth that of a_1-AT (PI); the *AACT* and *PI* genes exhibit homology (34) and are located in the same region on chromosome 14 (35) within 220 kb of one another (36). The abnormal *AACT* allele is inherited as an autosomal dominant trait (37). When combined *PI-AACT* haplotypes were examined, there was no evidence of linkage disequilibrium between defective *PI* alleles and *AACT* alleles (38). Both proteins are major "acute phase" reactants; because their plasma concentrations are known to rise in response to trauma, surgery, and infection, it is reasonable to expect that individuals having a defective *AACT* gene will have more trouble with cigarette smoke–induced bronchitis and pulmonary fibrosis than will individuals having the wild-type *AACT* gene similar to what has been found with the *PI* gene.

9.3 P450 Monooxygenase Polymorphisms

Cytochromes P450 are phase I enzymes (Table 7.2) that metabolize virtually all drugs and other environmental chemicals—even certain heavy-metal ions. These enzymes carry out alkyl and aryl hydroxylations; *N*-, *O*- and *S*-dealkylations; *N*-, *O*-, and *S*-dehalogenations; and even reductions (39, 40). There appear to be 49 cytochrome P450 (CYP) genes in the human genome (41), and an increasing number of human allelic variants are described each month (4, 42).

9.4 The Debrisoquine Hydroxylase Polymorphism

Poor metabolizers (PMs) of the antihypertensive drug, debrisoquine, were found in the mid-1970s to represent 6–10% of Caucasian populations, as compared with extensive metabolizers (EMs) who handle the drug 10–200 times more efficiently. The human gene (*CYP2D6*, a cytochrome P450), along with related genes and pseudogenes in the same subfamily, have been localized to chromosome 22q13.1. As with almost every ecogenetic disorder, important ethnic differences in the incidence of phenotypes exist; for example, the PM phenotype is virtually absent in Chinese, Japanese, Laplanders, and Inuits (16, 26). The "debrisoquine panel" now encompasses more than 40 drugs and environmental chemicals, including antiarrhythmics, antihypertensives, b blockers, monoamine oxidase inhibitors, morphine derivatives, antipsychotics and tricyclic antidepressants, and nitrosamines found in tobacco smoke (2, 26). Whereas more than 60 alleles attributed to the PM phenotype have been identified (43), the most common are the *CYP2D6*3*, *CYP2D6*4*, and *CYP2D6*5* alleles, accounting for more than 70% of all null alleles in Caucasians. The *CYP2D6*5* allele (actual deletion of the entire *CYP2D6* gene) represents 19% of PM individuals. The latest nomenclature update of the human *CYP2D6* alleles can be found on the Web (42).

The EM phenotype has been associated with increased risk of liver, gastrointestinal and lung cancer. Innumerable epidemiological and ethnic studies linking the *CYP2D6* allelic differences with toxicity and cancer have been reported.

In addition to the defective (PM) *CYP2D6* alleles, there are duplicated or multiduplicated active *CYP2D6* genes, resulting in the ultra-rapid-metabolism (UM) phenotype (44). In the mid–late 1990s 29% of an Ethiopian population, and 21% of a Saudi Arabian population were identified as UM individuals (44, 45). The frequency of UM patients in black, Asian, and European populations is only 1–2% (45).

9.5 Alcohol-Inducible CYP2E1

CYP2E1 catalyzes the monooxygenation of dozens of drugs but is especially relevant to ecogenetics because it metabolically potentiates low molecular weight procarcinogens—such as vinyl chloride and vinyl bromide, dimethylnitrosamine and diethylnitrosamine, acrylonitrile, urethane, styrene, benzene, carbon tetrachloride, chloroform, and trichloroethylene—to reactive (toxic, mutagenic, carcinogenic) intermediates. Acetone is an endogenous substrate for CYP2E1. CYP2E1 metabolism is induced by alcohol, acetone, and fasting. Nine mutant *CYP2E1* alleles have been identified so far (4, 42), and *CYP2E1*2* has been demonstrated to exhibit lowered enzymatic activity due to an important amino acid change (46). The *CYP2E1*5A/*5B* alleles has been reported as a risk factor in nasopharyngeal cancer (see Ref. 47, and Refs. cited therein), although this polymorphism is located in the 5' flanking region and has yet to be proven that it is correlated with increases in transcription rate of the gene—leading to enhanced CYP2E1 metabolism. Further work on this allele is needed to corroborate whether *CYP2E1*5A/*5B* mRNA levels and enzymatic activity are indeed augmented. Studies looking at possible associations between *CYP2E1* variant alleles and environmental toxicity or cancer are predicted to explode within the next several years (at the time of writing). The same is true of all other P450 polymorphisms listed in Table 7.3.

9.6 CYP1A1 Gene Polymorphism

A restriction fragment length polymorphism (RFLP) affecting the size of Msp I fragments of the human *CYP1A1* gene on chromosome 15q22-ter was noted in 1987 (48). In Japan, this RFLP appears to be associated with a higher incidence of lung cancer, especially when combined with the *GSTM1* (glutathione transferase mu) null mutation (Table 7.7). From these studies, it seemed plausible that the human *CYP1A1* structural gene, or a region near this gene, might be correlated with the inducibility phenotype and with increased risk of lung cancer. Studies with *CYP1A1* in other ethnic groups do not, however, find any correlation with lung cancer; Norwegians, American

Caucasians and blacks, Finns, and eastern Mediterraneans lack the association between the Msp I RFLP, the I462V mutation, and/or lung cancer. Thus, it now appears that the Msp I RFLP might explain some of the genetically predisposed increased risk among Japanese high inducibility individuals for particular types of cigarette smoke–induced cancer, but it does not hold true for other ethnic groups (4, 11). The I462V amino acid change in the enzyme active site was reported to increase enzymatic activity; however, two studies have shown that cDNA-expressed CYP1A1 enzymatic activity *in vitro* is not different between the *CYP1A1*1* wild-type and *CYP1A1*2B/*2C* allelic products (4, 49, 50). It remains plausible that, in the Japanese population, the Msp I RFLP polymorphism is in linkage disequilibrium with another mutation that is important for CYP1A1 inducibility or another gene (*CYP1A2?*) involved in tumorigenesis, whereas—in non-Japanese populations—these mutations are not in linkage disequilibrium.

Table 7.7. Relative Risk Estimate of Lung Cancer Types in Japanese Patients Having the Combined Genotypes for CYP1A1 and GSTM1 Genes[a]

	Ile/Ile		Ile/Val		Val/Val	
CYP1A1:						
GSTM1:	+	–	+	–	+	–
Lung cancer	1.0	1.7	1.7	1.4	2.3	5.8
Kreyberg I	1.0	1.8	1.3	1.8	1.6	7.9
Squamous cell CA	1.0	2.3	1.2	1.5	2.0	9.1
Kreyberg II (adenocarcinoma)	1.0	1.6	2.2	1.0	3.1	3.5

[a] Modified and condensed from Hayashi et al. 1992.

9.7 CYP1A2 (Arylamine Hydroxylase)

CYP1A2 metabolizes aromatic amine procarcinogens, including tobacco smoke–specific nitrosamines, such as 4-(methylnitrosamino)-1-(3-pyridyl-1-butanone (NNK). Between 15- and ≥ 60-fold differences in human CYP1A2 mRNA levels, 1A2 protein levels, and CYP1A2 activities have been reported, suggesting that interindividual differences in CYP1A2 expression might play a role in toxicity and cancer (4, 11). Although expressed constitutively (and inducible by cigarette smoke) in liver, CYP1A2 has not been detected in human lung and has been found at very low levels in the gastrointestinal tract, brain, and endothelial cells of blood vessels. With the use of caffeine as a probe, a trimodal distribution of the enzymatic activity (consistent with high/high, high/low and low/low genotypes) has been detected in four separate populations (51, 52). The genetic basis of this polymorphism has been extensively searched for, but is not yet understood (4, 42).

Two *Cyp1a2(-/-)* knockout mouse lines—showing different phenotypes—have been developed (53, 54). These mouse lines will be helpful in elucidating the role of CYP1A2 in toxicity and cancer.

9.8 Thiopurine Methyltransferase (TPMT)

TPMT is an enzyme that can be regarded in a detoxification pathway for 6-mercaptopurine (Fig. 7.8), commonly used in chemotherapy for acute lymphocytic leukemia. The frequencies of the high/high, high/low, and low/low genotypes are 87, 13, and 0.3%, respectively, in the Caucasian population. This means that, when given the recommended dosage [from the *Physician's Desk Reference* (PDR)] of 6-mercaptopurine, one out of approximately 300 patients would die as the result of too much chemotherapeutic drug, 13% would have a high probability of being cured of their disease, and 87% patients would have relapses in their leukemia due to undertreatment (Fig. 7.8). Because this pharmacogenetic difference can lead to dire consequences, acute lymphocytic leukemia

patients are now routinely phenotyped for TPMT prior to the initiation of 6-mercaptopurine chemotherapy; high/high patients are then usually given a 4 times higher dose, and low/low patients are given a 10–15 times lower dose, leading to a much better cure rate and survival rate for childhood leukemia (21). At least eight PM allelic variants have been characterized for the *TPMT* gene (4).

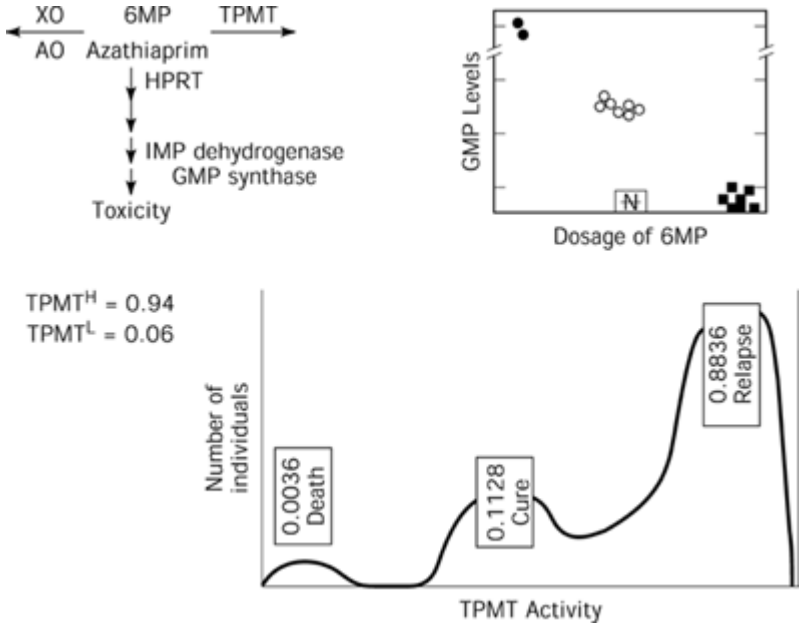

Figure 7.8. Diagram of 6-mercaptopurine (6MP) toxicity (which can occur in all cells but more so in rapidly growing malignant cells, due to disruption of purine biosynthesis), and the response of acute lymphocytic leukemia patients given the "recommended dose" of the chemotherapeutic agent. XO (xanthine oxidase), AO (adenine oxidase), and TPMT (thiopurine methyltransferase) are all enzymes that detoxify 6MP. Toxicity of 6MP occurs much more readily in individuals have the low activity allele, $TMPT^L$, than the high-activity allele, $TMPT^H$. About three in 1000 Caucasians are homozygous for the low/low genotype, and 87% are homozygous for the high/high genotype.

9.9 Paraoxonase Polymorphism

Paraoxon is the biologically active metabolite of parathion, an organophosphate insecticide. Interestingly, paraoxonases (PON1,2,3)—calcium-dependent A-esterases— are found in human plasma, and we have long believed that this enzyme must exist for some reason other than detoxifying organophosphates (which were first synthesized in the mid twentieth century). PON1 is now known to be an apoJ high density lipoprotein (HDL)-associated enzyme that hydrolyzes many toxic organophosphates, including sarin, and must play a role in cardiovascular homeostasis. The enzyme functions of PON2 and PON3 are not yet understood. The frequencies of the high/high, high/low, and low/low *PON1* genotypes are approximately 50, 40, and 10%, respectively, in Caucasians. Again, striking ethnic differences worldwide have been described (Fig. 7.9) (16). The *PON1*2* allele and *PON2*3* allele, both resulting in a low activity subunit of the enzyme represent mutations: R192Q, arginine changed to glutamic acid at position 192 (55), and C311S, cysteine changed to serine at position 311 (56). The organophosphates allegedly used as biological warfare, and pyridostigmine used as an antidote of anticholinesterase poisoning, have caused some to speculate that the "Gulf War syndrome," in which striking variations in illness occurred among some but not other soldiers in this 1991 war, might be explained at least in part by the paraoxonase polymorphism (57).

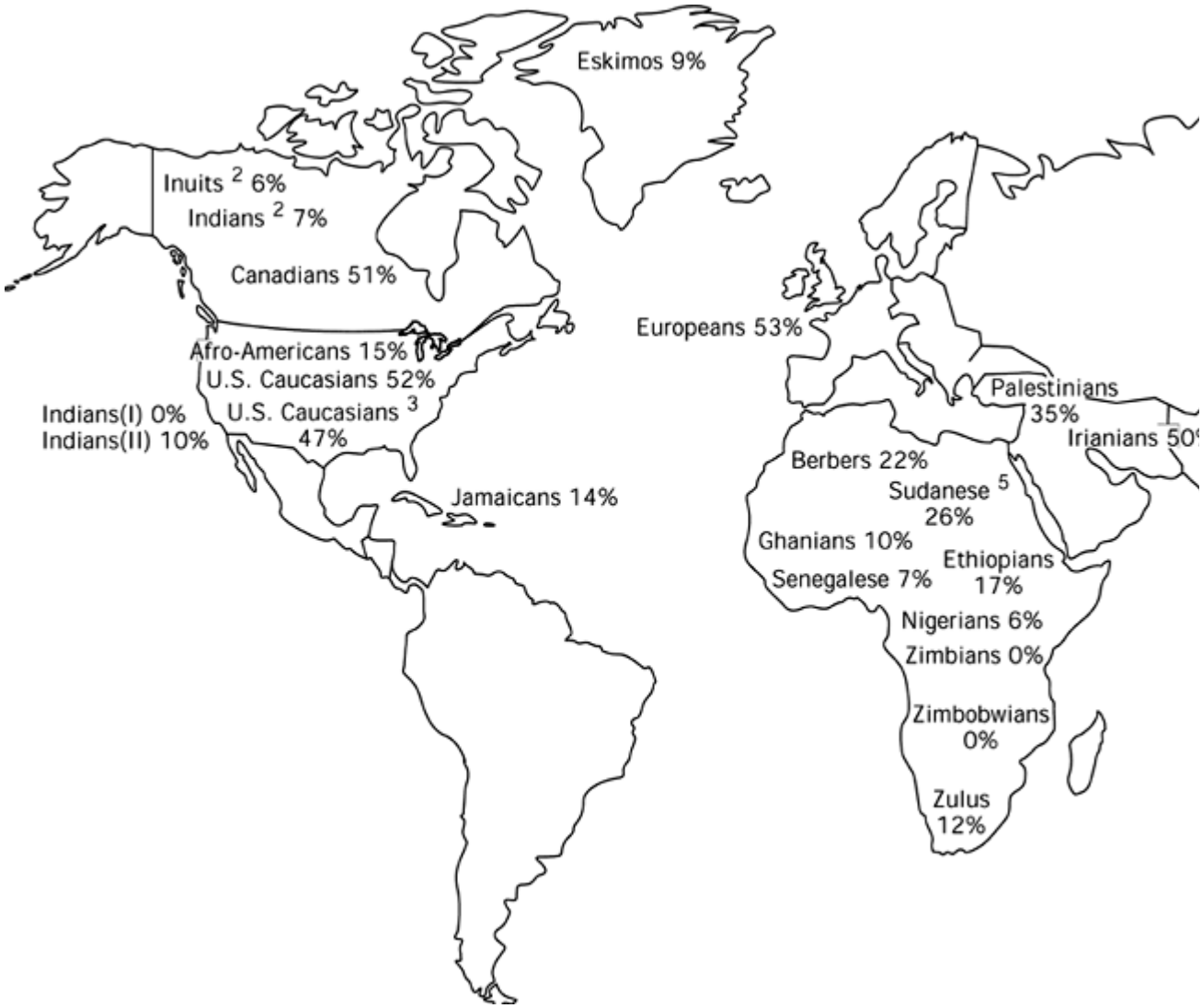

Figure 7.9. Genetic differences in paraoxonase. Reproduced with permission from Kalow and Bertilsson (16).

9.10 Aldehyde Dehydrogenase (ALDH2) Polymorphism

Out of the 17 human *ALDH* genes cloned and characterized by the late 1990s (58, 59), the mitochondrial *ALDH2* has the most clinical significance. When drinking alcohol, the enzyme alcohol dehydrogenase (ADH) converts ethanol to acetaldehyde, which is the toxic metabolite.

If the detoxification of acetaldehyde by ALDH2 is not rapid enough, alcohol intake tends to cause acetaldehyde buildup, facial flushing, rapid heart rate, and a drop in blood pressure (60). Interestingly, an inactive genetic variant of *ALDH2*—which represents a point mutation near the COOH terminus of the enzyme protein—occurs in some populations at a frequency as high as 50%, and there are very striking ethnic differences (Table 7.8. ALDH2 is a tetramer, and if the tetramer contains even one inactive subunit, the whole tetramer is enzymatically inactive. This means that ALDH2 deficiency is inherited as an autosomal dominant trait).

Table 7.8. Distribution of ALDH2 Isozyme Deficiency in Different Populations[a]

Population	Percent Deficient in ALDH2

Japanese	44
Central, East, and Southeast Asian	30–50
South American Indian	40–45[b]
North American Indian	2–5
European, Near-East, and African	0

[a] Data modified and condensed from Goedde and Agarwal 1986.
[b] Different mutation from that in Asians and North American Indians.

9.11 Phenylthiourea Taster/Nontaster Polymorphism

Proposed to be the first clinical example of an ecogenetics difference (3), the inability to taste phenylthiourea (PTU) was described as an autosomal recessive trait (24). In 1950 the frequency of "PTU nontasters" among American Indians and Africans was reported to be only 2 and 3%, respectively, compared with 30% PTU nontasters in the United States; hence, this was also the first appreciation of ethnic differences in response to an environmental agent. The mechanism for PTU nontaster is not yet known, but is presumed to be receptor-mediated.

9.12 Ryanodine Receptor/Ca^{2+} Release Channel (RYR1,2,3)

In response to particular inhalation anesthetics and muscle relaxants, the occasional patient will develop sustained muscle contraction and a fever of >44 °C, which can often be fatal; this was termed *malignant hyperthermia* (MH). The incidence of MH in humans is quite rare—1 : 12,000 to 1 : 40,000 (24). It was then realized that MH occurs in both humans and pigs and is caused by a mutant allele in the ryanodine receptor (*RYR1*) gene. The RYR is a calcium-release channel protein of high molecular weight (M_r = 565,000–590,000) (61). The *RYR1*2* allele (R614C), is the same amino acid variant in both humans and pigs Further studies have confounded the field, because three *RYR* genes have now been found: two loci on human chromosome 17q, and another on 19q. Moreover, another *RYR1* mutation (R2434H, inherited myopathy) has a possible association with central core disease.

9.13 The Ah Receptor (AHR) Polymorphism

The AHR polymorphism was originally identified from studies of inducible benzo[*a*]pyrene metabolism in mice. Aryl hydrocarbon hydroxylase (AHH; benzo[*a*]pyrene 3-hydroxylase; now named *cytochrome P450*, CYP1A1) was found to be highly inducible and controlled by a high affinity AHR in some inbred mouse strains, and a low affinity AHR in other strains. This difference was shown not to be due to changes in the *Cyp1a1* gene itself, but rather in the *Ahr* gene that encodes a receptor; the lack of inducibility is inherited as an autosomal recessive trait in genetic crosses between C57BL/6 and DBA/2 mice. There is convincing evidence, from inbred mouse studies, that allelic differences in the *Ahr* gene, which encodes the AHR, can result in striking differences in interindividual susceptibility to cancer, mutagenesis, birth defects, and cell-type-specific toxicity of the liver, eye, ovary, bone marrow, and immune system; some of the toxicity or cancer reported in mice have also been reported in clinical studies (62). Fig. 7.10 shows the enzyme reactions of CYP1A1 and CYP1A2; these two enzymes, encoded by the *CYP1A1* and *CYP1A2* genes, are regulated by the AHR in the mouse and human. There is a cascade of events by which environmental chemicals enter the cell, displace an (as yet unknown) endogenous ligand from the AHR, and lead to CYP1A1 and CYP1A2 induction (62–65) and chronic oxidative stress (66).

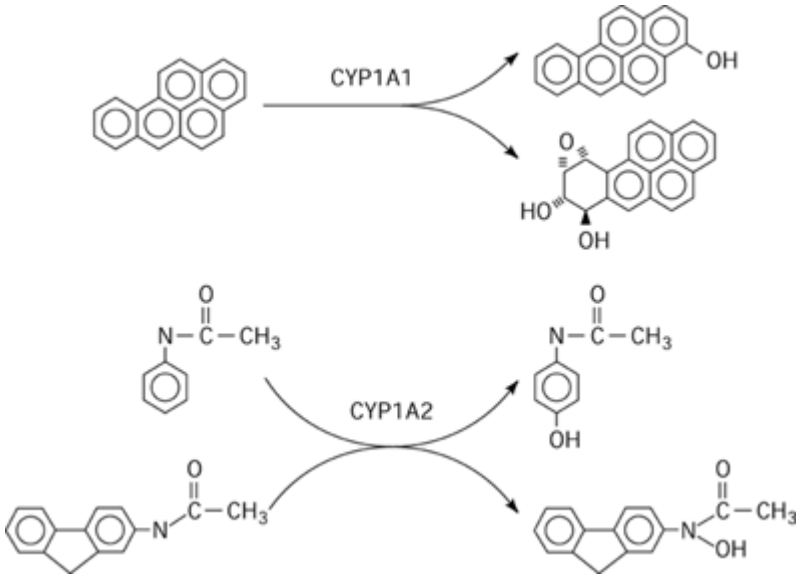

Figure 7.10. Enzymic reactions of CYP1A1 and CYP1A2. Polycyclic hydrocarbons, such as benzo [*a*]pyrene shown here, are substrates for CYP1A1; conversion of the 7,8-oxide to the *trans*-7,8-diol is carried out by epoxide hydrolase. Aryl amines, such as acetaminophen and 2-acetylaminofluorene shown here, are substrates for CYP1A2 (10).

Clinical correlations between genetic differences at the *AHR* locus and certain types of toxicity and forms of cancer have been suggested (4, 62, 67–70), but an experimental assessment of this hypothesis is, of course, hampered by the ethical difficulties of carrying out definitive experiments in humans. Heavy exposures of human populations to dioxin, halogenated hydrocarbons, or cigarette smoking have led to the manifestations of malignancies, birth defects, chloracne, mental problems, early onset of menopause, and immunosuppression—but no cause–effect relationship between the AHR phenotype and these types of toxicities or cancers has been rigorously demonstrated to date.

Using 20–40 cm^3 of blood from venipuncture, numerous laboratories have studied peripheral white cell cultures in the presence of mitogens and CYP1A1 inducers, in order to assess the human AHR phenotype and relationship to cancer (11). There is a continuous gradient from low to high inducibility phenotypes, with more than 12-fold differences between the lowest and highest inducibility phenotype (71). Studies from a number of independent laboratories have suggested that, among cigarette smokers, the highest inducibility (AHR^H) phenotype is at greater risk (estimates run between 3- and 20-fold) than the lowest inducibility (AHR^L) phenotype for bronchogenic carcinoma (Fig. 7.11), laryngeal carcinoma, and cancer of the oral cavity, but not cancer of the kidney, ureter or urinary bladder. These data are consistent with the fact that cells in contact with incoming cigarette smoke might be more prone to carcinogenesis than tissues distant to smoke inhalation. However, the mitogen-activated lymphocyte 3- or 4-day culture assay is not trivial to carry out, many laboratories have experienced difficulties in reproducibility of this assay, and numerous modifications of the assay were introduced in the 1980s and 1990s. Consequently, the reporting by several laboratories of an absence of association between the AHR^H phenotype and bronchogenic cancer (11) is likely to reflect technical difficulties in the white blood cell culture assay.

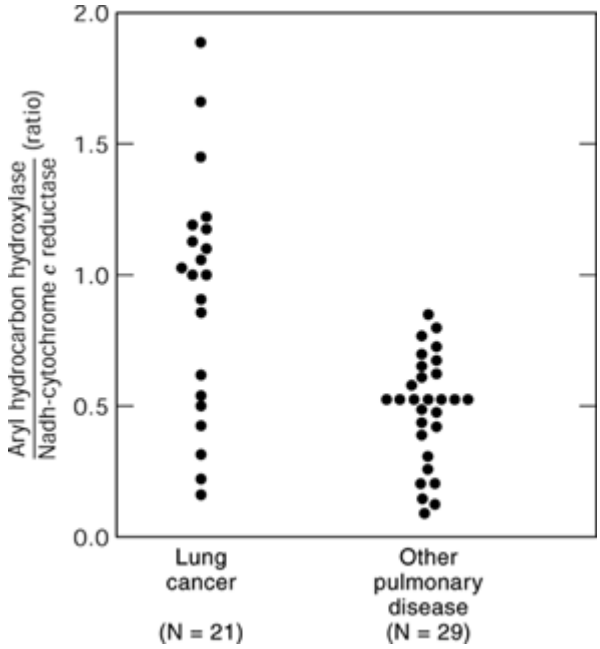

Figure 7.11. Ratio of CYP1A1 (aryl hydrocarbon hydroxylase) activity to microsomal reductase activity in 21 freshly diagnosed lung cancer patients and 29 (matched for age, sex, and cigarette smoking history) patients with other pulmonary disease. At least 12 of the lung cancer patients exhibit CYP1A1 inducibility that is significantly greater than that in any of the patients without cancer. The original study was reported by Kouri et al. (1982) [redrawn from Nebert and Gonzalez, (40), and permission of the copyright holder].

The fact that there are conflicting results from several laboratories underscores the importance of developing a reliable and simple noninvasive test, such as a DNA marker, for determining the AHR genotype in large populations. Such screening of human populations would resolve these conflicts in the literature.

The cDNAs for the C57BL/6 (*Ahr*^{b1} allele) and DBA/2 (*Ahr*^{d} allele) mouse have shown that there are five coding polymorphisms between the two alleles (72). Of these, the mouse A375V (and the corresponding human A381V) mutation appears to be one alteration that is critical for *in vitro* ligand affinity and possibly for CYP1A1 inducibility (11, 73–75).

The *Ahr(-/-)* knockout mouse line has been shown to exhibit impaired development of the liver and immune system, splenic atrophy, hyperkeratosis of the skin, and cataracts (76). This mouse line should be very helpful in delineating further the role of the AHR in toxicity and cancer.

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10 Ethnic Differences and the “Edge Effect”
Hundreds of clinical trials have revealed not only that the rates of metabolism differ among individuals within the same ethnic group but also that the mean rates of drug metabolism differ significantly between ethnic groups. Fig. 7.12 is a representative example of such a study. In this report, the rate of codeine glucuronidation is shown to be slower in Chinese than in Caucasians.

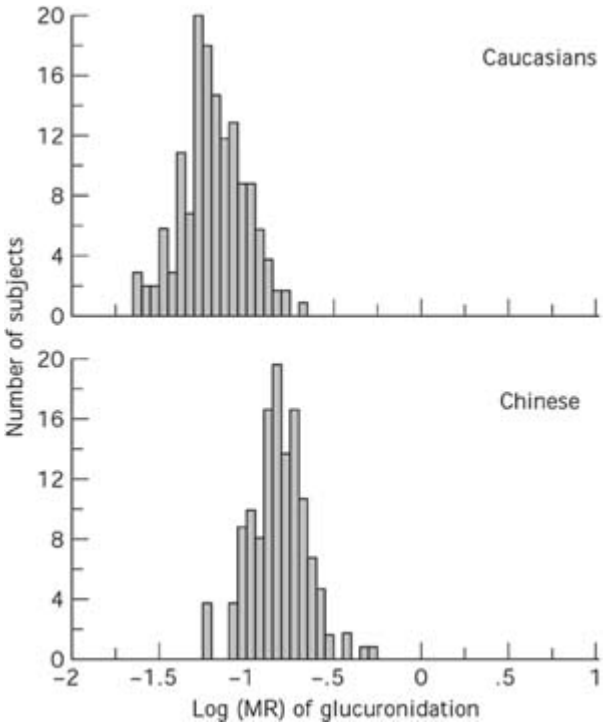

Figure 7.12. Frequency distributions of the $\log_{10}$ MR (metabolic ratio = parent drug divided by metabolite) of codeine glucuronidation. Total number of subjects, $N = 149$ and 133 for Caucasians and Chinese, respectively. Reprinted with permission from Yue et al. 1989 and permission from the copyright holder, Blackwell Scientific Publishers, Ltd., Oxford.

What significance can such ethnic differences have, for populations exposed to the same levels of hazardous waste, or for populations of workers exposed to the same concentrations of occupationally hazardous chemicals? Figure 7.13 illustrates the "edge effect," where the rate of metabolism (or clearance of a chemical) might be associated with a significant proportion of individuals at one end or the other on this graph. Clearly, if the same exposure of a chemical occurs in the workplace, and similar factories having workers of different ethnic groups are located in different parts of the United States or in different countries, the "percentage of workers exhibiting a toxic response" might differ quite dramatically.

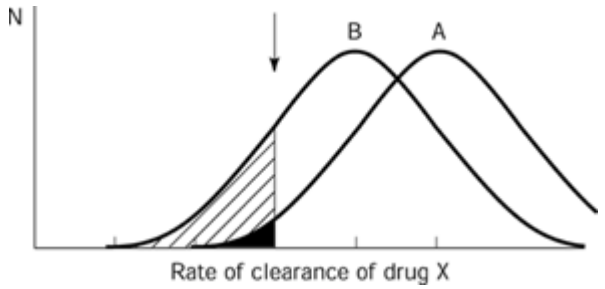

Figure 7.13. The "edge effect" of different averages from hypothetical curves A and B, representing normal frequency distributions for the elimination capacity of chemical X in two populations. The *abscissa* denotes the rate of chemical clearance, and the *ordinate* (N) indicates the number of individuals who show a particular rate of clearance. The *arrow* denotes the critical clearance rate below which the chemical causes toxicity. Curves A and B were drawn with identical standard deviations but their means are one standard deviation apart; i.e., the difference between the means is small compared with the range of variation within each population. In population studies, such small differences are often disregarded. The data imply that about 2% of population A (*solid*) and 16% of population B (*striped*) would suffer toxicity. Obviously, this eightfold difference between the two

ethnic populations would grow substantially if the *arrow* were shifted toward the left. Reprinted with permission from Kalow and Bertilsson (16), and permission of the copyright holder, Academic Press, Ltd., New York.

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11 Why these Drug Metabolism Polymorphisms Exist

As mentioned earlier in this chapter, spontaneous mutation rates occur at frequencies between 1 in 10^6 and 1 in 10^8. Any allele that persists in a population at a frequency of <1 in 10^6 is thus regarded by geneticists as "having a reason for existing in that population, even though we might not yet understand the reason." Possible mechanisms for why a particular allelic variant might persist at high frequencies in a population include (*1*) balanced polymorphisms (in which presence of the mutant allele confers some advantage to the heterozygote), (*2*) genetic bottlenecks, and (*3*) founder effects (77). Many of the aforementioned polymorphisms exhibit striking ethnic differences in addition to interindividual differences among humans of the same ethnic group. From current epidemiological data for many of these genes discussed, it is not clear that the heterozygote offers any distinct clinical advantage over either homozygote. However, it is interesting to note that differences in the incidence of one phenotype between ethnic groups can be as large as 100-fold; for example, the incidence of G6PD deficiency is 0.4% versus 53% in Ashkenazic Jews and Sephardic Jews, respectively (24). One explanation for this degree of variability may relate to geographic differences in diet over thousands of years. Figure 7.14 illustrates the estimated rates of divergence for various ethnic groups over many thousands of years. From the periods of time since divergence of different ethnic groups (e.g., 10,000 years, 35,000 years), it is clear that this would be long enough for allelic variants to arise and persist in response to the selective pressures of a particular diet (e.g., tropical fruit versus goat milk and grains).

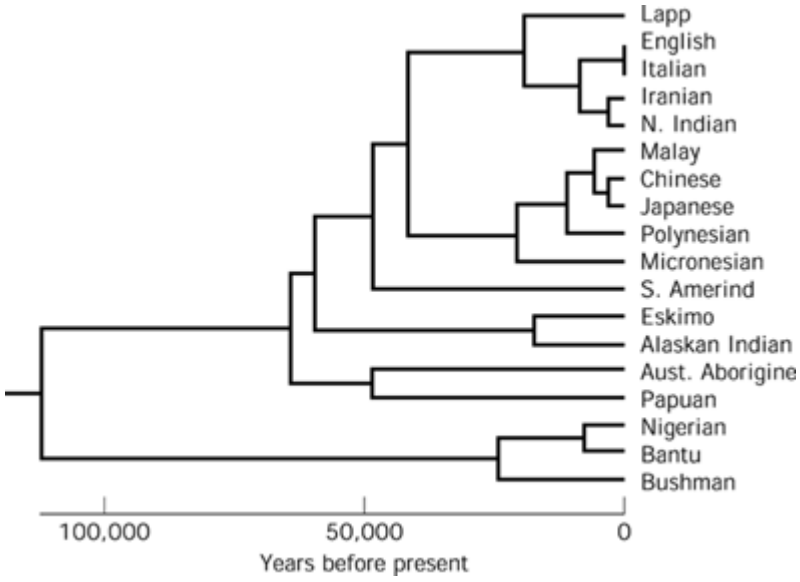

Figure 7.14. Genetic distance between various populations. Modified from Nei and Saitou 1986, and reproduced with permission from the authors and the copyright holder A. R. Liss, Inc.

Another explanation for ecogenetics variability might be the evolution of balanced polymorphisms. The classic example of a compensating, or "shared benefit," polymorphism (Table 7.9) is the sickle cell trait; whereas the homozygous carriers of this trait die (or fail to reproduce) because of severe anemia, the much larger number of heterozygotes resist malaria better than do wild-type homozygotes. It is becoming appreciated (78) that there are several classes of diseases in which the homozygote bears the risks while the heterozygote is believed to hold a distinct survival advantage: (*1*) resistance to bacterial and viral pathogens, (*2*) improved prenatal survival, and (*3*) improved postnatal survival in response to particular environmental stresses. These diseases are summarized in Table 7.9. Considering the ecogenetics polymorphisms described in this chapter, one might postulate that the homozygote bears the risks, whereas the heterozygote holds some distinct survival advantage (s). Considering the discussion at the beginning of this chapter—that DMEs are very old enzymes that are responsible for numerous critical life functions (9, 79)—it is reasonable to assume that at least some of the human DME allelic differences represent balanced polymorphisms that we presently cannot yet appreciate, such as improved rates of implantation, prenatal growth, postnatal development in response to dietary selective pressures, or resistance to bacterial or viral infections. As more DME genes are cloned and their functions uncovered, the reasons for the DME polymorphisms should become more apparent.

Table 7.9. Examples of a Balanced Polymorphism in Which the Heterozygote Appears to Have a "Shared Benefit" over Either Homozygote

Sickle cell anemia = resistance to malaria
G6PD deficiency = resistance to malaria
Congenital adrenal hyperplasia = protection against *Hemophilus influenzae B* infections
Tay–Sachs disease = resistance to tuberculosis
High pepsinogen I (gastric secretion) = resistance to tuberculosis
Idiopathic hemochromatosis = protection against iron loss (menses)
Non-insulin-dependent diabetes mellitus = protection against intermittent/limited food intake
Cystic fibrosis[a] = resistance to cholera toxin and/or bronchial asthma

[a] The cystic fibrosis transmembrane conductance regulator (CFTR) mutant allele might have arisen and been maintained in the population because the heterozygote might exhibit enhanced resistance to cholera and/or asthma, although a founder effect is also suspected of having played a role (discussed in Ref. 78).

DMEs, the DME receptors, and drug transporters have evolved over several hundreds of millions of years for critical life functions (e.g., cell division, sporulation, homeostasis, defense against infection, differentiation, apoptosis and neuroendocrine functions). In animals DMEs more recently expanded to include the role of detoxification of dietary products, evolving plant metabolites and, of course, drugs (8, 9, 79). There is a growing number of developmental disorders caused by "inborn errors of metabolism" that represent defects in a DME gene, which further underscores the fact that DMEs often modulate critical life processes. For example, congenital adrenal hyperplasia (CAH) is caused most commonly by defects in the *CYP21* gene but can also be caused, although rare, by mutations in the *CYP17*, *CYP11B1*, *CYP11B2*, and *CYP11A1* genes (80). Vitamin D–dependent rickets is an autosomal recessive trait caused by a defect in 25-hydroxy-D_3 1a-hydroxylase (*CYP27B1*), a kidney mitochondrial P450 (81). Mutations and deletions in the microsomal fatty aldehyde dehydrogenase (*FALDH*) gene were shown to be the cause of Sjögren–Larsson syndrome—characterized by mental retardation, spasticity, and ichthyosis—indicating the requirement of this enzyme for neurocutaneous homeostasis (82). Mutations in the *CYP1B1* gene are

responsible for primary congenital glaucoma (buphthalmos), implying that failure of the CYP1B1 enzyme to metabolize some endogenous substrate leads to this affliction (83). Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of autosomal recessive disorders leading to cirrhosis and liver failure before adulthood; mutations in the *MDR3* transporter gene are associated with PFIC (84).

12 Conclusions

Many studies have demonstrated the importance of phenotypic polymorphisms in DME genes and DME receptor and drug transporter genes as risk factors in the development of cancer, toxicity, and other diseases associated with chemical exposure. The genetic bases of many of these polymorphisms have been elucidated, and noninvasive genotyping methods that can be applied to large populations have been developed. The study of the relationship between genetic polymorphisms, cancer susceptibility, toxicity, and environmental exposure is a new, exciting and promising area of research. The identification of genetic factors—which, acting in conjunction with the amount of environmental exposure, might increase the interindividual risk of toxicity or cancer—will undoubtedly have important implications for the prevention, early diagnosis, and intervention of human disease.

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Regulations and Guidelines In the Workplace

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1.0 Introduction and History

Occupational diseases can be used as the first historical markers for concern about toxic substances in the workplace. The passage in 1798 of the Act for the Relief of Sick and Disabled Seamen established The Marine Hospital Service, which was later named the Public Health Service. This was the first real legislation that dealt with occupational disease. Most of the seamen who benefited in the early years probably had traumatic injuries or infectious diseases, but it is certain that some suffered from chronic exposures. In 1835, McCready described the role of trades, professions, and occupations in the development of disease and noted several toxic substances of importance (1), lead and dusts. In 1860, Freeman described problems with mercury among hatters. Actual legislation to regulate the workplace was slow to develop and was confined to conditions that affected children, for example, hours worked and ages when children could begin work (1a).

Research and technology provide the rationale and the methodologies used to develop legislation, regulations, and guidelines that reduced workplace hazards. However, the main factors bringing about the passage of laws and/or regulations are likely to be social. These have included catastrophes, such as mine explosions, asbestos disease, epidemics, and the Gauley bridge episode, political movements such as the environmental and civil rights movements, and organizations capable of pressing for legislation, such as labor organizations, community groups, and trade associations.

In the early part of this century, regulations and guidelines to control toxic substances in workplaces emerged out of social forces such as those introduced by labor unions and social reformers, one of whom was Alice Hamilton. She was instrumental in putting workplace health and safety on the agenda for U.S. federal activities during the early 1900s. Federal efforts were located in the Office of Industrial Hygiene and Sanitation of the U.S. Public Health Service.

States were at the forefront of early efforts on worker health. Anna Baetjer (1b) reported that a commission on Hygiene of Occupations and Railroads was established under the Health Department of Ohio in 1886. Early efforts to investigate and make recommendations to eliminate and/or prevent occupational disease were instigated by New York and Ohio in 1913, followed by Connecticut in 1928. In 1905, the Massachusetts Health Department had investigators of dangerous occupations. Later, this early program was placed in the Massachusetts Department of Labor (2).

It is of interest to note that the first academic programs to support these efforts were instituted before 1920. For example, C.E.A. Winslow gave a course in industrial hygiene in the Department of Biology and Public Health at MIT in 1905, followed by the University of Pennsylvania where there was a doctorate in public health in 1906 that emphasized industrial hygiene. In 1919, the University of Cincinnati established a one-year Certificate of Public Health in Industrial Hygiene (3).

An example of the roles various organizations had in the United States in establishing exposure levels can be found in the preamble to the benzene standard (4). A committee of the National Safety Council on Benzol chaired by C.E.A. Winslow reported that, even at 10 ppm or less, one in three workers were affected. The Committee notes the importance of substituting another solvent where possible (5). In the 1940s as a result of a death in the range of 40–80 ppm, Massachusetts lowered its permissible limit to 35 ppm. The American Conference of Governmental Industrial Hygienists (ACGIH) recommended a threshold limit value (TLV) of 100 in 1946, 50 in 1947, and 35 in 1948. In 1963, a TLV of 25 was recommended (6). Another private organization, the American National Standards Institute (ANSI), recommended a limit of 10 ppm. This value became the first PEL for benzene adopted in 1971 in the rulemaking 6(a).

In 1936, the Industrial Hygiene Committee of the State and Provincial Health Authorities of North America published a list of the duties and qualifications for physicians and engineers in industrial hygiene, that are similar to those recommended today. In addition to the professional requirements, this list included certain desirable personality characteristics: "*ability to establish contact with plant executives, foremen, and laborers; initiative; tact; good judgement, and address*" (1).

Among governmental bodies, the development of guidelines and regulations covering toxic substances was varied. Certain states developed both exposure limits and practices for reducing exposures, for example, New York, Massachusetts, and Pennsylvania, whereas others had few regulations. Most of these guidelines or regulations were in the Labor or Health Department codes. The U.S. Department of Labor first issued guidance for toxic substances encountered in the workplace through the Bureau of Labor Standards. In a review of the requirements that the state governments had for workplace safety and health, there is a compilation of the various provisions, responsible agencies, and selected subjects such as mines, workmen's compensation, reporting requirements, women and minors, and vocational rehabilitation. The sources used are provided. The requirements range greatly. Examples of several states are given in Table 8.1. It should be noted that even among the states that have one of the most extensive sets of requirements, Pennsylvania, a

comprehensive standard to protect coke oven workers did not result until after the federal Occupational Health and Safety Act was passed in 1970. One can speculate that the comprehensive nature of this federal standard as well as the federal inspection to enforce its provisions brought about safer working conditions (7).

Table 8.1. Selected Requirements in Three States Prior to OSHAct[a]

			Reporting of Occupational		Medical Surveillance		
State	**OEL[b]**	**Inspections**	**Injuries**	**Diseases**	**Lead**	**Solvents**	**Silica**
Texas	Limited	Yes	Yes	No	No	No	No
Pennsylvania	Limited	Yes	Yes	Yes	Yes	Yes	Yes
South Carolina	Limited	Yes	Yes	Yes	No	No	No

[a] From Ref. 7.
[b] OEL—Occupational Exposure Limits.

From these early beginnings, guidelines to prevent illness from toxic substances were developed as part of recommendations issued by various private organizations, the National Safety Council, and the American National Standards Institute (ANSI) in the 1920s and 1930s, and the ACGIH (TLV's) in 1941.

Other organizations provided guidelines for various toxic substances that would provide protection for workers. For example, the American Petroleum Institute published a series of pamphlets on toxic substances (8).

Among the governmental bodies in the United States, the development of guidelines and regulations for toxic substances evolved over the first half of the twentieth century by a fragmented process. Certain states developed both exposure limits and practices for reducing exposures. In the United States, two major sources of numerical limits for various chemical and physical agents were set by ANSI, which is made up of professionals mainly from industry, government, and sometimes academia. ACGIH membership consisted of professionals employed in government (federal, state, or local) and academia, but input was routinely sought from industry specialists.

The TLV Committee of the ACGIH, established in 1941, was composed of six nationally recognized industrial hygienists and toxicologists not associated with private industry. The first list comprising 144 substances with their Maximal Allowable Concentrations (MAC) was promulgated in 1946 as recommendations to industry. In 1943, the Division of Industrial Hygiene of the U.S. Public Health Service published a prior list of 45 substances. Before 1955, no formal documentation of these values was issued. The early documentation was for Committee use only as an aid in revising limits at some future time. Documentation published by the Committee appeared in 1962 and comprised 267 substances. A second revised edition appeared in 1966 and included almost 400 substances. Now, supplements appear annually as new substances are added or as revisions are made in the list (9).

The criteria and procedures of the ACGIH TLV Committee are governed by the following philosophy:

Threshold Limits for industrial settings are based on the premise that, although all chemical substances are toxic at some concentration experienced for a period of time, a concentration exists for all substances from which no injurious effect will result no matter how often the exposure is repeated (9).

However, the ACGIH recognizes this as a desirable goal but has adopted the following philosophy: Threshold Limit Values (TLVs) are airborne concentrations of substances to which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects. Because of wide variation in individual susceptibility, a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit; a smaller percentage may be affected more seriously by aggravation of a preexisting condition or by development of an occupational illness. Individuals may also be hypersusceptible or otherwise unusually responsive to some industrial chemicals because of genetic factors, age, lifestyle, medication, or previous exposures. Such workers may not be adequately protected from adverse health effects from certain chemicals at concentrations at or below the threshold limits (10, 11).

TLVs were prepared only for the use of industrial hygienists, who could exercise their own judgment in applying these values. They were not to be used for legal purposes (1).

Several approaches for deriving occupational exposure limits (OELs) from animal data have been proposed and put into use during the past 40 years. Approximately 50% of the 1968 TLVs were derived from human data, and approximately 30% were derived from animal data. By 1992, almost 50% were derived primarily from animal data. Of those TLVs based on human data, most are derived from effects observed in workers who were exposed to the substance for many years. Consequently, most of the existing TLVs were based on the results of workplace monitoring, compiled with qualitative and quantitative observations of the human response (9). In recent times, TLVs for new chemicals have been based primarily on the results of animal studies, rather than human experience (12).

It is noteworthy that in 1968 only about 50% of the TLVs were intended primarily to prevent systemic toxic effects. Roughly 40% were based on irritation, and about 2% were intended to prevent cancer. By 1993, about 50% were meant to prevent systemic effects, 35% to prevent irritation, and 5% to prevent cancer (13).

TLVs are based on the best available information from industrial experience and human and animal experimental studies—when possible, from a combination of these sources (11, 14). The rationale for choosing limiting values differs from substance to substance. For example, protection against impairment of health may be a guiding factor for some, whereas reasonable freedom from irritation, narcosis, nuisance, or other forms of stress may be the basis for others. The age and completeness of the information available vary, consequently, the precision of each TLV is different. The most recent TLV and its documentation should always be consulted to evaluate the quality of the data upon which that value was set.

The issue of threshold effects is controversial, and scientists argue for and against threshold theories. Beginning in 1988, concerns were raised by numerous persons regarding the adequacy or health protectiveness of TLVs. The key question raised was, do the TLVs protect enough workers (15)?

Ziem and Castleman argued both that the scientific basis of the standards was inadequate and that they were formulated by hygienists who had vested interests in the industries being regulated (16).

A follow-up study by Roach and Rappaport (17) attempted to quantify the safety margin and

scientific validity of TLVs. They concluded that there were serious inconsistencies between the scientific data available and the interpretation given in the 1976 Documentation by the TLV Committee. They also noted that the TLVs were probably reflective of what the Committee perceived to be realistic and attainable at the time (17). This approach has been criticized, but it reflects the OSHAct where feasibility is critical criterion.

The TLV procedures and documentation continue to be debatable. It is clear that the process by which the TLVs and other OELs will be set will probably never be as it was between 1945 and 1990. It is likely that in the coming years, the rationale, as well as the degree or risk inherent in a TLV, will be more explicitly described in the documentation for each TLV. It is also certain that the definition of “virtually safe” or “insignificant risk” with respect to workplace exposure will change as the values of society change (18).

OELs have also been set by OSHA and NIOSH. Under the OSHAct, exposure limits are set via specific procedures. Criteria documents and literature reviews published by NIOSH serve as a basis for Recommended Exposure Limits (RELs). These RELs provide a scientific basis for OSHA to use in preparing a proposal (19), however, it should be noted that the constraints in the OSHAct require considering technical and economic feasibility, so that the permissible exposure limits (PELs) that OSHA sets are usually greater than the RELs that are based only on health considerations.

After a court decision that required OSHA to demonstrate the effect of a new standard, the number of adverse health effects reduced by lowering the PEL, OSHA has conducted quantitative risk assessments for the substance proposed for regulation showing the impact on illness, injury, or deaths at the old versus the proposed new PEL.

OSHA enforces approximately 400 PELs. These limits were adopted in 1970 under the Occupational Safety and Health Act and came from the 1968 list of the ACGIH TLVs and the standards of the American National Standards Institute (ANSI). An attempt was made in 1989 to adopt 428 chemicals from the 1989 TLV list as legally binding PELs, but legal challenges by various groups ultimately resulted in overturning these newly adopted values in 1992. The courts found that OSHA's approach was not consistent with the requirements set forth in Section 6(b) of the Act (20). The standards should be based on research, demonstrations, and experiments.

Regulations and Guidelines In the Workplace
Eula Bingham, Ph.D., L. Faye Grimsley, MSPH, CIH

2.0 Legislation, Standards and Guidelines in United States for Health and Safety in the Workplace
Standards, regulations, and guidelines are major tools for protecting workers and consumers from chemical and physical hazards in the workplace and the environment. In the United States as in other countries, there are specific procedures for developing standards, regulations, and guidelines for the workplace. In many countries, the governments pass the legal framework or laws that provide the basis for standards/regulations, guidelines, and exposure limits. The U.S. Congress passes laws that govern workplaces in the United States. To put those laws into effect, Congress authorizes certain governmental agencies such as the Department of Labor's Occupational Safety and Health Administration (OSHA) and Mine Safety and Health Administration (MSHA), the Environmental Protection Agency (EPA), and the Department of Transportation (DOT) to create and enforce rules.

Because laws often do not include all the details, regulations or standards are promulgated to describe specific rules for the legal requirements. Once the regulation is in effect, agencies then educate affected entities, such as employers and employees, as to how to comply. In some instances, guidelines are issued by governments and are not considered legally enforceable. Guidelines are sometimes developed by trade organizations to provide advice to members. The enforcement of the

legal requirements is usually delegated to a part of the agency separate from regulations or standards writing.

A process is followed to create regulations. First, an authorized agency such as OSHA decides that a regulation may be needed. The agency gathers information and provides an Advance Notice of Intended Rulemaking to the Federal Register. This notice provides an opportunity for interested persons to comment on the need for a standard. The need for new regulations may be based on new law, court order, public petition, or agency initiative. The proposal is published in the Federal Register, so that members of the public can consider it and send their comments to the agency. The agency receives all the comments, revises the regulation as appropriate, and issues a final rule. At each stage in the process, the Federal Register notices are available from the agency and are posted on the Internet. The specific processes to promulgate standards by OSHA are set out in section 6b and 3(8) of the OSHAct (4, 21).

The steps vary to some extent from those for regulations in that specific comment times are required as well as public hearings, if requested and a regulation follows. When a standard is completed, it is printed in the Federal Register as a final rule that includes the rationale, and the scientific and technical basis for the rule. The final rule without the supporting rationale is "codified" by being published in the Code of Federal Regulations (CFR). The CFR is the official record of all regulations created by the U.S. federal government. It is divided into 50 volumes, called titles, each of which focuses on a particular area. Almost all environmental and workplace regulations appear in Titles 40 and 29, respectively. The CFR is revised yearly, and one-fourth of the volumes is updated every three months.

The way research, technology, social and political movements interact determines the combination of laws, regulations, and guidelines that control toxic substances in the workplace. Standards are set as a measurable reference point consisting of specific guidelines by which the desired objective can be quantified and achieved (15). Regulations and guidelines for toxic substances in the workplace have been developed primarily to address injury and illness prevention, communicate hazards via training, and control hazards.

With passage of the Occupational Safety and Health Act in 1970 (OSHAct), workplace regulations and guidelines to control toxic substances were transformed and OSHA was established. Under the OSHAct, OSHA is authorized to issue and enforce regulations and standards that protect employees who work in businesses engaged in interstate commerce. Under Sections 6(a), 6(b) and 3(8) (4, 21), the process and criteria for promulgating standards for toxic substances in the workplace are provided. The federal or state governments (acting under special provisions provided in the OSHAct) can enforce final standards in the workplace. OSHA also has the authority to enforce an employer's obligation to protect employees from recognized hazards that are causing or likely to cause death or serious physical harm, even in the absence of a specific standard. This obligation is called the "general duty clause" (section 5(a) of the OSHAct), states:

"Each employer (1) shall furnish to each employee a place of employment which is free from recognized hazards that are causing or likely to cause death or serious physical harm to his employees; (2) shall comply with occupational safety and health standards promulgated under this Act" (21).

When the OSHAct was passed, it required the first standards to be national consensus standards or established federal standards as outlined in Section 6(a). Section 6(b) and 3(8) of the Act outline the criteria and guidelines for setting OSHA standards.

2.1 Types of Standards

Occupational health and safety standards have been set to cover four primary industry sectors that include General Industry which is found in 29 CFR 1910, Construction 29 CFR 1926, Maritime 29 CFR portions of 1915–1919, and Agriculture 29 CFR 1928. OSHA has three categories of standards

defined as follows:

(A) Standard means a standard which requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide a safe or healthful employment and places of employment; (B) National Consensus standard means any standard or modification thereof which (1) has been adopted and promulgated by a nationally recognized standards-producing organization under procedures whereby it can be determined by the Secretary of Labor or by the Assistant Secretary of Labor that persons interested and affected by the scope or provisions of the standard have reached substantial agreement on its adoption, (2) was formulated in a manner which afforded an opportunity for diverse views to be considered, and (3) has been designated as such a standard by the Secretary or the Assistant Secretary, after consultation with other appropriate Federal agencies; and (C) Established Federal Standard means any operative standard established by any agency of the United States and in effect on April 28, 1971, or contained in any act of Congress in force on the date of enactment of the Williams–Steiger Occupational Safety and Health Act (22).

In addition, a further breakdown of Consensus Standard was established to assist in implementing regulations, and they are defined as follows:

Specification standard is defined as a standard that sets detailed requirements for protecting employees from a workplace hazard. Vertical Standard is defined as an OSHA standard pertaining to a specific industry, such as construction or maritime trades. Performance Standard is defined as a standard that sets general requirements for protecting employees from a workplace hazard, allowing employers to choose their own means for complying with the regulation (23).

2.2 Other U.S. Agencies that Establish Workplace Regulation of Toxic Substances

Within the United States, some of the most common guidelines and regulations are established by the EPA and OSHA. The major U.S. federal agencies that have standards, regulations, or guidelines dealing with toxic substances are presented in Table 8.2. These laws regulate some aspect of toxic substances in the workplace. The OSHAct remains the most extensive piece of safety and health legislation in the United States and regulates conditions in six million private business establishments (23). However, other legislation and authorities have a major role in controlling chemical and physical exposures in the workplace.

Table 8.2. Federal Laws and Agencies Affecting Toxic Substance Control[a]

Statute	Year Enacted	Responsible Agency
Toxic Substance Control Act	1976	EPA
Clean Air Act	1970; amended 1977 & 1990	EPA
Federal Water Pollution Control Act (now Clean Water Act)	1972; amended 1977	EPA
Safe Drinking Water Act	1974; amended 1977	EPA
Federal Insecticide, Fungicide, and Rodenticide Act	1947; amended 1972, 1975, 1978	

Act of July 22, 1954 (codified as Section 346 (a) of the Food, Drug, and Cosmetic Act)	1954; amended 1972	EPA
Resource Conservation and Recovery Act	1976	EPA
Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)	1980; amended as SARA 1986	EPA
Marine Protection Research and Sanctuaries Act	1972	EPA
Asbestos Hazard Emergency Response Act (AHERA)	1986	EPA
Food, Drug, and Cosmetic Act	1938; amended 1997	FDA
Food additives amendment	1958	FDA
Color additives amendment	1960	FDA
New drug amendments	1962	FDA
New animal drug amendments	1968	FDA
Medical device amendments	1976	FDA
Fair Packaging and Labeling Act	1976	FDA
Public Health Service Act	1944; amended 1997	FDA
Federal Meat Inspection Act	1967; amended 1997	USDA
Poultry Products Inspection Act	1957; amended 1997	USDA
Egg Products Inspection Act	1970	USDA
Poison Prevention Packaging Act	1970	CPSC
Lead Based Paint Poisoning Prevention Act	1973; amended 1976	CPSC, HHS, HUD
Hazardous Materials Transportation Act	1975; amended 1976	DOT—Materials Transportation Bureau
Federal Railroad Safety Act	1970	DOT—Federal Railroad Administration
Ports and Waterways Safety Act	1972	DOT and Coast Guard
Dangerous Cargo Act	1952	
Occupational Safety and Health Act	1970	OSHA, NIOSH
Federal Mine Safety and Health Act	1977	Labor (Mine Safety and Health Administration) and NIOSH

[a] CPSC = Consumer Products Safety Commission
DOT = Department of Transportation
EPA = Environmental Protection Agency
FDA = Food & Drug Administration
HHS = Health and Human Services
HUD = Housing & Urban Development
NIOSH = National Institute for Occupational Safety & Health

OSHA = Occupational Safety & Health Administration
USDA = United States Department of Agriculture
SARA = Superfund Amendments and Reauthorization Act

You will find some of the other legislation and regulatory agencies that have promulgated standards in the United States to address employee health and safety in Table 8.3. When the OSHAct was passed, the recognition of other agencies came in the form of a special provision in section 4(b) (1), which states "Nothing in this Act shall apply to working conditions of employees with respect to which other Federal agencies, and State agencies acting under section 274 of the Atomic Energy Act of 1954, as amended (42 U.S.C. 2021), exercise statutory authority to prescribe or enforce standards or regulations affecting occupational safety or health" (21).

Table 8.3. Regulations To Protect Workers from Toxic Agents in the U.S. Workplace[a]

Statute	Responsible Agency	Part/Section	Requirements[b]
Toxic Substance Control Act (TSCA)	EPA	TSCA Sections 8 (c, d, & e)	Premarketing testing and reporting of chemicals; and Reporting of substantial risks
Federal Insecticide, Fungicide, and Rodenticide Act	EPA	40 *CFR*, Part 170	Testing may deny registration, warnings, re-entry limits
Resource Conservation and Recovery Act	EPA	40 *CFR*, Part 263	Training
Asbestos Hazard Emergency Response Act (AHERA)	EPA	40 *CFR*, Part 763	Training
Hazardous Materials Transportation Act	DOT	49 *CFR*, Parts 171-180	Training and labeling
Occupational Safety and Health Act	OSHA	29 *CFR*, Part 1910 29 *CFR*, Part 1915 29 *CFR*, Part 1917 29 *CFR*, Part 1918 29 *CFR*, Part 1926	Promulgates health and safety regulations and enforces training requirements
Federal Mine Safety and Health Act	MSHA	30 *CFR* Parts 1-199	Promulgates health and safety regulations and enforces training requirements

[a] EPA = Environmental Protection Agency
DOT = Department of Transportation
OSHA = Occupational Safety & Health Administration
MSHA = Mine Safety and Health Administration
CFR = Code of Federal Regulations

[b] Refer to appropriate statutes and regulations for specific requirements.

2.2.1 Mine Safety and Health Administration (MSHA) Health and safety conditions in the mining industry are regulated by the Federal Mine Safety and Health Act of 1977 (MSHAct). This law, whose enactment was prompted by a number of mine disasters in the 1970s, amended the Federal Coal Mine Health and Safety Act of 1969 and repealed the Metal and Nonmetallic Mine Act of 1966, bringing many types of mines that previously had been covered by a variety of earlier laws under one system of regulation.

MSHA was created to set and enforce standards and established an independent Federal Mine Safety and Health Review Commission to hear challenges to MSHA citations. MSHA has jurisdiction over work activities in mines, and also over work activities on the roads leading to and from mines; on the roads belonging to the mine property; over the lands, structures, equipment, and property used in connection with mines; including milling operations; and over the work of preparing coal or other mined minerals, including custom coal preparation facilities. The MSHAct requires MSHA to inspect every underground mine at least four times a year and every surface mine at least twice per year.

The MSHAct procedures for setting standards are similar to those set by the OSHAct for OSHA. MSHA must publish a proposed standard in the Federal Register for comment and give interested parties the opportunity to request a hearing.

MSHA may issue emergency temporary standards when it determines that miners are “exposed to grave danger from exposure to substances or agents determined to be toxic or physically harmful, or to other hazards,” and that emergency action is needed to protect the miners. However, the agency must begin permanent rulemaking to address the hazard as soon as it publishes the emergency rule and must issue a permanent standard no more than nine months later. MSHA may modify the application of a permanent standard when petitioned to do so by a mine operator or a representative of the miners employed at the time, by a process that is similar to OSHA's process for variances from OSHA standards.

An interagency agreement signed between OSHA and MSHA on March 29, 1979, clarifies the jurisdictional authorities of the two agencies. As a general rule, the agreement specifies that MSHA will exercise its authority on mine sites and in milling operations. However, where the provisions of the mine act do not cover or otherwise do not apply to job-related hazards at these sites, or where MSHA has statutory jurisdiction but no MSHA standards exist that are applicable to particular working conditions, the OSHAct will apply.

OSHA may also exercise its authority over an employer who has control over working conditions at a mining or milling site, if that employer is neither a mine operator nor an independent contractor subject to the mine act, if application of the OSHAct to this type of employer would provide a more effective remedy than citing a mine operator or independent contractor that does not have direct control over those conditions (24).

MSHA has broad authority to develop, promulgate, and enforce mandatory health and safety standards to protect the health and safety of the nation's miners. MSHA's authority to regulate in the area of radiation is derived from its statutory mandate to protect and promote occupational safety and health in the mining and milling of minerals, including those that expose the miner to radioactivity. In addition, MSHA may exercise jurisdiction over any equipment used in mining that potentially exposes miners to radioactivity. MSHA had codified regulations dealing specifically with radiation in Title 30, subchapter N, Part 57, of the Code of Federal Regulations (24a).

The Powerplant and Industrial Fuel Use Act of 1978 substantiates MSHA's authority to protect

existing and future housing, property, persons, and public facilities located adjacent to or near active and abandoned coal, uranium, metal, and nonmetallic mines against mining hazards (24).

2.2.2 Department of Health and Human Services (HHS) Food and Drug Administration (FDA) Under the Radiation Control for Health and Safety Act of 1968, FDA is authorized to promulgate and enforce performance standards for controling radiative emissions by electronic products. FDA's regulations promulgating these standards are set forth in Title 21, Subchapter J, of the Code of Federal Regulations (24a). Although not specific for workers, provisions to protect consumers can also protect workers in some industries such as drug manufacturing and food production (24b).

National Institute for Occupational Safety and Health The National Institute for Occupational Safety and Health (NIOSH) has primary responsibility for certifying and approving respirators. After enactment of the OSHAct, NIOSH and the U.S. Bureau of Mines (USBM) promulgated 30 CFR, Part 11, which outlined the procedures for respirator approval. After reorganization of the USBM, function for respirator certification and approval were eventually transferred to the MSHA in 1977, and respirators were jointly approved by NIOSH and MSHA (25).

In 1995, a final rule (42 CFR part 84) was issued that addressed NIOSH and MSHA's certification requirements for respiratory protective devices. The provisions of this rule now give NIOSH exclusive authority for testing and certifying respirators. Certain mine emergency devices will continue to be jointly certified by NIOSH and MSHA (26).

2.2.3 Department of Transportation (DOT) The Federal Hazardous Materials Transportation Law (Federal Hazmat Law), formerly the Hazardous Materials Transportation Act, is the basic statute that regulates hazardous materials transportation in the United States. Under this law, DOT has broad authority to issue and enforce regulations for the safe transportation of hazardous materials, including radioactive materials, on the nation's highways. In addition, the Hazmat Law specifically directed DOT to issue regulations regarding the transportation of radioactive materials on passenger-carrying aircraft, railways, and waterways (27).

Pertinent regulations are codified in Title 49 of the Code of Federal Regulations. The Hazardous Materials Regulations (HMR; 49 CFR Parts 171–180) cover five areas and include hazardous materials definition/classification, hazard communication, packaging requirements, operational rules, and training. Those relating specifically to radioactive materials cover labeling, shipping, rail transportation, air transportation, carriage by vessel, and highway transportation (28).

2.2.4 Environmental Protection Agency (EPA) Several statutes administered by the EPA provide basic authorization for it to regulate worker health and safety directly, for example, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which promulgates reentry limits for pesticide application in fields thus protecting farm workers. FIFRA also requires labeling and protections from low-level ionizing radiation. Other EPA statutes provide for indirect regulation that can impact worker health. The Clean Air Act regulates the emissions of pollutants, including radioactive materials, into the air. The Clean Water Act regulates the discharges of pollutants into waterways and sewage systems, including radioactive materials, except for those (source material, special material, and by-product material) regulated under the Atomic Energy Act. The Safe Drinking Water Act protects against contaminants, including radioactive materials, in public water systems, and underground injection which may contaminate public water systems. The Resource Conservation and Recovery Act (RCRA; Solid Waste Disposal Act, as amended) covers the disposal of hazardous wastes, and which requires worker training. The Toxic Substances Control Act (TSCA) regulates manufacturing, distribution, processing, use, and disposal of toxic substances, including radioactive materials, except for those regulated under the Atomic Energy Act, and the Marine Protection, Research, and Sanctuaries Act of 1972 regulates ocean dumping of all materials, including all radioactive materials. Several provisions of TSCA impact workers' health such as Section 8 c, d, and e. These sections require pre-market toxicity testing, reporting of chemicals, and reporting of

substantial risk.

In addition, under the Atomic Energy Act as amended by the Uranium Mill Tailings Radiation Control Act of 1978, EPA has authority to set standards for disposal of uranium mill tailings at active and inactive sites. Under Reorganization Plan No. 3 of 1970, EPA is further authorized to establish generally applicable environmental standards for protecting the general environment from radioactive material. These standards are promulgated by EPA but implemented by the Nuclear Regulatory Commission (NRC) and the Department of Energy (DOE). The standards are published in Title 40, Subchapter F, of the Code of Federal Regulations.

Also under Reorganization Plan No. 3, EPA is responsible for advising the President generally with respect to radiation matters that directly or indirectly affect health, including guidance for all Federal agencies in formulating radioactive standards and in establishing and executing cooperative programs with the states (29).

2.2.5 Nuclear Regulatory Commission (NRC) The NRC's authority to regulate radiative exposure, particularly in workers in DOE operations (under private corporations contracted to DOE), is derived principally from the regulatory authority of the Atomic Energy Commission (AEC). All licensing and related regulatory functions of the AEC were transferred to the NRC by the Energy Regulation Act of 1974, which created the NRC. Under this legislation, the NRC has broad authority to license and regulate the use and distribution of special nuclear material, source material, and by-product material and to establish minimum criteria for the issuance of licenses. In addition, the NRC has broad authority to regulate licenses. These authorities have been implemented by the NRC through regulations set forth in Title 10 of the Code of Federal Regulations, Parts 20, 30–35, 40, 50, 51, 70, and 71.

Title II of the Uranium Mill Tailings Radiation Control Act of 1978 extended NRC's licensing authority over by-product material to include uranium and thorium mill tailings. The act also subjects this class of by-product material to more extensive regulatory requirements than provided for other by-product material and authorizes the NRC to take appropriate measures to protect public health and safety and the environment from radiological hazards associated with such material.

In view of the overlap between the responsibilities of NRC and other agencies, NRC has entered into various Memoranda of Understanding with the DOT, the EPA, the Coast Guard, the Army Corps of Engineers, the Council on Environmental Quality, the Air Force, DOE, FDA, NOAA, and the FAA (30).

2.2.6 Coast Guard/Maritime Under U.S. maritime law, the U.S. Coast Guard (USCG) has authority over safety on tank and passenger vessels. Among Coast Guard standards pertaining to the safety of maritime employees are those regulating lifesaving equipment on tank vessels, fire-fighting equipment on tank vessels, lifesaving equipment on passenger vessels, and special construction arrangements and other provisions for carrying anhydrous ammonia, combustible liquids, and other dangerous cargoes in bulk (31).

In a memorandum of understanding (32), OSHA and the Coast Guard have agreed that OSHA retains its authority under the OSHAct to respond to complaints by seamen aboard Coast Guard-inspected vessels regarding alleged discrimination for safety-related activity. OSHA also has the authority to order vessel owners to post notices informing employees of their right to complain about working conditions to the Coast Guard, OSHA, or to the employer, and to be free from retaliatory discrimination.

The Outer Continental Shelf Lands Act gives the Coast Guard and the Department of the Interior's Minerals Management Services (MMS) the authority to set and enforce standards to regulate hazardous working conditions on the outer continental shelf.

Standards set by MMS pertain to safety in drilling operations by offshore rigs, well completion, and well workover; production safety systems; platforms and structures, including inspection and maintenance; and employee training (30).

The Coast Guard's regulations pertain to mobile offshore units—vessels engaged in drilling operations—rather than stationary rigs. They include rules for inspection and certification of vessels, including testing of firefighting equipment and lifeboats, design and equipment, including location of firefighting equipment and lifeboats, and operations, including practice drills and stowage of safety equipment.

There is also an agreement, Memorandum of Understanding (MOU), between OSHA and the Coast Guard regarding enforcement of standards covering working conditions for which the Coast Guard has no specific standards of its own. The Coast Guard notifies OSHA whenever a Coast Guard inspection finds apparent violations of OSHA rules and cooperates with any subsequent enforcement activity that OSHA undertakes.

Under the Federal Water Pollution Act, the Coast Guard has been delegated the authority to respond to discharges of oil into U.S. waters. Under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), the Coast Guard has been delegated the authority, as the designated On-Scene Coordinator, to respond to the release of hazardous substances into the environment within the U.S. coastal zone.

Coast Guard employees, other government employees, and contract personnel involved in oil spill response activities must comply with all applicable worker health and safety laws and regulations. The primary regulation is OSHA's hazardous waste operations and emergency response (29 CFR 1910.120). Other regulations may be applicable if employees are involved in cleanup operations at uncontrolled hazardous waste sites being cleaned up under government mandate and in certain hazardous waste treatment, storage, and disposal operations conducted under the Resource Conservation and Recovery Act of 1976 (RCRA). The regulations apply to both emergency response and post-emergency cleanup of hazardous substance spills. Most oils and oil spill responses are also covered in 49 CFR Part 172. The rules cover employee protection during initial site characterization and analysis, monitoring activities, materials handling activities, training, and emergency response (29, 31).

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3.0 Governmental Regulation of Toxic Chemicals in Workplaces
3.1 Rationale for Workplace Exposure Limits
Occupational health professionals are faced with the challenge of evaluating and controlling exposures to the thousands of chemicals used in the workplace. There are only a few hundred occupational exposure limits worldwide to provide guidance with regard to safe levels.

The rationale for setting occupational limits varies, depending upon the chemical and the country or specific organization that establishes the exposure limits. Some exposure limits are set to avoid nuisances such as odor, whereas another may be to prevent irritation or chronic diseases such as cancer. Overall, the goal of most occupational exposure limits is to protect workers during their entire working lifetime, which is approximately 40 years. Approximately 23 countries and organizations have established and published occupational exposure limits using various criteria (33). Some of the most common are presented in Table 8.4. In the United States, OSHA, ACGIH, NIOSH, and AIHA have set forth occupational exposure limits. The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area is responsible for

developing the Maximum Allowable Concentrations (MAKs).

Table 8.4. Selected Countries/Organizations That Have Occupational Exposure Limits[a]

Country	Enforcement (Monitored and Enforced)	Type of Standard Set[b]			
		TWA	STEL	Ceilings	BEI
Australia	N	Y	Y	Y	N
Ontario	Y	Y	Y	Y	—
European Community	Y	Y	Y	Y	Y
Germany	Y	Y	Y	Y	Y
Japan	N	Y	Y	Y	Y
Sweden	Y	Y	Y	Y	—
United Kingdom	Y	Y	Y	Y	—
USA-ACGIH	N	Y	Y	Y	Y
USA-NIOSH	N	Y	Y	Y	Y
USA-OSHA	Y	Y	Y	Y	Y

[a] Table 4 abridged from Ref. 31a.

[b] TWA = Time Weighted Averages
STEL = Short-term Exposure Limits
BEI = Biological Exposure Indices

Exposure limits for most workplace air contaminants are based on the premise that although all chemical substances are toxic at some concentration when experienced for a period of time, a concentration (e.g., dose) does exist for all substances at which no injurious effects should result, no matter how often the exposure is repeated (9, 11). Thinking differs throughout the world with regard to the amount of chemical exposure that constitutes a safe level. For example, one country might think that the optimal value and goal to be sought is zero concentration. Table 8.5 lists the numerical occupational exposure limits for many chemicals throughout the world. For this reason, the criteria and procedures for setting limits differ (9). Zero exposure is the goal that should be set forth, but it is not generally the reality in the workplace.

Table 8.5. Occupational Exposure Limits for Selected Substances and Countries/Organizations[ab]

	Arsenic (Inorganic)[a]		Lead (Inorganic)[a]		Asbestos (Crocidolite)[a]		Silica (Crystalline)[a]	
Country/Organization Unit	TWA	STEL	TWA	STEL	TWA	STEL	TWA	STEL

Australia	ppm					0.1 f/cc		
	mg/m^3	0.05		0.15			0.2	
Germany (MAK)[cd]	ppm							
	mg/m^3			0.1			0.15	
Japan	ppm							
	mg/m^3	0.5		0.1				
Poland	ppm							
	mg/m^3	0.01		0.05			1.0	
Sweden	ppm							
	mg/m^3	0.03		0.05			0.1	
United Kingdom	ppm							
	mg/m^3	0.1		0.15		0.2 f/cc		0.3
USA-ACGIH (TLV)	ppm					0.1 f/cc		
	mg/m^3	0.01		0.05			0.1	
USA-NIOSH (REL)	ppm					0.1 f/cc		
	mg/m^3		C0.002 < 0.1				0.05	
USA-OSHA (PEL)	ppm					0.1 f/cc	1.0 f/cc	[e]
	mg/m^3	0.01		0.05				
Venezuela	ppm							
	mg/m^3	0.5	0.5	0.15	0.45			

		Benzene		**Trichloroethylene (TCE)**			**Vinyl Chloride**	
Country/Organization	**Unit**	**TWA**	**STEL**	**TWA**		**STEL**	**TWA**	**STEL**
Australia	ppm	5		50		200	5	
	mg/m^3	16		270		1080	10	
Germany (MAK)[d]	ppm			50				
	mg/m^3			270				
Japan	ppm	10	25	25				2.5
	mg/m^3	32	80	135				6.5
Poland	ppm							
	mg/m^3	10	40	50			5	30
Sweden	ppm	1	5	10		25	1	5
	mg/m^3	3	16	50		140	2.5	13
United Kingdom	ppm	5		100		150		

	mg/m^3	16		550	802	7	
USA-ACGIH (TLV)	ppm	0.5	2.5	50	100	1	
	mg/m^3	1.6	8	269	537	2.3	
USA-NIOSH (REL)	ppm	0.1	1	25 (10-hr TWA)	C 2		
	mg/m^3	0.32	3.2				
USA-OSHA (PEL)	ppm	1	5	100	C 200	1	5
	mg/m^3	3	15				
Venezuela	ppm	10		100	150		
	mg/m^3	30		535	800		

[a] References (6, 19, 35, 36, 50, and 51) used to generate table.
[b] STEL = Short-term Exposure Limit
TWA = Time-weighted average
C = Ceiling
ppm = Parts of vapor or gas per million parts of contaminated air by volume
mg/m^3 = Milligrams of substance per cubic meter of air
f/cc = Fiber per cubic centimeter of air
[c] Respirable quartz
[d] Germany does not set specific OEL for carcinogens
[e] Formulae: (10 mg/m^3) ÷ (% SiO_2 + 2)

Occupational exposure limits established both in the United States and elsewhere are derived from a variety of sources and based on different methodologies. The majority were developed from human experience and animal data. Because the process of carrying out the scientific work to obtain the necessary experimental, clinical, and epidemiological data is complex, only a few countries have been able to set validated exposure limits for any substantial number of industrial chemicals.

Some countries have also developed guidelines for biological monitoring in addition to exposure limits for inhalation of chemicals. According to the ACGIH, biological monitoring consists of assessing overall exposure to chemicals that are present in the workplace by measuring the appropriate determinants in biological specimens collected from the worker at the specified time. The ACGIH has developed Biological Exposure Indices (BEIs) as reference values intended as guidelines for evaluating potential health hazards. Other countries, including the United Kingdom and Germany, have also developed biological exposure limits (see Table 8.4).

Enforcement of occupational exposure limits varies greatly from country to country. Some countries use them as guidelines to assist in compliance with the law. Others believe that the occupational exposure limits have legal force and are enforced by regulatory agencies. In the United States, the OSHA permissible exposure limits are the most common airborne exposure limits enforced. Table 8.4 lists selected countries and their enforcement practices for their exposure limits. However, such limits set forth by the ACGIH and other organizations are also used as guidelines in the workplace, and some companies report that they abide by the lowest values.

3.2 Exposure Limit Definitions and Special Notations

Occupational exposure limits have been set for airborne contaminants by many countries and organizations. Some have also established exposure limits for biological and physical agents. Limits are established to protect against peak exposures and chemical exposures that may have long-term effects. The terminology for exposure limits can be confusing. Following, you will find some of the most common exposure limits and definitions.

TLVs are defined as guidelines by the ACGIH (34), which represent airborne concentrations of substances and representative conditions under which employees, generally, may be repeatedly exposed without suffering adverse health effects. Specifically, the ACGIH has three categories of

exposure limit values and the following definitions are based on information from the TLV booklet and are defined as follows: (1) Threshold Limit Value—Time-Weighted Average (TLV-TWA)—the time-weighted average concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect; (2) Threshold Limit Value—Short-Term Exposure Limit (TLV-STEL)—is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. STELs were developed to set concentrations to which it is believed that workers can be exposed continuously for a short period of time without suffering from irritation, chronic or irreversible tissue damage, or narcosis of sufficient degree to increase the likelihood of accidental injury, to impair self-rescue, or materially reduced work efficiency, provided that the daily TLV-TWA is not exceeded; (3) Threshold Limit Value-Ceiling (TLV)—the concentration that should not be exceeded during any part of the working exposure.

Permissible exposure limits are established and published by OSHA and are legally enforceable. The PELs are TWA concentrations that must not be exceeded during an 8-hour workshift of a 40-hour workweek. These limits are deemed by the agency to be the highest level to which an employee may be exposed to a harmful substance or physical agent without harmful effects. The OSHA permissible exposure limits (PELs), are found in tables Z-1, Z-2, and Z-3 of the OSHA General Industry Air Contaminants Standard (29 CFR 1910.1000). OSHA has also set action levels for specific agents. The action level is defined as the concentration or level of an agent at which it is deemed that some specific action should be taken. Employers are required by OSHA to begin regular monitoring to measure ongoing exposure, and to use engineering controls and personal protective equipment if the action level is exceeded. Usually, in general practice the action level is set at one-half of the permissible exposure limit (10).

Recommended Exposure Limits (RELs) are set by the National Institute for Occupational Safety and Health (NIOSH) and are used as recommendations for criteria standards for specific substances identified by OSHA based only on projected health effects (feasibility is not a criterion). RELs are TWA concentrations for up to a 10-hour workday during a 40-hour workweek (19).

The German MAK value (“Maximale Arbeitsplatz-konzentration”, maximum workplace concentration) is defined as the maximum concentration of a chemical substance in the workplace air which should not have known adverse effects on the health of the workers nor cause unreasonable annoyance even when the person is repeatedly exposed during a 40-hour workweek (or 42-hour when averaged over four weeks in firms that have four work shifts). Usually, the MAK value is an average concentration obtained by integrating the concentrations determined during a period of up to one working day or shift. MAK values are established on the basis of the effects of chemical substances. When possible, practical aspects of the industrial process and the resulting exposure patterns are also taken into account; scientific criteria, for preventing adverse effects on health are decisive, not technical and economic feasibility (35). The values are estabished by the Deutsche Forschungsgemeinschaft (DFG), Federal Republic of Germany, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area.

The MAK values were developed for healthy persons of working age. The unconditional adoption of MAK and BAT (Biological Tolerance value for the working Material) values as guidelines during pregnancy is not possible because observance of these values does not guarantee in every case that the unborn child is reliably protected from the prenatal toxicity of the substances. The expression “prenatal toxicity” is taken in its broadest sense by the Commission; it includes any effect of the substance that elicits an alteration from the physiological norm in the offspring or causes permanent morphological or functional damage. Many substances have not yet been investigated or have not been thoroughly evaluated for prenatal toxicity. It is usually not safe to justify or quantify a risk of prenatal toxicity in man on the basis of animal studies. In the individual case, risk to a human can exist, even if the result of animal tests are negative, if the dose is significantly lower than the threshold dose determined in animal experimentation.

The Commission is testing the substances in the lists of MAK and BAT values to determine whether a risk of prenatal toxicity can be excluded by observance of MAK values and BAT values, whether such a risk has been reliably proved or must be assumed as probable on the basis of the existing data.

Substances have been classified according to their prenatal toxicity and grouped in following categories:

Group A: A risk of damage to the embryo or fetus has been unequivocally demonstrated. Exposure of pregnant women can lead to damage to the developing organism even when the MAK and BAT values are observed.

Group B: Currently available information indicates that a risk of damage to the embryo or fetus must be considered probable. Damage to the developing organism cannot be excluded when pregnant women are exposed, even when MAK and BAT values are observed.

Group C: There is no reason to fear a risk of damage to the embryo or fetus when MAK and BAT values are observed.

Group D: Classification in one of the groups A–C is not yet possible because, although the data available may indicate a trend, they are not sufficient for final evaluation.

MAK values cannot be established for a number of carcinogenic and mutagenic substances for the following reasons: cancer and mutations become manifest only after years and decades and under certain circumstances in future generations. After extended periods of exposure to low doses of these substances, the effects are extensively accumulated; whether or to what extent repair occurs can not presently be stated. However, because certain carcinogens are unavoidable in industrial processes and to some extent also occur naturally and because exposure to these substances cannot be completely eliminated, quantitative guidelines for protective measures and their analytical surveillance are necessary to ensure protection at work. The German Commission has set up technical exposure limits (TRK) in special cases. TRK values are not MAK values and are not listed in Table 8.5 for carcinogens (35).

Skin Guidelines Some substances are designated with skin notations because absorption of substances through the skin can make a significant contribution to systemic exposure to the employee or can even be the main exposure route. The ACGIH, OSHA and the German Commission have developed criteria to address skin absorption. Substances that have a “Skin” notation refer to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance. Substances are designated with an “H” when systemic exposure may be increased by cutaneous absorption (6, 34, 35).

Mixtures Special attention should also be given to the application of the exposure limits in assessing the health hazards from exposure to mixtures of two or more substances. The ACGIH and OSHA have established guidelines for exposure values for mixtures. The guidelines state that when two or more hazardous substances which act upon the same organ system are present, their combined effect, rather than that of either individually, should be given primary consideration. In the absence of information to the contrary, the effects of the different hazards should be considered additive, that is, if the sum of the concentrations divided by the corresponding threshold value exceeds unity, then the threshold limit of the mixture should be considered exceeded. Exceptions to this guideline may be made when there is a good reason to believe that the main effects of the different harmful substances are not in fact additive but are independent, for example, when purely local effects on different organs of the body are produced by the various components of the mixture. In such cases, the threshold limit ordinarily is exceeded only when at least one member of the series of concentrations and exposure limits itself has a value that exceeds unity. For examples and more information, see the ACGIH TLV booklet or OSHA standard 29 CFR 1910.1000 (34, 36). In general, the MAK value is valid only for exposure to a single pure substance, and the German Commission has refrained from

calculating MAK values for mixtures (35).

Carcinogens Several organizations and agencies provide guidelines for defining and classifying chemical or physical agents as carcinogens. Three of the most well-known agencies that have developed procedures and protocols for testing and classifying agents for carcinogenic potential are the National Toxicology Program (NTP), the International Agency on Research for Carcinogenicity (IARC), and the U.S. EPA.

First, the listing of a substance in the Annual Report on Carcinogens is mandated by Public Law 95-622. The evaluation of substances listed in the Annual Report is performed by scientists from the National Toxicology Program (NTP) and other federal health research and regulatory agencies. The listing of a substance in the Annual Report is descriptive and qualitative in nature and represents an initial step in hazard identification, which is generally considered the first step in the analytical process known as risk assessment. It is necessary to conduct a risk assessment to estimate the potential of any substance to harm human health. Risk assessments are not conducted by the NTP for substances in the Annual Report.

For the purpose of the NTP Report, “known carcinogens” are defined as those substances for which there is sufficient evidence of carcinogenicity from studies in humans to indicate a causal relationship between the agent and human cancer. “Reasonably anticipated to be carcinogens” are those substances for which there is limited evidence of carcinogenicity in humans and/or sufficient evidence of carcinogenicity in experimental animals. Sufficient evidence in animals is demonstrated by positive carcinogenicity findings in multiple strains and species of animals, in multiple experiments, or to an unusual degree with regard to incidence, site, type of tumor, or age of onset. Only substances for which the evidence of carcinogenicity has been peer-reviewed are evaluated for possible inclusion in the Annual Reports (37).

In 1969, the International Agency for Research on Cancer (IARC) initiated a program to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. The monographs' program has since been expanded to include consideration of exposures to complex mixtures of chemicals and of exposures to other agents such as radiation and viruses.

The objective of the program is to prepare, with the help of international working groups of experts, and to publish in the form of monographs, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The monographs represent the first step in carcinogenic risk assessment and may also state where additional research efforts are needed.

The monographs may assist national and international agencies in making risk assessments and in formulating decisions concerning any necessary preventive measures. The evaluations of IARC working groups are scientific, qualitative judgments about the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which regulatory measures may be based. Other components of regulatory decisions may vary from one situation to another and from country to country, responding to different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which is the responsibility of individual governments and/or other international organizations.

The overall evaluation of the carcinogenicity of substances has been categorized by the IARC. The agent, mixture, or exposure circumstance is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent, mixture, or exposure circumstances is a matter of scientific judgment, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

Group 1—The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans. This category is used when there is sufficient evidence

of carcinogenicity in humans.

Group 2A—The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans. This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.

Group 2B—The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans. This category is used for agents, mixtures, and exposure circumstances for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals.

Group 3—The agent (mixture or exposure circumstances) is not classifiable as to its carcinogenicity in humans. This category is used most commonly for agents, mixtures, and exposure circumstances for which the evidence of carcinogenicity is inadequate or limited in experimental animals.

Group 4—The agent (mixture) is probably not carcinogenic to humans. This category is used for agents or mixtures for which there is evidence that suggests lack of carcinogenicity in humans and in experimental animals (38).

The U.S. EPA has developed a similar system for stratifying evidence of human carcinogenicity. In the EPA system, chemicals are classified in one of five groups, based on the overall weight of the evidence for carcinogenicity. Group A comprises those chemicals for which there is "sufficient evidence from epidemiologic studies to suggest a causal association between exposure to the agents and cancer." Group B includes those compounds for which there is limited evidence of human carcinogenicity. As in the IARC scheme, this group is further divided into two subgroups, B1 and B, and the criteria for inclusion in B1 is limited evidence of carcinogenicity from epidemiological studies. B2 is for sufficient evidence in animals. The EPA system includes a group C, which comprises compounds that are designated as possible human carcinogens on the basis of a wide range of evidence, including limited long-term bioassays, short-term tests, and structure–activity relationships. Group D is for compounds that are not classifiable as human carcinogens, and Group E comprises compounds for which there is adequate epidemiological and experimental evidence that they are not human carcinogens. It is worth noting that EPA's classification of a chemical as a carcinogen often does not indicate whether the hazards exist for the inhalation or oral routes, even though EPA has acknowledged that cancer hazards may be route specific. The EPA Cancer Guidelines, unlike the OSHA Cancer Policy, discuss risk assessment methodology and suggest that as a special case of the multistage model, the linearized multistage model (LMS) is generally appropriate (39).

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4.0 Toxic Substance Exposure Prevention Guidelines

4.1 Communication of Chemical Hazards

The need for communicating health risks from chemical hazards in the workplace has resulted in a variety of classification schemes for toxicity data, so that organized interpretations of significance to humans can be made. These schemes typically exist as part of hazard communication, transportation, and labeling regulations, or as a part of various consensus standards, toxicity testing protocols, or independent publications (40). Unfortunately, the criteria used for hazard classification purposes are not always consistent (41–43). This can result in portraying a chemical differently by various classification schemes, thus leading to inconsistency and confusion, despite the fact that the same toxicity data have been used for classification. Examination of Material Safety Data Sheets (MSDSs) from two or more sources for the same chemical reveals such differences in interpretation. Efforts have been initiated to "harmonize" various classification schemes worldwide (44). However, a

disparity is likely to exist for some time to come. Consequently, the practicing occupational health professional needs to be aware of various health hazard classification systems to cope effectively with different regulations and the overall demands of hazard communication.

Many countries have requirements that address some aspect of chemical classification and labeling, but few have comprehensive systems. Different agencies have responsibility and authority for different parts of an overall system. Often there are different purposes or driving forces within different pieces of legislation and, although all have a general purpose of protecting people potentially exposed to the chemicals, the specific intents may vary. For example, the United States and Canada have workplace hazard identification systems that are based on the principle that workers have the “right to know” this information. Hence, they are driven by a necessity to communicate hazards to the ultimate users. In the European Community (EC), an added purpose is to facilitate trade within EC countries. Thus, there may be less emphasis on worker training. The degree of specificity also varies significantly among various schemes. The EC system is very specific and gives exact wording for label statements on particular categories of substances; however, the scope is narrower than comparable sysems in the United States and Canada where a performance-oriented, criteria-driven approach is used. This does not imply that one system is inherently better than another; rather the differences in the various schemes simply underscore how divergent results can occur (40).

4.1.1 OSHA Hazard Communication Standard The Occupational Safety and Health Administration (OSHA) recognizes that hazard evaluation is a process that relies heavily on the professional judgment of the evaluator, particularly in the area of chronic hazards. The performance orientation noted in the OSHA hazard identification standard of the hazard determination does not diminish the duty of the chemical manufacturer, importer, or employer to conduct a thorough evaluation to examine all relevant data and produce a scientifically defensible evaluation. Data used in making hazard determinations that meet the requirements of OSHA are human studies, animal studies, and other experimental data, for examples, mutagenesis.

OSHA's Hazard Communication Standard (29 CFR, 1910.1200) requires employers to inform workers of chemical hazards via MSDSs, container labeling, and training (45).

4.1.2 European Community's Classification of Dangerous Substances Within the European Community (EC), the objective of classifying chemical hazards is to identify the toxicological, physiochemical, and ecotoxicological properties of substances that may present a risk during normal handling and use. Individual chemicals and chemical mixtures are labeled in accord with identified hazard classes to warn and protect the user, the general public, and the environment. The EC label is intended to take into account all hazards in the form in which chemicals are placed on the market and not necessarily in any different form in which they may be used, that is, diluted. The most severe hazards are highlighted by specific symbols. Other hazards are specified in standard risk phrases and safety phrases that advise on handling precautions (46).

The data required for classification and labeling under EC provisions may be obtained from a variety of sources, for example, the results of previous tests, information required for the international transportation of chemical substances, information taken from reference publications in the scientific literature, or information derived from practical experience. EC rules do not require testing to classify chemical hazards. However, from a practical standpoint, testing is frequently conducted, especially for acute effects, by chemical suppliers to provide a rational basis for classifying and labeling.

4.1.3 Canada's Workplace Hazardous Materials Information System (WHMIS) The Workplace Hazardous Materials Information System (WHMIS) is the Canadian national system designed to ensure that all employers provide needed information and train employees properly in the handling of hazardous materials in the workplace. WHMIS is consensus legislation that represents input from government, industry, and labor. It is intended to ensure that the hazards of materials produced or

sold in, imported into, or used within Canadian workplaces are identified by suppliers and that standard classification criteria are used. Suppliers of chemical materials in Canada must convey hazard information in a specified manner by labeling on the containers of "controlled products" and by providing more detailed information in the form of material safety data sheets (MSDS). A controlled product for health purposes is defined for WHMIS under the Federal Hazardous Products Act as any material included in any of the classes outlined in the act (47). For health purposes, these classes include materials that cause immediate and serious toxic effects, materials that cause other toxic effects, biohazardous materials, and corrosive materials. Employers are responsible for evaluating all products produced in a workplace process using the hazard criteria identified in the Controlled Products Regulations.

Employers in Canada must ensure that supplier-provided containers of controlled products are labeled with WHMIS labels. As long as a controlled product remains in its supplier-provided container, the supplier label must remain attached to the container and be legible. For workplace processes, employers are required to furnish workplace warnings in the form of labels, tags, or appropriate markings. There is no specific format for workplace labeling; however, information on safe handling, hazard warnings, storage, and use of the controlled product must be provided. Reference must also be made to the availability of a Material Safety Data Sheet (48).

4.2 Worker Training Regarding Chemical and Physical Toxicity

Provisions are set forth in Section 21(c) of the OSHAct, for training and employee education. According to paragraph (c), "the Secretary, in consultation with the Secretary of Health and Human Services, shall (1) provide for the establishment and supervision of programs for the education and training of employers and employees in the recognition, avoidance, and prevention of unsafe or unhealthful working conditions in employments covered by this Act, and (2) consult with and advise employers and employees, and organizations representing employers and employees as to effective means of preventing occupational injuries and illnesses" (21).

Most regulations and standards set forth by OSHA and other agencies have training requirements. The training requirements vary for each standard but have been included in the regulation to increase an employee's awareness of health hazards in the workplace and to reduce injuries and illnesses. Employers are responsible for training employees about health hazards of biological, chemical, and physical agents.

Particularly, in the United States, the Federal Hazardous Materials Transportation Law requires the Department of Transportation (DOT) to regulate the training of all hazardous materials (hazmat) employees. The hazardous materials regulations (HMR) include training requirements in several sections of Title 49 Code of Federal Regulations (CFR) as follows: (a) General 173.1; (b) Specific 172.704; (c) Air 175.20; (d) Vessel 176.13; and (e) Highway 177.800, 177.816. Each employer that is covered by the regulation must train and test, certify and develop, and retain records of current training (inclusive of preceding three years) for each hazmat employee (during the period of employment and 90 days thereafter). The hazmat training must include general awareness/familiarization, function-specific, safety, and driver training for each hazmat employee who will operate a motor vehicle.

Initial training should be completed within 90 days of employment or change in job function. Recurrent training is required at least once every three years. The three-year period begins on the actual date of training. Relevant training received from a previous employer or source may be used to satisfy the requirements, provided that a current record of training is obtained from the previous employer or source.

Under the Superfund Amendments and Reauthorization Act of 1986 (SARA), OSHA and EPA are required to protect employees engaged in hazardous waste and emergency response operations. To enforce SARA, OSHA issued guidelines requiring employers to establish and implement site-specific plans for worker protection at hazardous waste sites and in emergency response operations, and to provide training, medical surveillance, protective equipment, and engineering controls for

hazards. SARA also requires OSHA to set limits for workers engaged in hazardous waste and emergency response operations and to set requirements for handling, transporting, labeling, and disposal of hazardous waste. To protect employees who do not fall within OSHA's jurisdication, EPA adopted OSHA's Hazardous Waste Operations and Emergency Response Standard (Hazwoper) (29 CFR 1910.120).

EPA is also responsible for administering specific guidelines for asbestos. The Asbestos Hazard Emergency Response Act of 1986 (AHERA), which requires school systems to inspect school buildings for asbestos hazards and to abate those hazards through removal, replacement, encapsulation, or other appropriate actions, addresses potential hazards to public and worker health resulting from such activities. The act requires contractors who perform such activities to be accredited through state governments.

The law requires EPA to develop model accreditation programs for the states. Under those accreditation plans, contractors are required to pass an examination that addresses such elements of asbestos safety and includes recognition of asbestos containing materials and knowledge of asbestos health hazards; assessing the risk of asbestos exposure, knowledge of respirators, appropriate work practices, and hazard-control measures; and knowledge of ways to prepare an area correctly for response action and of proper asbestos disposal.

EPA has jurisdiction over worker protection in the fields where pesticides and herbicides are used. Most of the regulations are in the category of training, labeling, and reentry times. OSHA regulations cover the manufacture of pesticides (29).

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5.0 Global Standards
A brief description of standards in several countries is provided here so that the reader can recognize the varied approaches to regulations for worker protection.
Australia
In Australia, occupational exposure standards for airborne contaminants in the workplace are set by the Australian National Occupational Health and Safety Commission (Commission). Section 38(1) of the National Occupational Health and Safety Commission Act of 1985 (Commonwealth Act) authorized the Commission to develop, facilitate, and implement a national occupational health and safety strategy. Within the Commission, the Expert Working Group (ESEWG) works under the Standards Development Standing Committee (SDSC) to recommend occupational exposure standards for individual chemical substances.

The first group of OELs established by the ESEWG in 1986 was adopted from the ACGIH TLVs. The Commission compared the ACGIH list with the lists of permissible exposure limits of other countries. When agreement was found among the lists, the Commission adopted the ACGIH value. If a discrepancy was found, the ESEWG reviewed the relevant information and selected the appropriate value.

Exposure standards set forth are meant to serve only as guides. They have no legal status unless they are adopted into Commonwealth, State, or Territory legislation (33).
Germany
The Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (Commission), an organization within the German Research Institute (Institute), publishes MAK occupational exposure limits for air contaminants in the workplace. MAK values are adopted as regulatory guidelines by the German federal government under the Ordinance on Dangerous

Substances.

The Commission selects chemicals for establishing MAK values. In establishing these values, primarily the effects of the compounds are taken into consideration by utilizing toxicological and work practice information.

The Commission also establishes biological exposure limits. A Biological Tolerance Value for the Working Material (BAT) is defined as the maximum permissible quantity of a chemical compound or its metabolites in blood or urine.

Through the Ordinances on Dangerous Substances as technical guidelines, the German government imposes MAK values in the workplace. Employers are responsible for testing and ensuring that they comply with MAK values (35).

Japan

The Japan Association of Industrial Health (Association) issues permissible exposure limits as reference values for measuring exposure to chemical and physical hazards. The Association is a private, academic organization consisting of committees.

The procedures used to establish exposure limits in Japan were substantially influenced by the ACGIH, and a majority of the initial exposure limits was adopted from the ACGIH TLV list.

Because the organization that establishes the exposure limits is a private entity, they hold no legal means of enforcement and are issued as only reference values. They are meant to serve as guidelines to industry and government (33).

Ontario

The Joint Steering Committee on Hazardous Substances in the Workplace established the Occupational Exposure Limits Task Force to set up and review exposure limits for the workplace. Due to limited resources and time, the OELs were based on the review of five other countries: Germany, Sweden, the Netherlands, the United Kingdom, and Norway. The Task Force decided to adopt OELS that were lower than Ontario's as part of a proposed list of new OELs. After a public comment period, the Task Force makes a final decision on OEL values, and they are made available through publications.

Ontario's OELs are normally adopted by regulation and are thus compulsory. The province has teams of inspectors who routinely inspect establishments.

If violations are found by inspectors, the maximum penalty for corporations is $500,000 and $25,000 plus one year in prison for individuals (33).

Poland

In 1976, a list of “maximum permissible concentrations” (MACs) of more than 300 potentially injurious substances came into force under the administration of the Ministry of Labor, Wages, and Social Affairs. By 1982, a new system had been implemented for establishing OELs based on national legislation. A group of experts uses health-based criteria for recommending MACs to the Polish Permanent Commission on Hygienic Standards. After acceptance by the Commission, the MAC values are promulgated by the Minister of Labor, Wages, and Social Affairs as legally binding regulations (49).

United Kingdom

The Control of Substances Hazardous to Health Regulations (COSHH) of 1988 introduced legal procedures for controling exposures to hazardous substances in the workplace.

Occupational exposure limits are set by the Health and Safety Commission's (HSC) Advisory Committee on the Toxic Substances (ACTS) in conjunction with its Working Group on the Assessment of Toxic Chemicals (WATCH).

Before setting OELs, WATCH reviews relevant primary literature (published and unpublished),

assessment is performed by a scientific committee, and endorsement is conducted within a superior committee structure. All standard chemical databases are searched, and contacts are made with relevant industry sources to obtain any available toxicological, exposure, and occupational health data.

Occupational exposure limits and other relevant legislation are enforced actively by inspectors of the Health and Safety Executive under extensive powers provided by the Health and Safety at Work Act of 1974 (33).

Venezuela

Occupational exposure values are revised and updated by the Venezuelan Commission of Industrial Standards, a government-headed committee comparable to the American National Standards Institute (ANSI). The OELs, termed "Candidates Ambientales Maximas Permissibles (CAMPS), were originally based on the 1978 ACGIH TLV, and occasional substances were added. The standards that are related to health and safety are legally enforceable (49).

European Union

Many member states within the European Union (EU) have formulated their own occupational exposure limits. For example, in Germany MAK values have been established. The European Commission (Commission) was seeking to harmonize EU-wide OELs, and in 1990, decided to set up an informal group of scientists known as the Scientific Expert Group (SEG) to advise on setting occupational exposure limits. In 1995, the SEG became an official committee and was commissioned to set up a formal basis for the work on the scientific evaluation of risk at the workplace related to chemical substances.

Specifically, the committee was to give particular advice on setting OELs based on scientific data and where appropriate shall propose values such as eight-hour time weighted average (TWA), short-term/excursion limits (STEL), and biological limit values.

The scientific reliability of the SEG recommendations is the cornerstone for any of the Commission's legislative proposals to set limit values for chemicals. In 1994, the Commission approved a Guidance note (as an internal working document) on procedures to set limits, which sets out the arrangements for the scientific review and evaluation to establish OELs in the European Union. It includes the procedures to be followed and at what stage interested parties can make their contribution to this procedure.

The procedures entail a detailed evaluation of criteria documents from different sources, identification of critical health effects, development of a summary document describing the recommended OELs and their basis, and a description of the critical effects. Once the summary document is agreed upon by the Committee, the Commission makes it available for public review and comments for about six months. After this review, the SEG makes recommendations to the Commission, which then develops legal proposals for OELs. The Commission's proposal for a legislative text is submitted to the Advisory Committee for Safety, Hygiene, and Health Protection at Work (ACSHH) for comments and approval.

Although specific enforcement provisions in the area of occupational compliance do not exist at the EU level, member states have an obligation to satisfy both their own and EU requirements (50).

Nordic Countries

Scientific data in the literature are available internationally and have allowed smaller countries to use this information as the basis for developing occupational exposure limits (OELs). This initiated the development of the Nordic Expert Group (NEG). The task of the NEG was to develop scientifically based criteria documents for use as a common scientific basis of OELs by the regulatory authorities in the five Nordic countries: Denmark, Finland, Iceland, Norway, and Sweden. Joint international ventures are therefore advantageous to the involved parties because writing criteria documents is a time-consuming and costly process.

The criteria documents from the NEG lead to the definition of a critical effect and dose–

response/dose-effect relationship. The critical effect is the adverse effect that occurs at the lowest exposure. There is no discussion of safety factors, and a numerical OEL is not proposed. Since 1987, criteria documents are published yearly by the NEG concurrently in English (13, 15).

Of the Nordic Countries, according to the available literature, Norway and Sweden do not enforce their OELs but use them to guide entities on complying with law.

5.1 Uniform Approach for Setting Occupational Exposure Limits

According to Lundberg (51) each country should use a standardized approach when building the documents. A summary of the approach and characteristics follow: A standardized criteria document should reflect the up-to-date knowledge presented in the scientific literature. The literature used should preferably be peer-reviewed scientific papers, but at least be available publicly. The scientific committee should consist of independent scientists from academia and government. All relevant epidemiological and experimental studies should be thoroughly scrutinized by the scientific committee, especially "key studies" that present data on the critical effect. All observed effects should be described. Environmental and biological monitoring possibilities should be pointed out. Data permitting, the establishment of dose–response and dose–effect relationships should be stated. A no-observable-effect level (NOEL) or lowest observable effect level (LOEL) for each observed effect should be stated in the conclusion. If necessary, reasons should be given as to why a certain effect is the critical one. The toxicological significance of an effect is thereby considered.

Specifically, mutagenic, carcinogenic, and teratogenic properties should be pointed out, as well as allergic and immunologic effects. A reference list for all studies described should be given. If a document states that only relevant studies have been used, there is no need to give a list of references not used or explain why. However, it could be of interest to list those databases that have been used in the literature search.

There are only minor differences in the way OELs are set in various countries that develop them. Therefore, it should be relatively easy to agree upon the format of a standardized criteria document containing the key information. From this point, then, the decision as to the margin of safety that is incorporated in the limit would be a matter of national policy (51).

Regulations and Guidelines In the Workplace

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1 Introduction

Knowing where to go to get relevant up-to-date as well as state-of-the-art information about the health effects of a chemical is essential for effective protection of workers and the environment. The means to access information is changing every day and the amount of occupational health and safety information is expanding. Finding information to prepare a MSDS, to respond to an emergency, to meet legislative and regulatory requirements, to determine the cause of an illness, or to develop a health and safety program can be challenging, overwhelming, and time-consuming. Toxicological information and data are of interest to more than workers, toxicologists, industrial hygienists, lawyers, and regulators. The general public is increasingly interested in the health effects of industrial chemicals.

Depending upon who wants the information and why they want it affects the use it will have and the amount of detail required about the chemical. For some, knowing that the basic health effects are respiratory or skin irritation is enough. For others, knowing the mechanics of the way the chemical works in the body will be of interest and required. For still others, the information is needed for an emergency so that whatever information is obtained must be gained quickly.

The recency of the information may affect which information sources are used. Electronic data bases, which have become a fact of life and are probably now the first source of reference for most people looking for chemical information and toxicological data, may not be the best resource. Electronic data bases can include both CD-ROMs and on-line databases available either directly from the service provider such as DIALOG, MEDLINE, or CCOHS or via the Internet. The government sources of information are usually free; however, there are fees for many of the other services. Comprehensive information and data are necessary to develop regulations to protect people and the environment from the effects of exposure from a chemical; all of this information may not be available from an electronic source. But electronic data sources are the places to go to quickly to find current toxicological data. There are a number of different methods of finding electronic data sources, and they are discussed later in the chapter.

There are a number of different types of safety, health, and toxicological information sources. These include traditional paper sources such as books, journals, and periodicals which were the typical sources of information before about 1970. There are also gray data. Gray data can include private or government research reports that have not been published, company catalogs, and material safety data sheets (MSDSs). These information sources are called gray data because they are difficult to find and are not always readily available (1). Still other sources of health and safety data are laws, standards, and patents in print. A preamble to a Federal OSHA health standard provides historical epidemiological data about a chemical.

This chapter discusses basic mechanics of information searching, general or traditional places to go for information, and then specific resources. To provide a chapter with just specific sources in this age of greatly expanding possible resources would be both a waste of time and a disservice to readers.

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2 Basics of Toxicological Literature Searching

In the old days of literature searching, people who wanted information would go to libraries and ask librarians for what they wanted. The librarian, familiar with the book and journal collection would direct the requester. Manual searches included looking in encyclopedias, going through card catalogs, and reviewing the abstracts provided by a number of different organizations. Now, however, information is available beyond the four walls of a building. In addition to the contents of a library, the library has access to the contents of other libraries, and in many instances the ability to access information on the World Wide Web, otherwise called the Web or the Internet. The Web makes available databases within the government, associations, academic libraries, and private industry. Many of them are free; some are not, and must be paid for either by an annual fee or on a per use basis. There are also CDs of databases containing toxicological information.

2.1 Search Strategy: Questions to Ask

What are some of the questions to ask before conducting a literature search or looking for information?

1. Why do I want the information, and what will I do with it?
2. How much information do I have already?
3. How soon do I need this information?
4. Do I need historical use information, toxicological data, or information about the chemical and physical properties?
5. Where is the best place to start?
6. What is the information that I need to conduct a literature search?

No matter where one starts, it may seem rudimentary, but knowing the correct spelling of the chemical and its correct chemical registry number are absolute essentials. If you have the wrong spelling or the wrong registry number, you would get information about the wrong chemical.

2.2 Information to Look for: Chemical Registry Numbers

There are several chemical registry numbers to use. The most commonly used registry number in the United States is one developed by the American Chemical Society (ACS). This registry contains over 19 million compounds. The ACS assigns a CAS number to a specific compound, regardless of the name or nomenclature system used. For all practical purposes, it is the social security number for a particular chemical.

Another registry number only for organic chemicals, was developed by Beilstein Institute, Frankfurt am Main, Germany. Beilstein currently maintains a computerized database of more than 7.5 million chemicals.

A third registry number was established by the National Institute for Occupational Safety and Health (NIOSH) in its Registry of Toxic Effects of Chemical Substances (RTECS). This registry number is a unique nine-position alphanumeric designation assigned to each prime chemical name.

Table 9.1 provides a summary of selected sources for obtaining chemical registry numbers and determining a chemical from only a chemical registry number or other limited information about a chemical.

Table 9.1. Selected Sources for Obtaining Chemical Registry Numbers and Other Identifying Information

Name of

Chemical Database	Source/Address	Information Available	Cost
American Chemical Society Chemical Registry	Internet or direct contact www.acs.org	CAS numbers for 19 million compounds.	ACS members: free nonmembers: fee/use
Beilstein CrossFire System	Internet: www.beilstein.com	Contains data on more than 7.5 million compounds dating back to 1648.	Fee
NIOSH RTECS	CCOHS: Internet or CD-ROM www.ccohs.ca	Profiles of more than 130,000 compounds	Fee for either format
	Chemfinder: Internet www.chemfinder.com	Limited information; links to other data; can access information with CAS Number	Free
NLM (SIS) ChemID*plus*	NLM Internet: igm.nlm.nih.gov/tehip(site currently unavailable)	Contains about 350,000 records, of biomedical and regulatory interest including drugs	Free
Acronym Database	Freie Universitat Berlin Institute of Chemistry Internet: www.chemie.de/tools	Will locate a chemical given only acronym; in English and German	Free
IUPAC Database of organic Chemicals	University of London, Queen Mary and Westfield College Internet: www.chem.qmw.ac.uk	Full text of IUPAC recommendations	Free
Pesticide Information Profiles	EXTOXNET Internet: ace.orst.edu/info/extonet	Specific information on pesticides	Free

2.3 How to Look for the Information: Using the Internet

Users can retrieve much information on their own. In 1995, Michael Blotzer published a user's guide to the Internet. This user's guide provides a road map for health and safety information, and it provides the reader with a means for understanding how to use the Internet (2). A number of journals and periodicals also publish lists of resources on the World Wide Web otherwise known as the Web (www). Journals such as *Chemical and Engineering News*, or *Science* provide new Web sites of interest to scientists; the periodical *Occupational Health and Safety* has a regular feature entitled "Computer Applications." Many professional organizations have Web sites at which there are safety links. These links can lead you to a number of other sources of information.

List Servers are subscriber-based computer-generated mailing lists designed so that subscribers of mutual interests can ask, discuss, or comment on topics of interest. There are several that have discussed topics as varying as flock worker's lung, the effects of isocyanate inhalation, and the odor threshholds of various chemicals. The reader is cautioned, however, that the List Servers in use now

may have changed, and there could certainly be additional ones. Examples of listservs pertinent to chemical information include

CHEMIND-L
CHEMINF-L

For information on signing up or joining a listserv, refer to *Internet User's Guide for Safety & Health Professionals* by Michael Blotzer (2).

2.4 Searching the Web

There are different ways to search the Web: search engines, directories, links, or knowing the Web address of the information desired. Search engines use software that crawls the Web and records the text on every page. When you make a query, the search engine goes into the depths of the page to find relevant keywords. Generally, the more times a keyword appears on a page, the higher it ranks on a list of results. Selected search engines include fast search (www.alltheweb.com), AltaVista (www.altavista.com), google (www.google.com), and Northern Light (www.northernlight.com). A directory is an organized selection of categories such as toxic, health, or chemistry. The content within those categories has been handpicked by humans. When you submit a query, it pulls up relevant sites from those in the library. Selected directory search sites include Yahoo (www.yahoo.com), Lycos (www.lycos.com), and Looksmart (www.looksmart.com). Links are provided by academic institutions, professional organizations, or governmental agencies to other locations on the Web where related and relevant information may be found.

However, it should be noted, that what is available when this chapter was written, may be only a small fraction of what is available when this book has been published. It is impossible to guess what will be on the Internet. Just use the premise that the information exists; the only question is where. With this in mind, how do you go about finding what you do not know may exist.

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3 Sources of Toxic Chemical Information

3.1 United States Government Technical Information Centers and Sources

The U.S. government expends a large amount of its budget on research and development. Much of this research is in the field of chemical toxicology. A number of governmental agencies are involved in this research. These agencies include the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), the National Institutes of Health (NIH), and the Department of Defense (DOD), to name a few. The research efforts of these departments yield thousands of reports every year. In addition, the government reviews the medical, health, and safety literature and publishes information that is obtained from these reviews.

Information resources within the U.S. government are becoming more and more available and accessible via the Internet. Following are selected sources of government databases and toxic chemical information.

National Technical Information Service (NTIS) NTIS, a part of the U.S. Department of Commerce, located in Springfield, VA, is a central source for documents in a variety of formats (printed, electronic, audio, etc.) relating to government sponsored efforts in scientific, technical, and business fields. The NTIS collection contains nearly three million titles. The Internet location for NTIS is www.ntis.gov. From this location, one can search for products, find out about on-line subscriptions, learn about services of federal agencies, and order reports and subscriptions to databases or other

information available from the NTIS. Orders maybe placed by telephone, mail, fax, or E-mail.

Telephone Orders:

Sales Desk: 1-800-553-6847 or 703-605-6000
Subscriptions: 1-800-363-2068 or 703-605-6060
Mail Orders: NTIS, 5285 Port Royal Rd., Springfield, VA 22161
Fax Orders: 703-605-6900
E mail: www.ntis.gov

National Institute for Standards and Technology (NIST) Located in the U.S. Department of Commerce, NIST has several databases that can provide reliable physical properties and related data. Several of these databases are on-line. These include NIST Chemistry WebBook and Polycyclic Aromatic Hydrocarbon Structure Index. These databases may be accessed at webbook.nist.gov/chemistry. (site currently unavailable)

National Institutes of Health National Library of Medicine (NLM) The NLM, located on the campus of the National Institutes of Health in Bethesda, MD, is the world's largest medical library. The Library collects materials in all areas of biomedicine and health care, as well as works on biomedical aspects of technology, the humanities and the physical, life, and social sciences. The collection stands at 5.3 million items—books, journals, technical reports, manuscripts, microfilms, phonographs, and images. The Internet address for NLM is www.nlm.nih.gov. NLM is located at 8600 Rockville Pike, Bethesda, MD 20894. Phone: 888-346-3656.

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4 Where are the Sources Found
The sources of information on toxic chemicals are found in libraries or electronically via computers. The computers may be located in academic institutions, governmental agencies, individual offices, or most anywhere.
4.1 Libraries
A number of library collections can be searched via the Internet. The premier library in the field of information on toxic chemicals is the National Library of Medicine. However, many universities, professional and labor organizations, and governmental agencies contain collections of printed materials that contain information on toxic chemicals. Telephone books, Internet Web sites, and local public libraries can provide the names of libraries that may have the information that you want. The easiest way to find a library is with your computer, if you can access the Internet and the Web.

The following libraries have their catalogs on the web:

- Norwegin Libraries which can be found at BIBSYS. BIBSYS is a shared library system of all Norwegian university libraries, the National Library, and a number of research libraries in Norway. This Web site provides a list of libraries in Norway. Internet address: www.bibsys.no.
- Online Computer Center (OCLC) is comprised of information from 17,000 libraries in the United States and 51 other countries and territories. The OCLC system helps libraries to locate, acquire, catalog, and lend library materials. Internet address: www.oclc.org.
- Library of Congress (Internet address: www.loc.gov) contains catalogs of all materials copyrighted in the United States. Catalogs of the Library may be searched at this Web site.

A number of college and university libraries have websites available for conducting literature searches. Their URL addresses are not being provided because their addresses are in continual flux. An *edu* at the end of a URL address signifies an academic institution.

Addresses on the Web at which information about libraries maybe obtained include

- Library Catalogs on the Web. Internet address: www.lights.com/webcats.
- National Library Catalogs Worldwide. Internet address: www.library.uq.edu.au.

4.2 Electronic Sources

Many sources of information on toxic chemicals can be found on the Internet, the World Wide Web, or on CD-ROM. As they used to say about the Telephone Yellow Pages, "Let your fingers do the walking." Table 9.6 lists electronic databases related to occupational safety and health that are available either on floppy disk, CD-ROM, or on the Web. This database list was generated by the International Labour Organisation (ILO).

Table 9.6. Databases Related to Occupational Safety and Health[a]

Database name[b]	Database type	Language	PC/floppy disks	CD ROM name
ACCIDENTS MINIERS	Full text	French	CD downloads	CCINFOdisc
AIDSCAN	Bibliographic	English	CD downloads	CCINFOdisc
AIDSLINE	Bibliographic	English	CD downloads	AIDSLINE
ARBLINE	Bibliographic	Swed/Engl		
BIOSIS (BA on CD)	Bibliographic	English		BIOSISCD ROM
CANADIAN LEGISLATION	Full text	Engl/Fre	CD downloads	LEGISLATION
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CANADIANA	Bibliographic	English	CD downloads	CCINFOdisc
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CASELAW	Full text	English	CD downloads	CCINFOdisc
CCOHS Publications	Full text	Engl/Fre	CD downloads	CCOHS
CESARS	Factual	English	CD downloads	CCINFOdisc
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ChemADVISOR	Factual/full	English	CD downloads	Chemical Advisor
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CHEMTOX	Full text	English		
CHRIS	Full text	English	CD downloads	CHEM BANK
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CISILO français (CISBIT)	Bibliographic	French	CD downloads	CCINFOdisc
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ClinMED,. MEDLINE Prof	Bibliographic	English	CD downloads	ClinMEDCD
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DATABASES	Factual	English	ASCII,WP,dBase4	
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ECDIN	Factual	English	CD downloads	ECDIN
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ENCYCLP. Chem.Engineering	Full text	English	CD downloads	KirkOthmerCD
EPACHEM	Full text	English	dBaseIII+	
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IRPTC/UNEP	Factual	English		UNChemicalCD
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LEO	Bibliographic	Fi/En/Sw		
MAJHAZ Chemical info	Bibliographic	English	IBM, dBaseIII+	
MBLINE	Bibliographic	Swe/Eng		
MEDITEXT	Full text	English	CD downloads	TOMES PLUS
MEDLINE 1966 to present	Bibliographic	English	CD downloads	MEDLINE 4 Vol.
MHIDAS	Factual	English	CD downloads	OSH-ROM
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NIOSHTIC	Bibliographic	English	CD downloads	OSH ROM/online
NIOSHTIC	Bibliographic	English	CD downloads	CCINFOdisc
NiPERACAB	Bibliographic	English	CD downloads	CCINFOdisc
NIVEAUX DE BRUIT	Factual	French	CD downloads	CCINFOdisc
NOISE	Factual	English	CD downloads	CCINFOdisc
NOMS DE MARQUE, FTSS	Full text	French	CD downloads	CCINFOdisc
NONIONIZING RADIATION	Factual	English	CD downloads	CCINFOdisc
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NURSING & ALLIED HEALTH	Bibliographic	English	CD downloads	SilverPlatter
OHMTADS	Full text	English	CD downloads	CHEM BANK
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OSHA databases	Full text/bibl.	English	CD downloads	OSHA disc
OSH-UK	Full text/bibl.	English	CD downloads	OSH-UK
PERINORM Standards	Bibliographic	En/Fr/Ge		PERINORM

PERSONNES RESSOURCES	Full text	French	CD downloads	CCINFOdisc
PEST BANK Product Data	Factual	English	CD downloads	PEST BANK
PEST BANK Tolerances	Full text	English	CD downloads	PEST BANK
PRIS EXPERIMENTAL PEST	Factual	English	CD downloads	CCINFOdisc
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PRIS MAX RESIDUES	Factual	English	CD downloads	CCINFOdisc
PRIS MINOR USE	Factual	English	CD downloads	CCINFOdisc
PRIS PEST MGT RESEARCH	Full text	English	CD downloads	CCINFOdisc
PRIS THESAURUS	Synonyms	English	CD downloads	CCINFOdisc
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RAYONNEMENTS NONIONISAN	Factual	French	CD downloads	CCINFOdisc
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REPERTOIRE TOXICOLOGIQUE	Full text	Fre/Eng		
RESOURCE-ORGANIZATIONS	Full text	English	CD downloads	CCINFOdisc
RESOURCE PEOPLE (Canada)	Full text	English	CD downloads	CCINFOdisc
RIPA	Full text	French	CD downloads	CCINFOdisc
RIPP	Full text	English	CD downloads	CCINFOdisc
RTECS	Coded text/bib	English	CD downloads	CHEM BANK
RTECS English	Full text/bibl	English	CD downloads	CCINFOdisc
RTECS français	Full text/bibl	French	CD downloads	CCINFOdisc
SAFE USE OF-CHEMICALS	Multimedia	English		SAFE USEOF Ch
SILDEMPLOI LIMITE	Factual	French	CD downloads	CCINFOdisc
SILD LACHERS	Factual	French	CD downloads	CCINFOdisc
SILD PRODUITSEXPER.	Factual	French	CD downloads	CCINFOdisc
SILD RECHERCHE	Full text	French	CD downloads	CCINFOdisc
SILD RESIDUS	Factual	French	CD downloads	CCINFOdisc
SILD THESAURUS	Synonyms	French	CD downloads	CCINFOdisc
STANDARDS & DIRECTORIES	Bibliographic	English	CD downloads	CCINFOdisc
TAPS	Full text	Finnish		
TDG/49CFR	Factual	English	CD downloads	CCINFOdisc
TOXLINE 1981 87	Bibliographic	English	CD downloads	TOXLINE
TOXLINE 1988	Bibliographic	English	CD downloads	TOXLINE
TRADE NAMES, (see	Full text	Eng/Fre	CD downloads	CCINFOdisc

MSDS)

[a] Obtained from ILO from their Web site.

[b] Sources of databases:

ARBLINE, DAISY (gloves), MBLINE	Al/Sweden
BIOSIS, ERIC	Silver Platter
CCINFO or CCOHS	Canadian Centre for Occupational Health (CCOHS)
CHEMTOX	Van Nostrand Reinhold
EARTH SUMMIT	United Nations
ECDIN	EC
ENCYCLP. Chem Eng	Bookstores
EPACHEM	EPA/USA
FACTS chem. accidents	TNO, Netherlands
HAZARDTEXT, MEDITEXT	Micromedex, Inc.
HOMMEL: buch gefar. Gut	Springer Verlag
KETURI, TAPS	FBLP, Finland
LEGISLATIVE REFERENCE	International Labour Organisation (ILO/CIS)
LEO	IOH, Finland
OSHA DATABASES	OSHA/USA
OSH-UK	HSE/U.K.
PERINORM Standards	AFNOR/BSI/DIN
REPERTOIRE TOXICOLOGIQUE	CSST, ESA

Internet addresses have been provided throughout this chapter. It is a sign of the times. Before the 1980s people asked, “What is your area code and phone number?” In the 1980s the question was, “What is your fax number?” Now the question is, “What is your E-mail address or Web site?”

Toxic Chemical Information Sources

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Use of Toxicological Data in Evaluating Chemical Safety
Gloria Rachamin, Ph.D.

1 Introduction

More than 70,000 chemicals are currently registered in the chemical substances inventory under the Toxic Substances Control Act (TSCA) in the United States (U.S.), and every year new chemicals are introduced to the market. Each chemical can produce toxic effects that may be reversible or irreversible. Exposure to chemicals in the workplace can result in a wide range of adverse health outcomes, for example pulmonary disease skin irritation and sensitization, neurotoxicity, lung and liver function impairment, cancer, and hereditary diseases.

Toxicological data provide the basis for evaluating the potential health risks of chemicals to humans. Information from human and animal studies is used to characterize the nature of the toxic effects of chemicals and to predict their risk to human health under given exposures. The ultimate goal of using data from such studies is to determine "safe" levels of human exposure to toxic substances. Because it is not possible to assure absolute safety to everyone for any chemical, "safe" does not imply risk-free but a level of risk that is acceptable in our society.

In practice, chemical safety is defined by setting numerical health-based exposure limits for chemicals, exposure levels below which the risk of adverse health outcome is acceptable. For more than 60 years, the American Conference of Governmental Industrial Hygienists (ACGIH) has developed "Threshold Limits Values" (TLVs) for airborne concentrations of substances that "represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects," as well as "Biological Exposure Indices" (BEI) for chemicals and their metabolites in body fluids. Similarly, regulatory agencies in the United States (e.g., Occupational Safety and Health Administration/OSHA, Environmental Protection Agency/EPA, Food and Drug Administration/FDA) and other jurisdictions have set exposure standards or guidelines to protect the health of the working population and the general public from exposure to chemicals. These standards include "Permissible Exposure Limits" (PELs) and "Recommended Exposure Limits" (RELs) for chemicals in the workplace, "Acceptable Daily Intake" (ADI) levels of chemicals in food, and "Reference Inhalation Concentrations" (RfC) for ambient air contaminants.

The term risk, in this context, refers to the probability of an adverse health outcome resulting from chemical exposure. The risk of experiencing adverse outcomes varies from minimal to high depending on the inherent toxicity (hazard) of the chemical, the level of exposure, and the susceptibility of the individual. Because of wide interindividual variation in susceptibility to chemicals, the risk of an adverse outcome for an individual is generally different from that defined for a population. Risk estimates may be qualitative, quantitative, or semiquantitative, depending on the data and methods used to derive them.

Agreement on what constitutes an acceptable risk for human populations involves a value judgment and is often an object of intense controversy. As a result of the U.S. Supreme Court ruling on the proposed benzene standard in 1980, OSHA has been required to demonstrate that its proposed standards reduce significant risks to worker health. Significant was suggested to be an increase in lifetime risk of developing cancer greater than 1 in 1,000 (1). In contrast, most regulatory agencies whose mandate is to protect public health, (e.g., USEPA, FDA, Health Canada) consider an excess lifetime cancer risk of 1 in a million acceptable.

In addition to providing the basis for deriving numerical exposure limits, toxicological data are used to identify and classify chemicals based on their toxic effects. Toxicity classification systems have been developed in various jurisdictions, including the United States, Canada, and European Community, to communicate information on the nature of chemical hazards more simply to workers and other end users. It is important to note that toxicity classification systems are usually hazard-based and not risk-based; the substance is classified on the basis of its toxic effects observed in experimental studies rather than on the level of risk it may present to human health under given exposure conditions. Recently the Organization for Economic Cooperation and Development (OECD) endorsed globally harmonized classification criteria for acute toxicity and other toxic end points, including cancer and developmental toxicity (2).

During the past two decades, reliance on toxicological principles and experimental data has become an integral part of the process that regulatory agencies use to control human exposure to chemical hazards. The results of chemical risk assessment, along with socioeconomic, technical feasibility, statutory, and political factors, provide input to risk management decisions to regulate a substance and on exposure control options (3–5). Before regulating a chemical, it is necessary to determine the potential of a substance to cause harm to humans and that the exposure is likely to occur.

Within the U.S. regulatory framework, risk assessment is defined as the process of systematic scientific characterization of potential adverse health effects resulting from human exposure to hazardous agents (3, 4). It consists of four main steps: hazard identification, dose–response assessment, exposure assessment, and risk characterization. Exposure assessment characterizes actual exposure to a chemical in a specific population. The outputs from the dose–response assessment and the exposure assessment are used to characterize the risk of adverse health outcome for this population.

The qualitative and quantitative evaluation of toxicological data (hazard identification and dose–response assessment, respectively) to predict chemical health risks to exposed human populations and to derive exposure limits, using risk assessment methodologies, is traditionally referred to in toxicology as chemical hazard evaluation (6). This constitutes the process that is used to evaluate chemical safety. Note that the commonly used term “chemical safety evaluation” originated from drug safety evaluations. For drugs, a margin of safety is established by comparing the toxic dose to the effective therapeutic dose (7). For chemicals that have no beneficial effects, however, this ratio has no relevance. For nondrug chemicals, the term “margin of safety” has been adopted in risk assessment procedures to indicate the magnitude of the difference between an estimated dose to which a human population is exposed and the highest dose at which adverse effects are not observed in experimental studies.

To evaluate chemical hazard, data are required on all the toxic effects that a chemical can produce by acute or chronic exposure. The most direct evidence comes from well-conducted studies in humans under conditions that are identical to those of the exposed population. In most cases, however, human data are not available, and surrogate data from animal studies are extrapolated to humans by using different risk assessment methodologies. The validity of toxicological predictions obtained by extrapolating from experimental data depends on the quality of the data, the methods used, and the degree of uncertainty.

The purpose of this chapter is to provide an overview of the process of chemical safety evaluation in the context of the regulatory risk assessment paradigm from the perspective of occupational toxicology. As seen in Figure 10.1, toxicological data from studies of the chemical in humans and animals, including physicochemical, toxicokinetic, and mechanistic data, are used in this evaluation. First, the adverse effects are identified and categorized by toxic end point. Next, the dose–response relationship for each end point is characterized, and the overall evidence is evaluated to determine the hazard class of the substance. If the toxicological database for a chemical is adequate, potential health risks to humans are then estimated, and exposure limits are derived by using risk assessment methodologies. Depending on the dose–response relationship (threshold or nonthreshold) of the

adverse effect that is observed at the lowest dose (critical effect), three general risk assessment approaches can be applied: safety/uncertainty factor, low-dose extrapolation risk model, and a unified benchmark dose approach. Note that various risk assessment procedures have been developed over the years and continue to evolve as science advances. A new terminology has also emerged in large part from environmental risk assessment work that focuses on community exposures to chemicals.

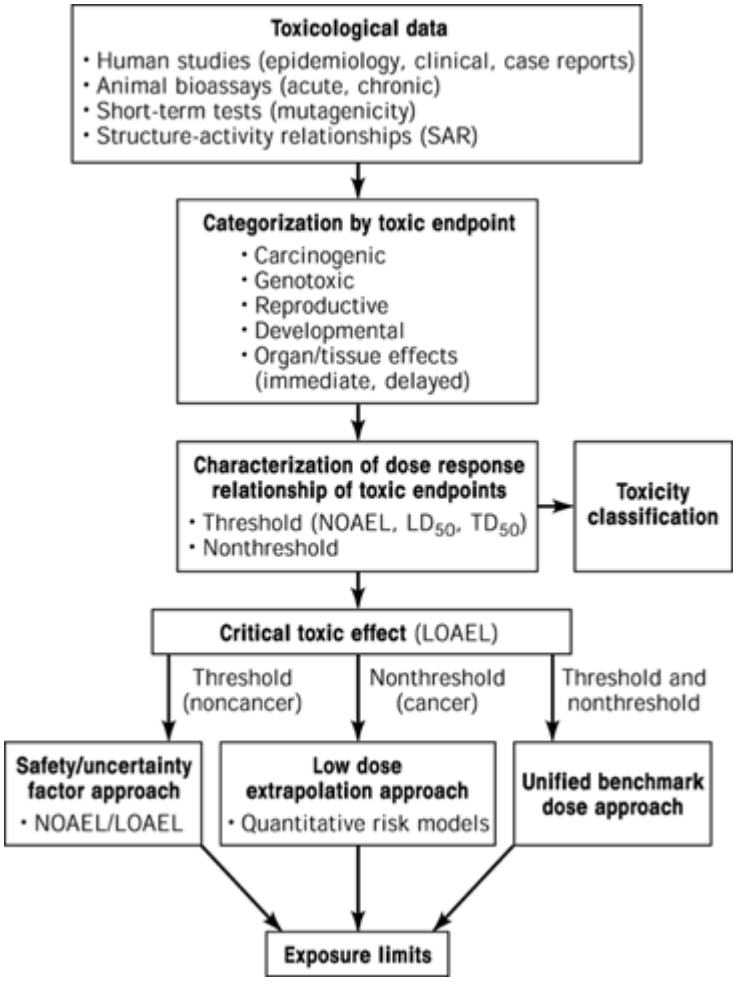

Figure 10.1. Chemical safety evaluation roadmap. This is a flowchart of the process of chemical safety evaluation indicating input and output data and the main steps (see Appendix 1 for definitions).

Toxicological principles are an integral part of chemical risk assessment, so basic toxicological concepts and references are included in Appendix 1. Key references on risk assessment that were used in preparing this chapter include government publications (3, 4, 8–18), books (19–23), reviews (6, 24–27), and other original papers cited in the text.

Use of Toxicological Data in Evaluating Chemical Safety
Gloria Rachamin, Ph.D.

2 Toxicological Data
A large volume of toxicological data is required to identify and characterize the nature of the toxic effects of chemicals and to predict their potential risk to humans under given exposure conditions.

To evaluate chemical safety, regulatory agencies use data from both human and animal toxicological studies. Such data can be obtained from various sources, including published literature, computerized databases, and submissions from chemical manufacturers.

Four main categories of toxicological data are used to evaluate chemical safety: human studies, whole body animal bioassays, short-term tests, and structure-activity relationship (SAR) data. Short-term tests and SAR data are used primarily to screen chemicals for mutagenicity or potential carcinogenicity and to support the interpretation of *in vivo* human and animal studies. Data from human studies are often scarce or inadequate, in practice, so whole body bioassays in animals provide the main source of toxicological information.

2.1 Human Studies

Studies of exposed humans provide the most direct evidence for predicting potential chemical hazard. The main source of human data available is from epidemiological studies, particularly in the working environment where exposures are relatively high. Data are available for some chemicals, from well-controlled clinical studies and also from case reports.

Analytical epidemiological studies, which include case-control and cohort studies, are most useful in identifying an association between human exposure and adverse health effects. Epidemiological studies under occupational settings attempt to determine whether an adverse health outcome is associated with a specific chemical exposure in the workplace. Benzene is an example of a substance that was first found to be carcinogenic in studies of workers, and only later was shown to cause cancer in animal studies (24, 28–30). The use of epidemiological studies, however, is generally limited due to several factors, including lack of adequate exposure data, confounding exposures, and a study population that is too small to detect a statistically significant effect (see section 3.1.1). In addition, from a public health perspective, positive findings in human studies are not desirable because the objective is to prevent disease before humans are harmed. Early detection of excessive exposure using biological markers in epidemiological studies is a valuable method for implementing interventions to prevent disease.

The advantage of clinical trials is that exposures can be controlled and quantified, and subjects can be selected to include susceptible individuals. Other than clinical trials for therapeutic agents, the use of this study design is limited because it is not ethical to expose humans to a potentially harmful agent. Only short-term reversible effects (e.g., irritation) of a chemical can be investigated in clinical trials but not the potential to cause chronic disease such as cancer.

Case reports of adverse effects in an individual are usually of limited value as evidence of causal association because they are not controlled studies and rely heavily on the recall of possible chemical exposure. Nevertheless, these observations should not be overlooked because the first suggestion that a number of substances cause disease such as cancer and peripheral neuropathy came from case that reports. Case reports can be used as indicators of the need to carry out controlled studies.

2.2 Whole Body Animal Bioassays

Studies of experimental animals provide the main source of data for assessing chemical safety. They provide information on the toxicity of a chemical under controlled experimental conditions (dose levels, effects measured, population size). Animal toxicity tests are particularly important because they provide an opportunity to identify toxic chemicals before people are actually exposed to them and, therefore, prevent potential adverse health effects.

In general, animal studies have a high predictive value for human health risks. Almost all known chemical carcinogens in humans cause cancer in some animal species. Further, it has been shown that exposure of animals to toxic agents in high doses is a valid method for discovering potential hazards to humans. Results can be extrapolated from high exposures in animal studies to lower exposures typically experienced by humans (see section 6.2).

To evaluate chemicals before humans are exposed, the U.S. TSCA requires the manufacturer of a new chemical to submit to the EPA any available toxicological data on the chemical before

manufacturing or distributing it. It has only limited authority, however, to order that toxicity tests be done. Similarly, premanufacturing or premarketing notification and submission of toxicological data on new chemicals is also required in other jurisdictions, including Canada and the European Community.

There are no set toxicity test protocols for every new chemical because the need is determined on the basis of the specific chemical, its intended use, and the toxic effects produced by structural analogues. A battery of screening tests is usually conducted first to determine whether further testing is required. Regulatory agencies (e.g., USFDA, USEPA) and other bodies such as the OECD have developed guidelines for toxicity tests. It is expected that toxicity tests to support the introduction of a new chemical to the market follow these guidelines. The guidelines are based on good laboratory practice (GLP) and provide direction on experimental design and methodology.

Numerous toxicity tests for evaluating chemical hazard have been developed and continue to evolve as scientific knowledge increases. It is generally recommended that bioassays be conducted in two mammalian species, one rodent and one nonrodent (usually dog or primate). The oral route of administration is used most often, but tests via inhalation and skin exposure are also performed when these are relevant. The following is a summary of the main types of bioassays that are used to identify toxic effects, target organs, and dose ranges of a chemical that causes adverse effects, emphasizing the principles and significance of each test (7, 31, 32).

2.2.1 Acute Toxicity The acute toxicity test is usually the first experiment performed with a new chemical. Different doses of the chemical are administered orally to groups of adult males and females of one or two species of rodents, most often the mouse and rat. If exposure via inhalation or skin absorption is expected, acute studies by inhalation and dermal exposure routes are also conducted. Most often the exposure duration in inhalation studies is 4 h. An acute dermal toxicity test is usually conducted in rabbits by applying the substance directly to the skin for 24 h. Mortality and other toxic end-point data are collected for up to 14 days after acute exposure.

The main objectives of this test are to obtain a quantitative estimate of the acute median lethal dose (LD_{50}, see Appendix 1) for comparing the potency with other substances, to identify target organs and clinical manifestations of acute toxicity, to determine whether an effect is reversible, and to provide guidance on the dose range for other studies. Acute toxicity tests, thus, identify highly toxic substances and their potential health hazards.

2.2.2 Skin and Eye Irritation/Corrosion The potential of a chemical to cause skin and eye irritation or corrosion is tested upon acute exposure, usually in rabbits. The agent is applied directly to the skin or the eye, and the degree of irritation from mild to corrosive is scored as specified in the test protocols. The Draize test (original or modified) is used to evaluate dermal irritation. The degree of skin irritation is scored for erythema, eschar, edema formation, and corrosive action.

2.2.3 Skin and Respiratory Sensitization Sensitization is a process mediated by the immune system whereby first exposure to a substance does not cause adverse reactions, but repeated exposure induces a significant immune response that may not be limited to the contact site. Many procedures have been developed to test the potential of a chemical to cause allergic sensitization to the skin or the respiratory tract upon repeated exposure. Skin sensitization is the most common form of sensitization in industrial settings, although respiratory sensitization also occurs often with some substances (e.g., toluene diisocyanate, trimellitic anhydride).

Sensitization tests are usually conducted in guinea pigs, a highly sensitive species. In general, a sensitization test protocol involves exposing the animals to multiple doses of the test substance during a period of two to four weeks. About two weeks after the last treatment, animals are challenged with a low dose of the test substance. Depending on the specific test, the animals are evaluated for an allergic response to the skin (e.g., erythema, or edema) or the respiratory tract (e.g.,

bronchoconstriction or asthma).

2.2.4 Subacute Studies These studies are conducted to obtain toxicity information after repeated exposure for one month or less and to establish doses for subchronic studies. Typically three or four doses are administered to the animals in their feed. Clinical chemistry and histopathology are performed 14 days after exposure.

2.2.5 Subchronic Studies Subchronic studies are conducted in two species by the oral route (or intended route of exposure) with at least three dose levels, most commonly for 90 days. The main goals of these studies are to establish a no-observed-adverse-affect level (NOAEL, see Appendix 1), and to further identify and characterize the specific toxic effects of a chemical on organs or tissues after repeated administration. The lowest observed adverse effect level (LOAEL, see Appendix 1) may also be obtained in these studies. The NOAEL and LOAEL depend on the doses and number of animals tested. These parameters are used to develop standards and have numerous regulatory implications. In addition to characterizing the dose–response relationship after repeated exposure, subchronic data provide information for appropriate doses in chronic studies.

2.2.6 Chronic/Carcinogenicity Studies Long-term or chronic exposure studies are conducted to assess cumulative toxicity or effects that require a long latency period. They are similar to subchronic studies, except that the duration of exposure is longer. Chronic studies are usually conducted in rodents for exposure durations of 6 months to lifetime (18–24 months for mice, 2–2.5 years for rats). Ideally, the design and conduct of chronic toxicity studies should allow the detection of general toxicity, including neurological, physiological, biochemical, and exposure-related morphological changes. The studies often include evaluation of carcinogenic effects following lifetime exposure, so that a separate carcinogenicity study is not required. Thus, animals are used as surrogates for humans to identify agents that pose potential risk for cancer induction in humans.

To detect a small but statistically significant increase in cancer incidence at the low doses that are usually encountered in human exposures, it is necessary to use a very large number of animals. Because this is impractical, a high dose is administered to the known most sensitive species to increase the probability of detecting a statistically significant increase in cancer incidence with a small number of animals (at least 50). This high dose, called the maximum tolerable dose (MTD), is usually estimated from subchronic studies. The U.S. National Toxicology Program (NTP) defines the MTD as the dose that suppresses body weight gain by no more than 10% in a 90-day subchronic study. Additionally, one or two lower doses and a control group are also tested.

2.2.7 Reproductive and Developmental Toxicity Studies Developmental toxicity is defined as the occurrence of an adverse health effect anytime during the life span that results from chemical exposure before conception (either parent), during prenatal development, or postnatally until puberty. Teratogenicity is the induction of birth defects by exposure during development between conception and birth. Reproductive toxicity is the occurrence of adverse effects on the male or female reproductive system resulting from chemical exposure.

Four types of tests, usually in rodents, are used to study potential effects on development and reproduction. General fertility and reproductive performance are tested by administering the chemical to male and female rats before mating and throughout gestation. Typical end points measured are the percentage of females that become pregnant, the number of stillborn and live offspring and the weight, growth, survival and general condition of offspring in the first three weeks of life. Teratogenic effects are tested by administering the chemical to pregnant females during organogenesis (day 6–15 of gestation in rats). The fetuses are removed by Cesarean section a day before the estimated time of delivery. The numbers of live, dead, and resorbed fetuses are recorded. Live fetuses are weighed, half of each litter is examined for skeletal abnormalities, and the other half for soft tissue anomalies.

Perinatal and postnatal toxicity are examined by administering the compounds to rats from the

fifteenth day of gestation throughout delivery and lactation. Birth weight, survival, and growth rate during the first three weeks of life are measured.

A multigenerational study is also often conducted to determine the effects of chemicals on the reproductive system. Male and females rats (F_0 generation) are exposed shortly after weaning throughout breeding, gestation, and lactation. The offspring (F_1 generation) are bred at about 140 days of age to produce the F_2 generation, and exposure is continued. Thus, both the F_1 and F_2 generations would have been exposed in utero and via lactation. F_1 and F_2 litters are examined as soon as possible after delivery, and indexes of fertility, gestation, viability, and lactation of F_0 and F_1 females are determined.

2.3 Short-Term Studies (Mutagenicity Tests)

Short-term tests have been used primarily to evaluate the potential mutagenicity of a chemical. A mutagenic chemical interacts with the genetic material in the nucleus of germ or somatic cells and produces changes that can be transmitted during cell division. Germ cell mutations damage the DNA in sperm or egg cells and can result in hereditary diseases or congenital abnormalities in offspring. Somatic cell mutations are implicated in the development of diseases such as cancer but are not heritable. The initiation of chemical carcinogenesis is thought to be via mutagenesis.

There are numerous short-term mutagenicity tests (33). The more commonly used tests include gene mutation assays in bacteria (*Salmonella*/mammalian microsome assay or Ames test), mammalian assays for chromosome damage *in vivo* (metaphase analyses or micronucleus assay in rodent bone marrow), and cytogenetic assays in cultured Chinese hamster or humans cells (chromosomal aberrations, micronuclei, aneuploidy). Of these tests, the Ames test (34) is the most widely used assay and allows evaluation of the mutagenicity of the chemical and its metabolites.

Screening for mutagens in short-term bacterial assays is a rapid and inexpensive method that is often used to predict potential carcinogenicity of chemicals in humans. Data indicate that the Ames mutagenicity test, combined with an evaluation of the chemical structure, allows identification of a large proportion of genotoxic (directly acting on the DNA) rodent carcinogens. Positive mutagenic response was also found with substances that are known human carcinogens. Although a similar relationship would be expected with germ cell mutagenicity, due to lack of data one can not evaluate the ability of the Ames test to predict mammalian germ cell mutagenicity.

2.4 Structure–Activity Relationships (SAR)

When the toxicity of a chemical is not known, toxicological data from another chemical with similar structure can be used to predict its potential to produce adverse health effects. It is assumed that a key molecular structure of the chemical termed “structural alert” is responsible for causing the toxic effect. This method has been used by regulatory agencies primarily to identify potential carcinogenic hazards. Examples of carcinogenic structural alerts include *n*-nitroso or aromatic amines, amino azo dye structures and phenanthrene nuclei. Eight of the first 14 occupational carcinogens regulated by OSHA belong to the aromatic amine class (25). The USEPA relies on SAR in the initial evaluation of premanufacturing submission of data for new chemicals. Computer-based SAR programs have been developed that are quite good in predicting the carcinogenicity of chemically related compounds. This method is applicable only when the toxicity of structural analogues has been studied.

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3 Adequacy of Toxicological Data

Several factors need to be considered in evaluating the adequacy of the toxicological database for a

chemical, including the quality of individual studies, the completeness of the database, the relevancy of studies to exposed populations, and the overall weight of evidence. Professional judgment must be exercised in evaluating the data. To bridge data gaps, default inferences are used by regulatory agencies based on science policy and the application of the precautionary principle.

3.1 Qualitative Evaluation of Toxicological Data

It is of utmost importance that chemical safety evaluation is based on data from well-conducted scientific studies. Criteria for assessing the quality of individual epidemiological and animal studies have been published to provide guidance (10, 16). These criteria address primarily the evaluation of factors related to the study design and methods used, including test subjects, controls, dose levels, exposure duration and frequency, measured end points, and statistical analysis. Some of the following specific issues need to be addressed in evaluating human and animal studies.

3.1.1 Human Studies There are three main areas of concern in assessing the quality of an epidemiological study. They relate primarily to the design and methodology used to measure exposure, measure health outcome, and to control confounding variables.

In most cases, direct measurements of exposure are not available or are inaccurate or unrepresentative. The accuracy and relevance of exposure measurements in epidemiological studies may also be questionable due their long-term nature. For example, exposure levels change over time with different industrial hygiene practices and as a result of individuals changing jobs.

Response data in epidemiological studies are usually reported as incidence, standardized mortality ratios, and relative risk ratios. It is important to carefully evaluate the study design, including selection of exposed and control groups, power to detect statistically significant association between exposure and effect, and the methods used to ascertain disease. For example, the causes of death in studies that report mortality data may be questionable because they are obtained from death certificates but are rarely confirmed by autopsy.

Epidemiological studies are designed to detect association between exposure and adverse health outcome. Various host risk factors, however, including preexisting health conditions or lifestyle habits such as smoking can influence the health index assessed. Often, an individual is also exposed to multiple chemicals that may not be identified or quantified. It is important to determine whether the study addresses and controls for risk factors and confounding exposures.

The following criteria have been developed to evaluate the causality of an association between adverse health outcome and chemical exposure in epidemiological studies (35):

1. Strength of association. This is usually expressed as a risk ratio of mortality or disease in an exposed population relative to an unexposed population. The higher the risk ratio, the more likely it is that the association is causal.
2. Consistency (reproducibility). Causal association is supported when positive results are found in several studies done independently by different investigators using different populations.
3. Specificity. Causality is more than likely if a particular exposure is associated with only one illness, for example, the relationship between vinyl chloride exposure and liver angiosarcoma.
4. Temporal relationship. Exposure should precede the development of the disease by a biologically relevant time period (i.e., latency).
5. Coherence of the evidence. An epidemiological inference of causality should not conflict with what is known about the history and biology of the disease.
6. Biological gradient. This requires demonstrating dose–response relationships between the exposure level and disease rate.
7. Biological plausibility. A causal association is strengthened when there are biological mechanisms that explain association between the substance and the disease.
8. Experimental verification. Removal of the substance should be followed by a decline in the

incidence of the disease.

3.1.2 Animal Studies The main issues to be considered in evaluating animal studies are the appropriateness of the test species as a model for humans, the study design, and its validity.

Several animal models for identifying carcinogens may not be appropriate because they have a high incidence of spontaneous tumors or the relevance to the tumor induced in humans may be questionable. Studies have shown that thyroid tumors mediated by hyperstimulation in rodents and renal tumors mediated by alpha2u-globulin induction in male rats do not predict human cancer due to species differences related to the mechanism of tumor production (25, 36). Acrylonitrile-induced carcinoma of the Zymbal gland (ear canal gland) has been reported in animals, but there is no counterpart organ in humans (20).

The study design should be consistent with good laboratory practice and include clear definition of all exposure elements, including dose, route, exposure schedule and duration, physicochemical properties of the substance, species, age, and gender. The study should include controls comparable to test animals in all respects except for the treatment variable. It should provide adequate data to establish a dose–response relationship, and a valid test must be performed that is relevant to humans. Studies should include appropriate statistical analysis, and conclusions should be justified by the data in the report and consistent with current scientific knowledge.

3.2 Completeness of Database

An ideal toxicological database should include all of the toxic effects that a chemical can produce by acute or chronic exposure via different routes of exposure and in several test species. It should also include data on the dose–response relationship for each adverse effect. Often, however, there is limited information on a chemical, and data gaps exist. It is important, therefore, to determine the magnitude of insufficiency of the database for a chemical because it will impact on whether risk assessment can be conducted and on the rating of uncertainties.

3.3 Selection of Principal and Supporting Studies

To predict human risks and set exposure limits, it is important to select studies that match the characteristics of the population for which the risk is characterized (e.g., workers). Variables to be matched include the identity and physicochemical properties of the substance (CAS Number, purity, dust, vapor, etc.), route of exposure, exposure level, dose rate, fraction of lifetime exposed, biokinetics, and mechanisms of toxicity (20).

Principal studies that contribute most significantly to the assessment of the potential toxicity of a chemical and to setting exposure limits need to be identified. Obviously, inhalation studies in humans are most relevant for deriving air standards for chemicals in the workplace. Supporting studies that provide information on the chemical with respect to the mechanisms of action, metabolism, and toxicokinetic data can also be used to refine the dosimetric adjustment.

3.4 Weight of Evidence

All available human and animal data should be considered to assess whether the weight of evidence supports a conclusion about potential adverse health outcomes in humans. This involves integrating evidence from all diverse data to evaluate the overall strength, consistency, and biological plausibility of the association between the chemical exposure and the adverse outcome (10).

Indicators of stronger association between exposure and adverse effect include low LD_{50}, low NOEL, high potency, evidence of a dose–response gradient, high incidence rate, large excess risk, and high level of statistical significance. High consistency is demonstrated if the association is found in various studies in several animal species, different routes of administration and dose regimens, and in epidemiological studies. The biological plausibility is further evaluated with respect to other scientific information that is related to causal mechanisms, including the gradient response observed, short-term *in vitro* studies and SAR data, toxicokinetics, mechanisms of toxicity, preclinical indicators of disease, and biological monitoring of exposure.

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4 Classification by Toxic Effect
An adverse effect, in the context of risk assessment, has been defined as any alteration in structure or function that is clearly deleterious to the living organisms or a degree of injury such that the body's normal compensatory and protective mechanisms are overwhelmed, resulting in irreversible or only partially reversible functional changes (10, 14).

Toxicological data are reviewed to identify the adverse effects that a chemical induces under given experimental exposure conditions. The acute lethality test is first evaluated to determine the median mortality dose (LD_{50}, see Appendix 1) for a chemical. The LD_{50} provides an index of potency relative to other chemicals but has limited value in assessing morbidity.

In evaluating chemical hazard, adverse health effects are usually grouped into five general categories based on toxic end points: carcinogenic, genotoxic, reproductive, developmental, and organ/tissue effects (e.g., irritation, sensitization, neurotoxic). The term “systemic toxicity” has been used in risk assessment in reference to all toxic effects other than cancer and gene mutations (13). In addition to general scientific principles, the following are special issues that need to be considered in evaluating these toxic end points (toxicity tests are described in section 2.2).
4.1 Carcinogenicity
A chemical carcinogen has been defined by the USEPA (8, 12, 16) as any substance capable of inducing neoplasia in humans or laboratory animals. The evidence for carcinogenicity is usually derived from long-term animal bioassays described in section 2.2.6.

4.1.1 Tumor Type In evaluating animal studies, the general practice by regulatory agencies is to assign almost the same weight to benign and malignant tumors, particularly if data suggest that benign tumors can progress to malignancy. The analyses of tumors are usually organ-specific or site-specific rather than for overall incidence of tumors. A statistically significant increase in the incidence of tumors in exposed animals compared to controls is considered indicative of carcinogenic potential.

4.1.2 Carcinogenicity Classification Classification of a chemical as an animal carcinogen is usually based on the weight of evidence from positive studies. The IARC's weight of evidence classification system (see Table 10.1) and other similar systems such as that of the EPA are used to classify carcinogens (37, 38). According to the EPA (8), a chemical is an animal carcinogen if it causes an increase in malignant or malignant and benign tumors in multiple species or strains or in multiple experiments, or even in a single experiment if the incidence is particularly high, the site or type of tumor is unusual, or the onset is at an early age. The EPA (16) has proposed changing the carcinogenic classification to a simpler descriptive weight of evidence system consisting of three categories: known/likely, cannot be determined and, not likely. The National Toxicology Program (NTP) criterion for classifying a chemical as a carcinogen is that it must be carcinogenic in at least one site in one sex of F344 rats or B6C31 mice.

Table 10.1. IARC Weight of Evidence Classification for Carcinogenicity[a]

Group 1	The agent is carcinogenic to humans
	— *sufficient* evidence of carcinogenicity in humans

Group 2A	The agent is probably carcinogenic to humans — *limited* evidence in humans and *sufficient* evidence in experimental animals — only *limited* evidence in humans or only *sufficient* evidence in experimental animals in the presence of other supporting data
Group 2B	The agent is possibly carcinogenic to humans — *limited* evidence in humans in the absence of *sufficient* evidence in experimental animals — *sufficient* evidence of carcinogenicity in experimental animals and *inadequate* evidence or no data in humans — *limited* evidence in experimental animals with other supporting data and inadequate or no data in humans
Group 3	The agent is not classifiable as to human carcinogenicity — category used for agents that do not fall into any other group
Group 4	The agent is probably not carcinogenic to humans — category for agents for which there is *evidence suggesting lack of carcinogenicity* in both humans and experimental animals — occasionally used for agents for which there is *inadequate* evidence or no data in humans and *evidence suggesting lack of carcinogenicity* in experimental animals which is "consistently and strongly supported by a broad range of other relevant data"

[a] Assembled by Calabrese and Kenyon (19) from IARC (37).

Overall, animal bioassays have high predictive value for human carcinogenicity. IARC considers chemicals that demonstrate sufficient evidence of carcinogenicity in animal experiments as potential human carcinogens. Almost all chemicals that IARC evaluated as carcinogenic in humans showed positive results in animal bioassays (39–42). Animal bioassays successfully predicted human carcinogenicity of many chemicals including 4-aminobiphenyl, diethylstilbestrol, mustard gas, aflatoxin, bis-chloro methyl ether, estrogens, vinyl chloride, 1,3-butadiene, dioxin, and formaldehyde (39, 43).

4.1.3 Test Dose Levels The use of high doses such as the maximum tolerated dose (see section 2.2.6) in bioassays is highly controversial. These doses are usually much greater than those experienced by humans, but some reported occupational exposures have been close to the doses of rodent carcinogens that are used experimentally (44).

The validity of the assumption of dose–response relationships with MTD has been questioned because it was suggested that overloading of metabolic and repair pathways may occur at higher doses and lead to overt toxicity, but this may not happen at low doses. Tissue damage from high doses can lead to regenerative cellular proliferation that may promote carcinogenesis. Although some studies reported cellular proliferation, a review of 52 long-term bioassays suggested that for most chemicals it is not the primary cause for carcinogenic response (43).

4.1.4 Carcinogenic Potency Gold et al. (45) recently published a supplement to the carcinogenic potency database (CPDB) that has been developed to provide a systematic and unifying analysis of the published results of chronic, long-term animal cancer tests on individual chemicals. According to this publication, the database includes the results of a total of 5620 experiments on 1327 chemicals

that have been reported in 1250 published papers and 414 National Cancer Institute/NTP Technical Reports. The TD_{50}, an index of potency, was estimated for each set of tumor incidence data reported and presented in a plot format. Gold et al. (45) further reported that 11 of the 25 chemicals that were tested in monkeys did not cause cancer (an additional three showed equivocal results), despite strong carcinogenic evidence in rodent or human studies. The authors suggested that this may be due to the fear that these studies lacked power to detect an effect. Among chemicals that were carcinogenic in both monkeys and rodents, potency values correlated highly between the two species.

4.1.5 Mechanisms of Carcinogenicity The dose—response relationship is one of the most contentious issues in evaluating animal carcinogens. Because animal bioassays are conducted at dose orders whose magnitude is greater than human exposure, mathematical models are used to extrapolate data from high doses in animals to low doses in humans to obtain a quantitative estimate of human risk (see section 6.2). Quantitative risk assessment of carcinogens has been widely used in the United States particularly for environmental carcinogens. The choice of a mathematical model depends on the mechanism of carcinogenesis of a chemical and on the science policy of selecting the more conservative model.

Chemicals can produce cancer via genotoxic (directly acting on DNA) or nongenotoxic (epigenetic) mechanisms (46). The current theory is that genotoxic carcinogenesis is a nonthreshold phenomenon that proceeds through initiation, promotion and progression. Initiation is an irreversible alteration of DNA caused by a chemical carcinogen. Promotion represents the process of replication of initiated cells that demonstrate a growth advantage over uninitiated cells. Progression is the irreversible change from benign lesion to malignancy. There is a general agreement that carcinogenesis is likely to be a nonthreshold phenomenon for classical carcinogens such as vinyl chloride and benzo(a) pyrene (24). The mechanisms of nongenotoxic carcinogenesis do not involve direct interaction with the DNA but as yet are poorly understood. There is debate over whether carcinogenesis is a threshold phenomenon for nongenotoxic carcinogens such as dioxin and trichloroethylene.

The decision whether to evaluate a chemical as a genotoxic or epigenetic carcinogen has a major impact on the derivation of exposure standards. For example, the estimated acceptable daily intake for dioxin in the United States is about 15 times lower than that in Canada. Because dioxin has been considered a genotoxic carcinogen in the United States but not in Canada, different risk assessment methods were applied that resulted in a large difference in the standards adopted by the two jurisdictions (24).

4.2 Genotoxicity (Mutagenicity)

Mutagenicity tests are used to predict carcinogenicity or to predict human germ cell mutagenicity. Data obtained are used to support findings in bioassays. The predictive value of short-term genotoxic tests depends on several factors, including the characteristics of the chemical, its mechanisms of action, and the sensitivity and specificity of the test used.

A mutagen can interact with the DNA to induce several alterations (33) including point mutations (changes in the base sequence of DNA), and structural or numerical chromosomal aberrations. Structural aberrations include deficiencies, duplications, inversions, and translocations. Numerical aberrations are gains (e.g., trisomy) or losses of whole chromosomes or sets of chromosomes (aneuploidy).

The development of batteries of short-term tests to predict which chemicals are carcinogens is an area of continuous research and debate. A comparison of results from four widely used mutagenicity tests with cancer bioassays of 73 chemicals in rodents showed a concordance of about 60% (47). An analysis of data for 301 chemicals tested for carcinogenesis in mice and rats showed that when the Ames test data was combined with “structural alerts” (see section 2.4), 93% of the structurally alerting chemicals that were carcinogenic in both these species were also mutagenic in the Ames test (33, 48–50). Positive mutagenic response was also reportedly associated with substances known as human carcinogens.

The IARC has recommended that short-term tests alone should not be used to determine whether an agent is carcinogenic nor to predict reliably the relative carcinogenic potencies of chemicals in animals. The IARC's (51) weight of evidence system for evaluating genetic activity of chemicals in short-term tests is based on four end points (DNA damage, mutation, chromosomal effects, and cell transformation) and the level of phylogenetic complexity of the test system ranging from prokaryotes to humans *in vivo* (see Table 10.2). According to the EPA's criteria for evaluating evidence for mutagenicity in germ cell DNA, a positive test in a well-characterized gene mutation assay in mammalian germ cells strongly suggests that the chemical would be mutagenic in human germ cells.

Table 10.2. IARC Scheme for Assessing Evidence of Genetic Activity in Short-Term Tests[ab]

Sufficient evidence	At least three positive entries, one of which must involve mammalian cells *in vitro* or *in vivo* and must include at least two of the three end points[b], DNA damage, mutation, and chromosomal effects
Limited evidence	At least two positive entries
Inadequate evidence	Only one positive entry or when too few data do not permit an evaluation of an absence of genetic activity or when there are unexplained, inconsistent findings in different test systems
No evidence	Applies when there are only negative entries; these must include entries for at least two end points and two levels of biological complexity, one of which must involve mammalian cells *in vitro* or *in vivo*

[a] *Source:* Assembled by Calabrese and Kenyon (19) from IARC (51).

[b] End points: *DNA damage* tests for covalent binding to DNA, induction of DNA breakage or repair, induction of prophage in bacteria, and differential survival of DNA repair-proficient/-deficient strains of bacteria.

Mutation tests for measuring heritable alterations in phenotype and/or genotype. These include tests for detecting the loss or alteration of a gene product and change of function through forward or reverse mutation, recombination, and gene conversion; they may involve the nuclear genome, the mitochondrial genome, and resident viral or plasmid genomes.

Chromosomal effects tests for detecting changes in chromosomal number (aneuploidy), structural chromosomal aberrations, sister-chromatid exchanges, micronuclei and dominant-lethal events. This classification does not imply that some chromosomal effects are not mutational events.

Cell transformation tests that monitor the production of preneoplastic or neoplastic cells in culture and are significant because they attempt to simulate essential steps in cellular carcinogenesis. These assays are not grouped with the end points listed before because the mechanisms by which chemicals induce cell transformation may not necessarily be the result of genetic change.

Data obtained from screening tests for mutagens are used for setting priorities for further testing of chemicals and provide input for making decisions on whether to develop a new chemical product or to regulate a substance. Many compounds have been evaluated for mutagenicity, and results have been compiled by various agencies, including a published list by IARC (51), the EPA's Gene-Tox database, and the U.S. Environmental Mutagen Information Center (EMIC, Tennessee).

4.3 Reproductive

Toxicity to the male reproductive system may be expressed as alterations to the male reproductive organs and/or related endocrine system. The manifestation of such toxicity may include changes in sexual behavior, fertility, pregnancy outcomes, or modifications in functions that depend on the integrity of the male reproductive system. Similarly, female reproductive toxicity includes, but is not

limited to, adverse effects on sexual behavior, onset of puberty, fertility, gestation, parturition, lactation, or premature reproductive senescence (17). (See also Chapter 3, "Reproductive Toxicology")

In evaluating chemicals for reproductive toxicity, it is important to distinguish between reproductive and developmental effects, particularly in multigenerational studies (see section 2.2.7). There is an overlap in the outcomes that are measured to evaluate reproductive and developmental toxicity, for example, the pregnancy outcome. An adverse pregnancy outcome in offspring of exposed males that are mated with unexposed females can be attributed to male reproductive toxicity. Similarly, such an outcome in the offspring of an exposed female, before gestation, that is mated with an unexposed male can be attributed to female reproductive toxicity. Difficulties arise in interpreting the results if males or females are exposed before conception and females are also exposed during pregnancy. Data from reproductive studies of different experimental designs can provide complementary information that can be integrated.

4.4 Developmental

The four general end points of developmental toxicity that are evaluated are death of the conceptus, structural abnormality, altered growth, and functional deficiency (11). Functional deficiency is not routinely evaluated for several reasons, including methodological difficulties and the time and cost involved.

Chemicals that cause adverse effects in developing offspring in animal studies are viewed as potential human toxins. Chemicals that cause adverse developmental effects at exposure levels that do not produce maternal toxicity present the greatest developmental hazard. The majority of chemicals that produce maternal toxicity in animal studies also cause adverse developmental outcomes (19). This complicates the interpretation of the observed adverse developmental effects in offspring because it is difficult to determine the influence of maternal toxicity on the adverse outcome. From a regulatory perspective, a developmental toxin is usually considered a substance that causes developmental toxicity in the absence of maternal toxicity or for which developmental effects are not specifically related to maternal toxicity.

4.5 Organ/Tissue Effects

This category includes all adverse effects that are not covered in the previous four categories. It encompasses all immediate and delayed systemic and local adverse effects that result from acute or chronic exposures and occur via threshold mechanisms. They represent a large proportion of chemically-induced adverse health outcomes that have been encountered in the workplace, including irritation, sensitization, neurotoxic effects, impaired pulmonary function, and liver or kidney pathology. Discussion of these effects is beyond the scope of this chapter.

Sensory irritation is unique because it is localized, rapid, noncumulative, and subjective. Occupational exposure limits have often been set on the basis of human data because it is difficult to determine irritation threshold from animal studies. An animal model in mice has been developed in which reduced respiratory rate provides an index of respiratory irritation.

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5 Characterization of Dose–Response Relationships

The quantitative relationships between dose and the incidence of adverse response (see Appendix 1) provide the basis for evaluating chemical hazard and the derivation of exposure limits. The approach used to assess the dose–response relationship depends on whether the chemical produces threshold or nonthreshold end points (19, 20).

5.1 Threshold and Nonthreshold Effects

A threshold dose–response relationship is used to evaluate chemicals that produce no adverse effects

below a certain dose. The underlying mechanism for a threshold is that multiple cells must be injured for an adverse effect to occur (52). A nonthreshold ("zero" threshold) dose–response relationship is used to evaluate chemicals that convey some risk of adverse response at any dose above zero. The mechanism of carcinogenesis is considered nonthreshold, whereby a genotoxic insult in a single cell is theoretically sufficient to produce a malignant tumor eventually.

Traditionally, the threshold dose–response relationship has been used for assessing noncancer end points and the nonthreshold approach for cancer end points. The use of a nonthreshold dose–response relationship to evaluate nongenotoxic carcinogens has been a subject of much debate because it has been suggested that these substances are likely to produce cancer via a threshold phenomenon (53). Both threshold and nonthreshold approaches have also been applied to evaluate reproductive and developmental toxins (54, 55).

5.2 Dose Scaling

To facilitate interspecies comparisons of the dose–response relationship for adverse effects, it is necessary to obtain an estimate of the human equivalent dose. The two methods that are most commonly used to convert animal dose or exposure to an equipotent dose for humans are based on body characteristics.

The first method calculates the equivalent human dose from an animal study by scaling (adjusting) the animal dose rate for animal body weight, often expressed as mg/kg body weight/day. Similarly, the second method is based on body surface area scaling by adjusting for differences in metabolic rate, using the factor of body weight to the power of 2/3 or 3/4. Body weight scaling, however, is simpler and has been used by the USEPA for risk assessment and derivation of numerical criteria.

Ideally, the concentration at the target site would provide the best dosimetry. A method has been developed to estimate target tissue exposure (concentration × time) using a physiologically based pharmacokinetic model that incorporates biological data and processes. Because input data on the biokinetics and mechanisms of toxicity are rarely available for animals or humans, it is difficult to verify the validity of using this model for dose scaling.

5.3 Critical Adverse Effect

The dose–response relationship is characterized for each of the adverse responses that a chemical produces by using data from the most relevant and scientifically sound studies. For threshold responses the NOAEL, TD_{50}, or LD_{50} are determined (see Appendix 1). Depending on the response that is modeled, each response to a chemical can have a different threshold. For nonthreshold end point, models for extrapolation from high doses to low doses below the observed range are applied (see section 6.2).

A chemical can produce various effects ranging from not toxic to very toxic or "frank effect level" (FEL) (25, 56). The critical adverse effect is defined as "the first adverse effect, or its known precursor that occurs as the dose rate increases" (14). Operationally, for threshold end points, the critical effect is the most conservative LOAEL. This end point is used to derive the exposure limit (see section 6).

Figure 10.2 shows a hypothetical example of a chemical that produces two adverse threshold effects at different dose ranges. Liver pathology occurs at higher doses than respiratory function impairment. In this case, respiratory impairment is considered the critical end point with a corresponding experimentally measured LOAEL. The highest dose level that does not produce a statistically or biologically significant impaired respiratory function is the NOAEL. The NOAEL or LOAEL can be used to derive the exposure limit (see section 6).

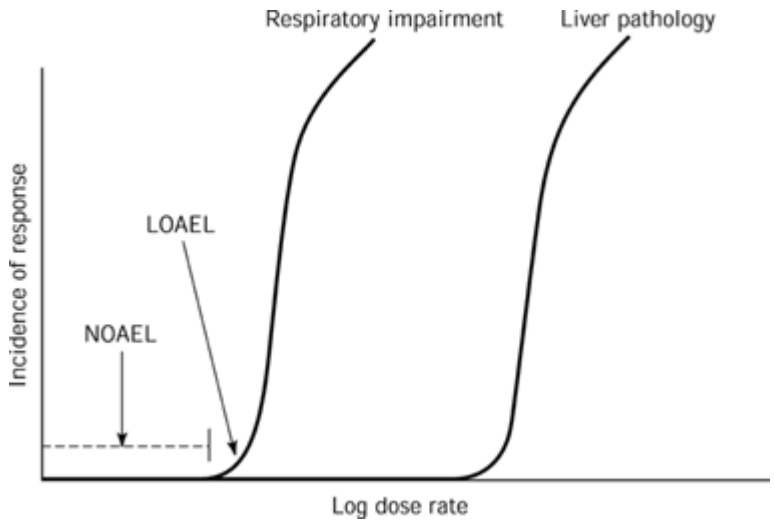

Figure 10.2. Hypothetical dose–response relationship curves for a chemical that produces two adverse threshold effects and illustrates the critical toxic effect, LOAEL, and NOAEL.

If a chemical produces both threshold and nonthreshold (cancer) adverse effects, exposure limits can be calculated on the basis of the threshold effect that is observed at the lowest dose and also on the nonthreshold end point (see section 6). For a nonthreshold effect, various curves of excess risk versus dose may be used to extrapolate downward from an experimental dose, depending on the quantitative risk model applied (see Fig. 10.3). Then the lowest concentration or the most conservative estimate for exposure limit is recommended.

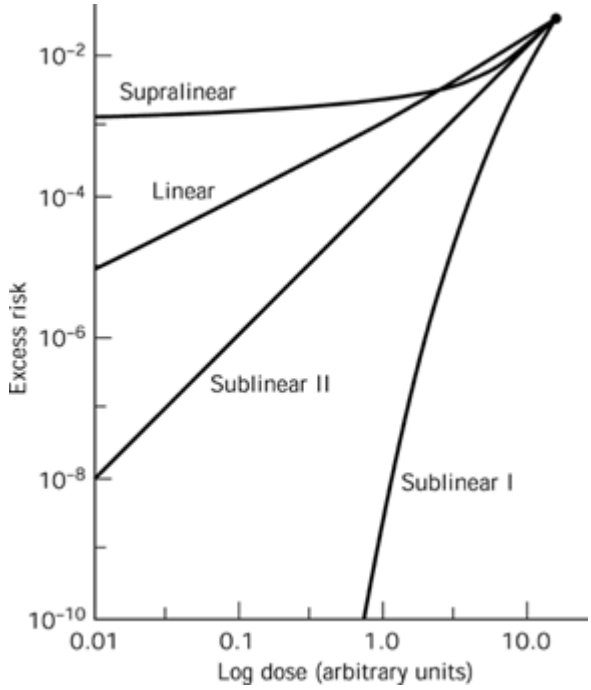

Figure 10.3. Alternative extrapolation models for the same experimental data set (from Ref. 3 with some modifications).

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6 Derivation of Exposure Limits
Traditionally, two different approaches have been used by regulatory agencies to derive exposure limits for substances that produce threshold and nonthreshold effects (19). The safety/uncertainty factor method has been used for threshold (noncancer) end points. For a cancer end point, the general approach has been to use a low-dose extrapolation risk model. Recently, a unified approach for threshold and nonthreshold effects has been proposed for deriving exposure limits by using the benchmark dose and uncertainty factors (57). The three approaches are described here.
6.1 The Safety/Uncertainty Factor Approach for Threshold Effects
The traditional safety/uncertainty factor approach of dividing the no-observed-adverse-effect level (NOAEL) of the critical effect by a safety factor has been widely used to derive "safe" exposure limits for chemicals that produce threshold effects (52). The ACGIH has used this approach for both threshold and nonthreshold effects in developing TLVs (58).

Historically, a safety factor of 100 has been applied to the NOAEL to account for all uncertainties, including interindividual and interspecies variation. Over the years, it became customary to divide this factor into two factors of 10 to account for interspecies and intraspecies variability, respectively (6).

Although the terms safety factor and uncertainty factor have the same meaning, the USEPA (13) recommended using the term uncertainty because "safety factor" may be inadvertently interpreted as absolute safety. It has further endorsed the use of uncertainty and modifying factors when deriving the oral reference (RfD) (13) and the reference inhalation concentration (RfC, USEPA 1994) for noncancer effects. The RfC (expressed in mg/m^3) is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime" (14). The same general principles apply to the derivation of the inhalation reference concentration and the oral reference dose (13, 14), but the RfC methodology has been expanded to account for the dynamics of the respiratory system as the route of entry. In the RfC method, the NOAEL from animal studies is converted to a refined dosimetric adjustment referred to as human equivalent concentration (HEC). The dose is also defined as the agent mass deposited per unit tissue volume delivered to specific target sites in the respiratory tract or made available to uptake and metabolic processes for systemic distribution. This methodology further distinguishes between gases or particulates and the type of effect the substance exerts, pulmonary or extra pulmonary.

The RfC is derived from the NOAEL (or the LOAEL, if the NOAEL is not available) as follows (14):

$$\mathrm{RfC} = \mathrm{NOAEL}_{\mathrm{HEC}}/(\mathrm{UF} \times \mathrm{MF})$$

where

$\mathrm{NOAEL}_{\mathrm{HEC}}$ = NOAEL adjusted for dosimetric differences between animal species and humans, expressed as human equivalent concentration (HEC).
UF = uncertainty factors suited to the characteristics of the data:

- 10-fold to account for interindividual variation in susceptibility among thehuman population
- 10-fold for interspecies variation between animal and humans
- Five-fold or 10-fold for extrapolating from data in a subchronic study to chronic or from less

than a lifetime study to a lifetime study

- Five-fold or 10-fold for extrapolating downward from LOAEL to a NOAEL. These uncertainty factors are based on historical and experimental data and are independent multiplicative factors (59–63).

MF = modifying factor, that is, an additional uncertainty factor which is based on professional assessment of the adequacy of the entire database (e.g., relevancy to humans and mechanistic and toxicokinetic data), ranging in magnitude from 1 to 10.

The NOAEL approach has been criticized for several reasons, including (*1*) the NOAEL must be by definition a tested experimental dose, (*2*) experiments that test fewer animals would result in a higher NOAEL and thus a higher or less protective exposure limit, (*3*) the use of the NOAEL ignores the rest of the dose–response curve, and (*4*) the NOAEL approach does not identify actual responses at the NOAEL and, depending on the experimental design, will result in regulatory exposure limits being set at various levels of risk (15, 64, 65).

In view of these limitations, an alternative approach using the benchmark dose (BMD) has been proposed by Crump (64). In this method the dose–response is modeled and the lower confidence bound for a dose at a specified response level, usually 1–10%, is calculated. The BMD can be used as an alternative to NOAEL in calculating the oral reference dose or inhalation concentration:

$$\mathrm{Rfc} = \mathrm{BMD}/\mathrm{UF} \times \mathrm{MF}$$

The UF and MF are the same as those used for the NOAEL or LOAEL. This method has been adopted by the USEPA (15) for noncancer effects and has been applied to developmental end points (54, 66).

6.2 Risk-Model Approach for Nonthreshold Effects

For cancer end points, the general approach has been to use a mathematical model to estimate the excess risk for a given dose (e.g. lifetime exposure to 1 mg/m^3 of substance in air) or the dose for a given risk (e.g., one in a million). Different dose–response models can be proposed to extrapolate from high doses in animal bioassays to low doses that might be encountered by humans, that is, extrapolation beyond the region in the dose–response curve for which experimental data are available (3, 67). Depending on the model chosen, the level of risk can vary by orders of magnitude at the same exposure level (see Fig. 3).

The risk extrapolation models can be divided into two general categories, namely, mechanistic models and statistical (or probability distribution) models (25) as follows. The mechanistic models (e.g., one hit, multihit, multistage, linearized multistage) use a mathematical equation to describe dose–response relationships that are consistent with postulated mechanisms of response. The mechanistic models assume that a response in a subject (animal, human) results from a random occurrence of one or more biological events (stochastic events). The distribution models (e.g., Log-probit, Logit, Weibull), on the other hand, assume that each individual has a tolerance level to a chemical and that this response level is a variable that follows a specific probability distribution function. These responses can be modeled by using a cumulative dose–response function, as in the case of the normally distributed dose–response curve.

The linearized multistage model (LMS) is the model most commonly used by regulatory agencies in the United States (68). This model, consistent with proposed genotoxic carcinogenic mechanisms, assumes that a series of ordered stages is required for a cell to undergo initiation, transformation, and progression to form a tumor. The USEPA uses the upper 95% confidence limit of this model on the basis of biological plausibility and conservatism. It has been argued, however, that the use of the upper 95% confidence limit reduces the model to a worst-case scenario and does not take into account carcinogenic mechanisms (24).

Until recently, these models have been used to extrapolate from high to low doses without considering interspecies variation. This raised the question whether carcinogenic potencies derived from these models are relevant to humans. A comparison of potencies across species for known human carcinogens (e.g., aflatoxin, vinyl chloride) showed relative concordance, at least within one order of magnitude (24). The prudent public policy has been to assume a similar ranking across species for animal carcinogens, unless there is convincing evidence to assume otherwise.

The advancement of physiologically based toxicokinetic (PBTK) and biologically based dose–response (BBDR) modeling in recent years has improved the application of risk extrapolation models. The PBTK model is used to estimate the "effective target tissue dose," thereby, reducing uncertainties associated with extrapolation across species from high to low dose and across routes of administration (69). The use of PBTK models in risk assessments of methylene chloride and perchloroethylene reportedly reduced risk estimates relative to those obtained from linearized models (24, 69).

BBDR models are intended to make mechanistic risk assessment models reflect specific biological processes (70). This type of model was reportedly applied effectively to epidemiological data on retinoblastoma and to animal data on kidney and liver tumors in the acetylaminofluorene "megamouse" study and to bladder cancer in saccharin-exposed rats (25, 71, 72). The carcinogenic risk assessment guidelines proposed by the USEPA (16) indicate that the biologically based or case specific model is the preferred approach for evaluating dose–response relationship for carcinogens. In the absence of such data, the use of a linear or nonlinear approach is recommended, depending on the mode of action of the chemical.

A recent comparative evaluation of threshold and nonthreshold risk assessment methods for establishing safe occupational exposure limits for vinyl halides (vinyl chloride, vinyl bromide, and vinyl fluoride) was reported (73). Safe levels derived from nonthreshold methods ((LMS model and BMD with linear extrapolation) were two- to three-fold below 0.5–5 ppm, whereas those derived by using the threshold approach methods (LOEL/LOEL and BMD uncertainty factor approaches) fell within the 0.5–5 ppm range. Similar results were reported for vinyl bromide and vinyl fluoride. The authors concluded that these results undermine the USEPA default assumption of nonthreshold for vinyl halides and support the threshold methods because reducing occupational exposure to vinyl chloride to 0.5–5 ppm has, so far, successfully eliminated vinyl chloride liver angiosarcoma.

6.3 Unified Approach for Threshold and Nonthreshold Effects Using Benchmark Dose and Uncertainty Factors

Recently, Gaylor et al. (57) proposed adopting a unified approach for establishing human exposure guidelines for both cancer and noncancer end points. They suggest that a lower confidence limit on the estimated dose to produce an excess incidence of adverse outcome in 10% of the individuals in human studies or of the test subjects in animal studies be used as a benchmark dose. Then, uncertainty factors can be applied to this dose. For severe irreversible adverse health effects, they recommend a total default uncertainty factor for animal data of the order of 10,000 which is comparable to current environmental guidelines, and for reversible adverse effects, a smaller uncertainty factor of 1000, which is comparable to that often used for LOAEL. The use of the benchmark dose approach has been indicated for both genotoxic and nongenotoxic carcinogens in the USEPA (16) proposed guidelines for carcinogenic risk assessment.

6.4 Occupational Versus Environmental Exposure Limits

Due to differences in population characteristics, exposure characteristics, risk assessment methods used to derive exposure limits, and acceptable risk levels, ambient air exposure standards are usually significantly lower than occupational exposure limits for the same chemicals. Ambient air standards intend to protect all people, including high risk groups such as children and the elderly, from continuous exposure over their life time and also take into consideration exposure from other media (water, soil, food). In the case of occupational exposure standards, it is believed that workers constitute a subpopulation that is healthier than the general population, and exposure is assumed to occur during an 8-h workday and 40-h workweek over a working life span of 48 years.

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7 Uncertainties in Chemical Safety Evaluation
In evaluating chemical hazards, it is most important that all sources of uncertainties are identified so that the limitations of the results are clearly understood. There are many sources of uncertainties, including extrapolation from high doses in animals to low doses in humans and across routes of administration, interspecies variability in biokinetics and mechanisms of toxicity, interindividual variation in biological response, poor specification of exposure conditions (concentration, duration, frequency and route of exposure, chemical identity), deficient control groups, and confounding factors in epidemiological studies. In some cases, an impact analysis of uncertainties can be conducted.

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8 Global Harmonization of Hazard Classification System (GHS)
Hazard classification systems have been developed in various jurisdictions to provide information on the toxic effects of chemicals to protect human health. They are used for communicating information on chemical hazards to workers or other end users so that appropriate precautions can be taken for safe chemical use. Hazard classification systems are usually incorporated into sector-specific regulations for transport, consumer products, and occupational health. Due to differences in chemical use and exposure, hazard classification schemes vary between sectors and within sectors among countries.

Toxicity classification criteria for chemicals in the workplace are included in the OSHA Hazard Communication Standard (29 CFR 1910.1200) and the Canadian Workplace Hazardous Materials Information System (WHMIS) legislation (74). In general, chemicals are categorized by toxic end points (e.g., acute toxicity, cancer, irritation, sensitization etc.) based on evaluation of the toxicological evidence against set classification criteria. Untested product mixtures are classified by the toxic effects of the ingredients using cutoff concentrations. Toxicity classification systems are usually based on the inherent toxicity of the chemical (e.g., cancer induced in rodents via oral administration) rather than on the risks that a chemical poses to human health under given exposures.

The OECD Advisory Group on Harmonization of Hazard Classification and Labeling was established 1994 to develop proposals for a harmonized classification system for the hazards of chemicals to human health and the environment (2). Member countries in this initiative include the United States, Canada, and the European Community (EC). Recently, the OECD released a report endorsing harmonized hazard classification criteria for acute toxicity, skin irritation/corrosion, eye irritation/corrosion, respiratory or skin sensitization, mutations in germ cells, cancer, and reproductive toxicity. The acute toxicity criteria in several jurisdictions and those endorsed by the OECD are compared in Table 10.3 (74). The OECD harmonized hazard classification system may eventually be implemented globally.

Table 10.3. Comparison of Acute Oral, Dermal, and Inhalation Toxicity Criteria among U.S. OSHA, CANADIAN WHMIS, EC, AND OECD*[abcd]*

Category	Oral LD_{50} Rat (mg/kg)	Dermal LD_{50} Rat or Rabbit (mg/kg)	Inhalation LC_{50} Rat, 4-h Gas (ppm)	Inhalation LC_{50} Rat, 4-h Vapor (ppm)	Inhalation LC_{50} Rat, 4-h Dust/Mist/Fume (mg/L)
OSHA					
Highly toxic	≤ 50	≤ 200	≤ 200	≤ 200	≤ 2
Toxic	>50 ≤ 500	>200 ≤ 1000	>200 ≤ 2000	>200 ≤ 2000	>2 ≤ 20
WHMIS					
Very toxic	≤ 50	≤ 200	≤ 2500	≤ 1500	≤ 0.5
Toxic	>50 ≤ 500	>200 ≤ 1000	—	>1500 ≤ 2500	>0.5 ≤ 2.5
EC					
Very toxic	≤ 25	≤ 50			≤ 0.25
Toxic	>25 ≤ 200	>50 ≤ 400			>0.25 ≤ 1.0
Harmful	>200 ≤ 2000	>400 ≤ 2000			>1 ≤ 5
OECD					
Class 1	5	50	100	0.5 mg/L	0.05
Class 2	50	200	500	2.0 mg/L	0.5
Class 3	300	1000	2500	10 mg/L	1.0
Class 4	2000	2000	5000	20 mg/L	5.0
Class 5	5000				

[a] Material in this table was derived from OSHA Hazard Communication Standard (29 CFR 1910.1200), WHMIS Resource Manual (73), European Community Directive 67/548/EEC (Annex VI) and OECD (2).

[b] OSHA LC_{50} values are for 1-h continuous inhalation (all the other LC_{50} values are for 4-h).

[c] OECD criteria are upper limit cut-off values for each class.

[d] EC inhalation LC_{50} values for gas or vapor in mg/liter/4-h are ≤0.5 for very toxic, >0.5≤2 for toxic, and >2≤20 for harmful.

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Appendix 1: Basic Toxicological Principles

The following is a summary of basic toxicological principles that are covered comprehensively in toxicology and pharmacology textbooks (7, 75).

Routes of Exposure and Fate in the Body

A chemical has to enter the body and reach sites of action ("receptors") at a concentration and for a length of time sufficient to produce toxic effects. Inhalation and absorption through the skin are the main routes of exposure to chemicals in the workplace. Accidental poisoning usually occurs by ingestion.

Metabolism is a term that refers to the total fate of a chemical in the body, including its absorption into systemic circulation, distribution to organs and tissues, biotransformation, and excretion. Absorption of a chemical into the blood and distribution in the body depend on the physicochemical characteristics of the substance. Depending on the specific chemical, biotransformation of the chemical usually occurs primarily in the liver and can result in chemical detoxification or activation to a toxic metabolite. Toxic chemicals and their metabolites are excreted via the kidneys or the lungs.

Toxicokinetics

Toxicokinetics quantitatively describes the rates of the various steps of chemical desposition in the body, absorption, distribution, and elimination by biotransformation and excretion. Mathematical models are used to describe the fate of chemical in the body and their validity is tested by comparing them with experimental observations. Variation in toxicokinetics among individuals and species plays an important role in differences in toxic effects.

Exposure Duration and Frequency

The terms acute, subacute, subchronic, and chronic refer to the duration of exposure to chemicals in animal studies via any route of exposure. Acute is defined as exposure to a chemical for less than 24 h. Repeated exposure for one month or less is subacute exposure, for one to three months is subchronic exposure, and for more than three months is chronic exposure. For many chemicals, the toxic effects that are produced following acute exposure are different from those produced by repeated exposure. To evaluate the toxic potential of a chemical, therefore, data from both acute and repeated exposure studies are required. In general, repeated exposure is a more common form of human exposure to chemicals and can result in delayed toxic effects.

The frequency of exposure is another important factor. Severe toxic effects that are produced by a single dose of a chemical may not occur if the total dose is divided and administered at several intervals. Depending on the elimination rate of the chemical from the body and the frequency of the dosing intervals, the chemical may or may not reach a toxic concentration. Even if the chemical does not accumulate, it still may be that some tissue damage occurs. The question is whether the interval between doses is sufficient to allow for complete repair. Chronic toxic effects, therefore, may be due to bioaccumulation of the chemical, to irreversible toxic effects, or to insufficient time for tissue recovery between dosing intervals.

Toxic Effects

Chemicals can produce a wide spectrum of undesirable effects ranging from deleterious (adverse, toxic) to slightly toxic. For many chemicals, toxic effects from acute exposure are different from those produced by chronic exposure. For example, acute exposure to benzene results in central nervous system depression, but chronic exposure can cause leukemia. Toxic effects may be reversible or irreversible and may occur immediately after exposure or after a long latency period as in the case of carcinogens. The effects may be local at the site of entry as seen with substances that are corrosive to the skin or irritating to the respiratory tract. Systemic effects require absorption and distribution of the chemical to a distant site where toxic effects occur. Usually, chemicals elicit their toxicity in specific sites or tissues called target organs.

Dose–Response Relationships (DRR)

The fundamental concept in toxicology is the dose–response relationship, which correlates the characteristics of exposure with the spectrum of effects. Although conceptually the same, in practice, there are two types of DRR:

1. “graded,” which describes the response of an individual to varying doses of a chemical, characterized by a dose–related increase in the severity of response; and
2. “quantal,” which characterizes the distribution of responses to different doses in a population by determining the dose required to produce a specific toxic effect (end point) in each individual; the presence or absence of a specific toxicity end point, such as death or a disease state, is called a quantal or all-or-none response.

The dose–response relationship assumes a causal association between the dose and response. The quantal dose–response–relationship is used extensively in toxicology, and the shape of the curve has

important implications in chemical risk assessment. It is customary to plot the response against the logarithm of the dose, and the resulting curve is typically S-shaped or sigmoidal (see Fig. 10.4a). Displaying the same data in a frequency histogram shows a normal frequency distribution bell-shaped curve (see Fig. 10.4b). The data can be further displayed in different ways for statistical analysis. Although typical, the dose–response relationship is not always normally distributed. Several concepts emerge from the classical dose–response curve of a normally distributed population (see figure 4) that are integral to evaluating chemical safety:

1. **The Median Toxic Dose (TD_{50}) and Lethal Dose (LD_{50})**

   The sigmoid curve has a relatively linear portion between 16 and 84% that represent the limits of one standard deviation of the mean. It is possible to statistically derive the single dose of a substance that would be expected to cause a toxic effect in 50% (or other percentage) of the subjects tested. If the response is mortality, then this dose is called the median lethal dose, or LD_{50} (LC_{50} is the median lethal concentration in inhalation studies). A relative toxicity index can be derived from the ratio of the TD_{50} of two different substances that produce an identical response or the ratio of the same chemical necessary to yield different toxic effects. The slopes of the curves, however, may differ.
2. **Threshold Dose, Lowest Observed Adverse Effect Level (LOAEL), and No Observed Adverse Effect Level (NOAEL)**

   A normally distributed sigmoid curve approaches 0% as the dose is decreased but theoretically never passes through 0%. The lowest dose of a chemical that evokes a quantal response is called the threshold dose, even if it cannot be measured experimentally. The identification of a threshold dose depends on the specific response measured, the sensitivity of the measurement, and the number of subjects. The LOAEL is the lowest experimentally measured dose that produces a toxic effect. The NOAEL is the experimentally measured dose that does not produce any adverse effect (Fig. 10.4a).

   The biological basis of thresholds for acute responses is well established and often is based on mechanistic information. The existence of a threshold for chronic responses is not as well defined, especially for carcinogens. Carcinogenic effects are often considered linear at low doses and do not exhibit a threshold. Thus, all doses are associated with a risk of cancer. Different methods of deriving “safe” exposure limits are applied to threshold effects and nonthreshold effects.
3. **Interindividual Biological Variation**

   It is evident from the normal frequency distribution curve (Figure 10.4b) that there are differences in susceptibility to chemicals among individuals in a population. Subjects who respond at the low end of the curve are hypersusceptible and those at the high dose end are resistant. It is important that individual differences and also species differences are considered when assessing chemical safety.

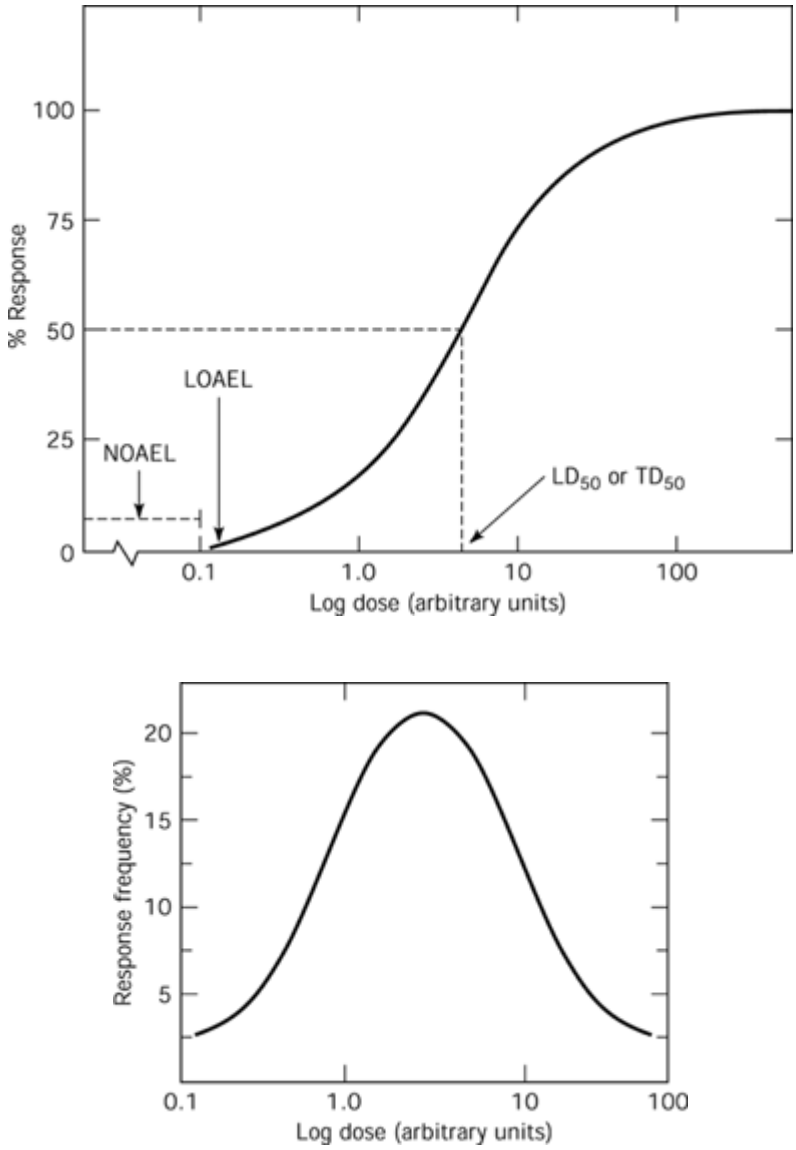

Figure 10.4. (a) A typical quantal dose–response relationship curve illustrating NOAEL, LD_{50} or TD_{50}. (b) Frequency distribution of response.

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Silica and Silica Compounds
Richard Lemen, Ph.D., Eula Bingham, Ph.D.

1 Introduction

The uses of silica and the potential health hazards for workers or others exposed to dust particles date back thousands of years and are documented. Hippocrates and Pliny both mentioned silica's ability to cause disease and Pliny even described miners who used forms of respiratory protection (1). In 1556, Agricola described in *De Re Metallica*, women living in the Carpathian mountains who oftentimes would have as many as seven different husbands in their lifetimes because the men who worked in the local mines were dying of pulmonary disease at very young ages (2, 3). In his 1713 edition of *De Morbis Artificum*, Ramazzini discusses an observation by Diemerbroeck from Holland

who gives an extremely graphic description of the effects of exposure to silica on stonecutters (4). “Diemerbroeck gives an interesting account of several stonecutters who died of asthma; when he dissected their cadavers he found, he says, piles of sand in the lungs, so much of it that in cutting with his knife through the pulmonary vesicles he felt as though he were cutting a body of sand.”

The first study of silicosis, in the time of the industrial revolution, was that of Johnstone in 1796 who noted the high mortality of needlepointers at Redditch, England (5). Knight first wrote of silica-induced disease in Sheffield during the early 1800s and later Thackrah, acknowledging Knight's work, described the dangers of sandstone dust in mining compared to the harmlessness of limestone dust and noted that bricklayers and limestone workers were long-lived whereas the sandstone masons usually died at an early age (6). Flint knappers, the makers of flints for flintlock guns, had high rates of silica-induced disease. Studies of the English and French knappers found that more than 75% died of “phthisis” compared to less than 10% in the general rural populations (7). Phthisis is an obsolete term for tuberculosis of the lungs derived from Greek meaning “a wasting away” or “consumption” (8). South African women who used sandstone grindstones for maize and corn developed diseases similar to those developed by the makers of the grinding stones (9, 10). Silicosis comes from the Latin, *silex*, meaning flint and is defined as “a pathological condition of the lungs due to inhalation of particulate matter containing free or uncombined silica, silicon dioxide, ... ” (5). The term's first use is attributed to Visconte in 1870 (5). By 1918, English workers received compensation for disability as a result of silicosis (11). Silicosis is a pneumoconiosis, but the terms must not be used synonymously. Silicosis, of all the pneumoconioses, has probably claimed the largest number of victims, either alone or in combination with tuberculosis, a condition frequently associated with silicosis (5). Betts gave the first description of acute silicosis in the United States (12). In 1932, the American Public Health Association (APHA) developed the definition for the fibrotic lung disease silicosis as

A disease due to breathing air containing silica (SiO_2), characterized anatomically by generalized fibrotic changes and the development of miliary nodulations in both lungs, and clinically by shortness of breath, decreased chest expansion, lessened capacity for work, absence of fever, increased susceptibility to tuberculosis (some or all of which symptoms may be present) and by characteristic X-ray findings.” (13).

In 1917, Dr. Alice Hamilton described the life of stonecutters in the Barre, Vermont area of the United States. She quoted a stonecutter as saying “sure I know it will get me. It got my father, it's got my older brother, it's only a question of time when it will get me.” Dr. Hamilton went on to describe stonecutters as having a high standard of living and decidedly above average compared to manual workers in education and intelligence, but she described the site of the mill as “dreadful” and of men “ ... carving tombstones and, as they did it, preparing themselves for their own graves.” Dr. Hamilton was so incensed at the fate of these workers that she could not contain herself and implored, in a speech, to the Consumers' League in Baltimore “ ... begged my hearers never to fulfill their duty to their beloved dead by means of a granite tombstone” (14). Dr. Hamilton went on to describe the introduction of the air hammer to the granite mines of the Barre, Vermont area and how the ensuing dust had given the Barre stonecutters a death rate from tuberculosis of 60.6 per 1,000, whereas the rural Vermont death rate was only 1.5 per 1,000 (14). Later the United States Public Health Service studied these workers and issued a report giving preventive measures to combat silicotuberculosis and silicosis resulting from the inhalation of silica-containing dusts for Barre workers and also for other exposed workers (15).

Silica is a natural mineral composed of silicon dioxide, which occurs in either the crystalline or amorphous form. Silica makes up 21% of the earth's crust and is the most common of all chemical compounds (16). Pure silicon dioxide crystals are found naturally in three polymorphic forms:

quartz, the most common; tridymite; and cristobalite. Each of the three is important to human health and make up the crystalline form of silica (16, 17). Both tridymite and cristobalite appear more fibrogenic than quartz (18). Silicon dioxide is an acidic oxide, which is practically insoluble in water, but can be attacked by hydrogen fluoride (16). The amorphous form of silicon dioxide, also called vitreous silica, does not pose a significant threat to human health because it has not been associated with pneumoconiosis. In the few reports that have claimed an association between amorphous silica and disease, the truly amorphous nature of the material has been in doubt (19). Therefore, for the purposes of this discussion, the review and comments relate to quartz (the most common silicate), which is sometimes called free silica.

Human exposures to silica were encountered from the first time man dug into the ground because silica deposits are found in every land mass and stratum from every era and period of geological time (20, 21). The use of silica in the production of glass probably dates back thousands of years (22).

It is difficult to get accurate figures on the use and production of silica because it is such a universal material and has a multitude of uses including glassmaking, ceramic making, foundry castings, abrasives, sandblasting, hydraulic fracturing, production of silicon and ferrosilicon metals, silica gel desiccants, builders for detergents, filtering material, furnace linings and beds, and fine silica as fillers in paints, rubber, paper, plastics, asphalt, scouring powders, cements, etc. Large quartz crystals are used in jewelry and for electronic applications, this latter application resulted from discovery of the crystal's dielectric and piezoelectric properties in 1880 (17). More recently, quartz crystals are being used in fiber optics (23).

The uses of silica are quite varied and so is the production of silica. Processing operations depend upon the nature of the deposit as well as the desired end product and include crushing, secondary milling to refine particle size, and other methods to further refine the particles (22).

World production was estimated by Davis and Tepordei at 182 million tons in 1983, Asia was the largest producer, followed by Europe, South America, North America, and Africa. This production pattern has been relatively stable for the last 10–15 years (22). The largest deposits of quartz crystals are in Brazil; minor deposits are in the United States, Angola, India, and Madagascar, and the mining methods are still quite primitive, most are extracted by hand tools (21, 23, 24). Fine particles of silica flour are used industrially as abrasive cleaners and as inert fillers in toothpastes, scouring powders, metal polishes, paint, wood fillers and road-surfacing mixtures, and in some foundry processes (25).

When the pneumatic hammer drill was introduced in 1897, it produced so much dust that it was named a “widow-maker.” Sandblasting was introduced about 1904 and resulted in numerous cases of silicosis. In 1936, British sandblasters, many of whom had acute silicosis, were said to survive an average of ten years compared to 40 years for those with chronic silicosis (26). In 1929, Sutherland and Bryson (27) and Sutherland et al. (28) detected silicosis by X ray in 25% of sandstone workers and 53% of granite workers.

Case reports and surveys by the U.S. Bureau of Mines and the Public Health Service documented the occurrence of pulmonary disease in various worker groups exposed to silica. Public attention was galvanized by the Gauley Bridge (WV) outbreak of acute silicosis among tunnelers of nearby pure quartz. This incident provided an impetus for industrial health reform in the United States and led in 1937 to dust control standards and to the Walsh–Healy legislation (29). Silicosis rates among granite workers in Vermont decreased dramatically during subsequent decades. From that time to the present, standards have been under continued reevaluation, and decremental changes in permissible exposures to “free” silica dust have reduced but have not eliminated silicosis as a health hazard.

Silica and Silica Compounds

Richard Lemen, Ph.D., Eula Bingham, Ph.D.

1.0 Silicon Dioxide
Silicondioxide has three main forms: silica, crystalline quartz; silica, crystalline cristobalite silica, crystalline tridymite is a mixture.
1.0.1 CAS Number:
[*14808-60-7*] (crystalline quartz or a-quartz); [*14464-46-1*] (crystalline cristobalite or a-cristobalite); [*15468-32-3*] (crystalline tridymite)
1.0.2 Synonyms:
Chalcedony; chert; coesite; cristobalite; cryptocrystalline silica; flint; jasper; microcrystalline silica; novaculite; quartz; quartzite; sandstone; silica sand; stishovite; tridymite; tripoli
1.0.3 Trade Names:
BRGM; D & D; DQ12; Min-U-Sil; Sil-Co-Sil; Snowit
1.0.4 Molecular Weight:
60.085 except tridymite, which is a mixture.
1.0.5 Molecular Formula:
SiO_2
1.1 Chemical and Physical Properties
1.1.1 General (Table 11.1).

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2.0 Amorphous Silica
2.0.1 CAS Number:
[*7631-86-9*]
2.0.2 Synonyms:
Amorphous silica; colloidal silica; diatomaceous earth; diatomite; fumed silica; fused silica; kieselguhr; opal; precipitated silica; silica gel; silica glass; silica soot; vitreous silica
2.0.3 Trade Names:
Aerosil; Cab-O-Sil; Celite; Ludox; Silcron G-910
2.0.4 Molecular Weight:
60.1
2.0.5 Molecular Formula:
SiO_2
2.1 Chemical and Physical Properties
2.1.1 General
2.2 Production and Use
A number of silicate or aluminosilicate minerals are commercially important in their own right and/or as starting materials for manufacturing other compounds or materials. These minerals encompass a wide range of chemical compositions and display a variety of physical properties. Thus, for example, the materials discussed following range from minerals that occur naturally as loose fibrous networks, for example, erionite, to dense cohesive clays, for example, kaolin and attapulgite. Occupational health interest in these minerals stems from two concerns. First, they may be toxic in their own right. Second, some of them may occur naturally in association with other silicon-containing minerals that are toxic, such as crystalline silica or asbestos. For the second reason, many epidemiological studies of workers who are occupationally exposed to these minerals are difficult to interpret because observed health effects may be attributable to any or all of the components of the

mixed exposure. For example, the observation of increased incidences of malignant and nonmalignant respiratory diseases among workers exposed to talc may be attributable to asbestos in the talc or to talc itself.
2.4 Toxicity
Not all forms of silica are equally pathogenic. In general, the relatively insoluble forms of amorphous silica can be fibrogenic but are less so than pure crystalline samples. Both fused (amorphous) and unfused (crystalline) silica produced nodules in rabbits following intraperitoneal injection of 200 mg dust, but the nodules produced by crystalline quartz were larger at three months; this difference became more marked with time (122). In rabbits, inhalation of 40 mg/mL amorphous silica for up to 1100 days caused only diffuse tissue reaction (123). However, intratracheal injection of amorphous silica (particles, < 1 mm) produced lesions on the lymph nodes in rats six months after infection, which were described as identical to those produced by quartz dust (124). Similarly, typical silicotic lesions have been produced in rats by intraperitoneal injection of 50 mg amorphous silica (125). Following exposure of rats by intraperitoneal injection, intratracheal injection, or inhalation of a variety of silica preparations, it was reported that solutions of silicic acid and silica gels were nontoxic and nonfibrogenic, that colloidal amorphous silica was toxic but not fibrogenic, and that crystalline quartz produced a maximal fibrotic response (126). The effects of samples of silica that were either completely amorphous or had a low content of crystalline material have been examined in rats, guinea pigs, rabbits and monkeys by a number of authors (127–140).

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3.0 Erionite
3.0.1 CAS Number:
[*66733-21-9*]
3.1 Chemical and Physical Properties
3.1.1 General Prismatic crystals in radiating groups; finely fibrous or wool-like; erionite is not known in other than fibrous form (141).

Density: 2.02–2.08
Color: White

3.2 Production and Use
Erionite is a natural zeolite consisting of aluminosilicate tetrahedra in finely fibrous or wool-like form. The name derives from the Greek word for wool. When ground, erionite particles resemble amphibole asbestos fibers morphologically.

Worldwide production of natural zeolites increased dramatically in 1989 and was estimated at 250,000 tons (142), of which 12,000 tons was mined in the United States. Until 1990, erionite was mined at two locations in the United States, but these operations have been stopped. No known production of erionite takes place in the United States now.

Natural zeolites have a number of commercial uses based on their ability to adsorb molecules selectively from air or liquids. They are used in wastewater treatment, in odor control products, and in cat litter. Historically, erionite was used as a metal-impregnated catalyst in a hydrocarbon cracking process. Now, however, because of health concerns described following, there are no known commercial uses of erionite in the United States.
3.3 Exposure Assessment
3.4 Toxicity
Erionite is of particular occupational health interest because of experimental and epidemiological

evidence that it is similar to asbestos in inducing mesothelioma and, perhaps, lung cancer. Groups of 40 (20 per sex) Fischer 344 rats were exposed to either fibrous erionite, a synthetic nonfibrous zeolite that has the same composition as erionite, or crocidolite asbestos by inhalation for 7 h/day, 5 days/week for 1 year (143). Pleural mesotheliomas were found in 27 of 28 rats exposed to fibrous erionite that survived for at least 12 months. One pulmonary adenocarcinoma and one mesothelioma were observed in rats exposed to nonfibrous synthetic erionite and one pulmonary squamous-cell carcinoma was observed in the rats exposed to crocidolite asbestos. In other studies in which erionite was administered to rats and mice by intrapleural or intraperitoneal administration, high incidences of mesotheliomas were produced (144).

Pulmonary and pleural fibrosis have been observed in humans living in areas where there are natural deposits of fibrous erionite (144). High mortality due to malignant pleural mesothelioma was noted in three Turkish villages where the environment was naturally contaminated by erionite. Erionite had been used in construction. Descriptive studies conducted in these villages strongly suggest that the incidences of mesothelioma and nonmalignant radiographic changes in the lung and pleura among residents are correlated with exposure to erionite. The IARC working group concluded that there was sufficient animal and human evidence of the carcinogenicity of erionite (144).

Erionite is a striking illustration that the ability to cause mesothelioma and nonmalignant pulmonary and pleural fibrosis is not confined to minerals of the serpentine and amphibole groups, that is, asbestos. Clearly the physical form of the fibrous material is as important in determining its biological activity as its chemical and mineralogical characteristics.

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4.0 Wollastonite
4.0.1 CAS Number:
[*13983-17-0*]
4.0.2 Synonyms:
Aedelforsite; gillebächite; okenite; rivaite; schalstein; tabular spar; vilnite
4.0.3 Trade Names:
Cab-O-Lite; Casiflux; F1; FW50; FW200; FW325; NCI-C55470; Nyad; Nyad G; Nycor; Tremin; Vansil; Wollastokup
4.0.4 Molecular Weight:
NA
4.0.5 Molecular Formula:
$CaSiO_3$

4.1 Chemical and Physical Properties
4.1.1 General Crystals commonly tabular; usually massive, cleavable to fibrous; also granular and compact. Twinning on (100) common. Structure changes to monoclinic at 1150°C (1120°C, 145); this form is sometimes called para-wollastonite or wollastonite-2M (146, 147). A 10% water slurry has a naturally high pH (9.9) (145).

Hardness: 4.5–5 on Mohs' scale
Density: 2.87–3.09
Specific Gravity: 2.1
Water Solubility: < 0.1 g/100 mL at 21°C
Color: Brilliant white; may be greyish, pale green or brownish with impurities (21, 146)

4.2 Production and Use
Wollastonite is a natural calcium silicate that typically occurs in deposits with other silicate minerals. When crushed, it tends to cleave into particles that have length to diameter ratios of 7 or 8 to 1. Fibrous forms of wollastonite are not uncommon.

The largest commercially exploited natural deposits of wollastonite are in the United States and Finland. Significant commercial production began in the United States in about 1950. The United States is currently the largest producer. It is estimated that 83,000 tons was produced in the United States in 1983 (144). There has been a dramatic increase in use (> 10% per year) in recent years, and production was estimated at 180,000 tons in 1988 (148).

Wollastonite was first mined for the production of mineral wool. The most important use at present is in ceramics which accounts for more than half of the consumption. Ceramic materials may include up to 70% wollastonite. It is also used as an extender in paints and coatings and as a filler in plastics. Some of the recent increase in use is attributable to its increasing importance as a replacement for asbestos. It is combined with binders, fillers, and organic fibers to make heat containment panels, ceiling and floor tiles, brake linings, and high-temperature appliances.
4.4 Toxicity
Occupational exposures to wollastonite involve a significant exposure to fibers (67). Fiber concentrations ranging from 1 to 45 fibers/cm^3 have been measured in air at a Finnish quarrying operation and concentrations between 8 and 37 fibers/cm^3 were measured in the flotation and bagging plant. Fiber concentrations in the air in a mill in the United States ranged from 0.8 to 48 fibers/cm^3.

Very little relevant information is available about the potential health effects of wollastonite. Intrapleural administration of wollastonite to rats resulted in a significant increase in pleural sarcomas when the implanted material contained fibers > 4 mm long and < 0.5 mm in diameter (67). Mild changes characteristic of pneumoconiosis and pleural thickening have been seen in some workers exposed to wollastonite at facilities in Finland and the United States (144). In one small cohort mortality study of workers at a Finnish quarry, there was no indication of increased cancer mortality. In view of the increase in the use of wollastonite as an asbestos replacement, much more research is needed regarding its potential health effects.

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5.0 Attapulgite
5.0.1 CAS Number:
[*12174-11-7*]
5.0.2 Synonyms:
Palygorskite
5.0.3 Trade Names:
Attaclay; Attacote; Attagel; Attasorb; Diluex; Min-U-Gel FG; Permagel; Pharmasorb-colloidal; 2000/P-RVM; RVM-FG; X-250; Zeogel
5.0.4 Molecular Weight:
NA
5.0.5 Molecular Formula:
$(Mg, Al)_2 Si_4 O_{10} (OH) \cdot 4H_2O$
5.1 Chemical and Physical Properties
5.1.1 General The structure of attapulgite is similar to that of minerals of the amphibole group and differs only in minor respects from that of sepiolite. It occurs as elongated, lath-shaped crystals in

bundles that comprise thin sheets composed of minute interlaced fibers.

Hardness: Soft
Density: 2.2
Color: White, gray; translucent; dull

5.2 Production and Use
This material is closely related to sepiolite and is categorized as a hormitic clay. Attapulgite has a structure similar to minerals of the amphibole group. This structure results in long, thin crystals that are similar to chrysolite asbestos fibrils (144). Attapulgite occurs in large deposits in the southeastern United States. The term “fuller's earth” has been used to describe commercially mined absorbent clays in the United States, and most of this material is attapulgite.

Worldwide attapulgite production in 1983 was estimated at about 1.1 million tons, of which 84% came from the United States (144). The primary use of attapulgite is as an animal waste absorbent (cat litter). Other important uses of attapulgite in the United States are as a component of drilling muds, as oil and grease absorbents, and in fertilizer and pesticide formulations.
5.3 Exposure Assessment
5.3.3 Workplace Methods No ACGIH TLV standards or guidelines have been developed for attapulgite (149).
5.4 Toxicity
The results of long-term surveillance of workers at two sites in the United States where attapulgite was mined and milled indicated that there was an increased prevalence of pneumoconiosis and that the incidence increased with age and with duration of exposure (144). A decrease in pulmonary function was associated with total cumulative exposure to respiratory dust in the workers at one of these facilities.

The evidence relevant to the possible carcinogenic effects of attapulgite was reviewed by the IARC working group (144). Studies in which attapulgite was administered to rats by either intraperitoneal or intrapleural administration indicated that attapulgite containing significant number of fibers > 5 mm long produced mesotheliomas and sarcomas. A single epidemiological study of miners and millers exposed to high concentrations of attapulgite dust for long durations indicated that there was increased mortality from lung cancer, but no information on smoking behavior was determined. The working group concluded that there was limited evidence that attapulgite was carcinogenic in experimental animals but that the human evidence was inadequate to support a conclusion.
5.5 Standards, Regulations, or Guidelines of Exposure
No exposure standards or guidelines have been developed for attapulgite by OSHA, NIOSH, or ACGIH (150–152).

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6.0 Sepiolite
6.0.1 CAS Number:
[*18307-23-8*], [*15501-74-3*]
6.0.2 Synonyms:
Meerschaum
6.0.3 Trade Names:
NA
6.0.4 Molecular Weight:

NA
6.0.5 Molecular Formula:
$Mg_2Si_3O_8 \cdot 2H_2O$
6.1 Chemical and Physical Properties
6.1.1 General Sepiolite is similar to attapulgite but has an additional SiO_4 tetrahedron at regular intervals on the chain, so that the united cell is about 50% larger than that of attapulgite (21); usually clay-like, nodular and fibrous; also compact massive (meerschaum) or leathery (mountain skin) (153, 154).

Hardness: 2–2.5 on Mohs' scale

Density: ~2

Color: White with tints of grey-green or red; also light yellow

6.2 Production and Use
A particularly pure form of sepiolite mined in Europe and the Middle East is known as "meerschaum" and has been used historically for carving pipes and cigarette holders. Sepiolite production in 1983 was less than half of the estimated 1.1 million of attapulgite in the world. A primary use of sepiolite was as an animal waste absorbent (cat litter).
6.3 Exposure Assessment
6.3.1 Workplace Methods No ACGIH TLV standards have been developed for sepiolite (155).
6.4 Toxicity
Little information is available regarding the potential effects of sepiolite. A limited study of workers and residents in a village in Turkey who were exposed to sepiolite during mining and trimming indicated that exposed individuals did have clinical and radiological evidence of pulmonary fibrosis but no cases of mesothelioma or other pleural diseases were observed. The IARC working group concluded that the animal evidence was inadequate and that there was no human evidence available to evaluate the potential carcinogenicity of sepiolite (144).
6.5 Standards, Regulations, or Guidelines of Exposure
No exposure standards or guidelines have been developed for sepiolite by OSHA, NIOSH, or ACGIH (150–152).

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7.0 Kaolin
7.0.1 CAS Number:
[*1332-58-7*]
7.0.2 Synonyms:
Kaolinite; china clay; bolus alba; porcelain clay; aluminum silicate hydroxide; Kaopectate; aluminum silicate (hydrated); aluminum silicate dihydrate
7.1 Chemical and Physical Properties
Kaolin is a hydrous aluminosilicate mineral that is found in large natural deposits of kaolinite in Georgia, South Carolina, and Texas (156). A typical kaolin contains 38.5% by weight aluminum oxide, 45.5% silicon dioxide, 13.9% water, and 1.5% titanium dioxide, with small amounts of calcium, magnesium, and iron oxides. A single crystal consists of a layer of silicon dioxide that is covalently bonded to a layer of aluminum oxide. When the clay is processed by centrifugal classification, it can be separated into fractions consisting of stacks of the hexagonal plates (< 2 mm in diameter and particles greater than 2 mm in diameter consisting of stacks of the hexagonal plates). Kaolin, as mined, contains other minerals including quartz, muscovite, and altered feldspars (157). The purification process removes much of the crystalline silica, so that commercial products

typically contain less than 3% crystalline silica and the respirable dust contains less than 1%. On the other hand, if kaolin is calcined, some of it may be converted to cristobalite.

Color: white to yellowish or grayish powder (149)

7.2 Production and Use
Domestic production of kaolin was estimated at 8.6 million tons in 1988 (158). More than 80% was produced in Georgia. A major use of kaolin is as a filter and a pigment in the manufacture of coated paper. Kaolin is also used as an extender and pigment in paints, in ceramics, rubber, thermosetting resins, and adhesives.
7.3 Exposure Assessment
7.3.3 Workplace Methods The recommended methods for determining workplace exposures to kaolin are NIOSH Method #0500 for total dust and #0600 for respirable dust (31).
7.4 Toxicity
The health effects of exposure to kaolin dust by inhalation have not been adequately studied. Historically, reports of respiratory diseases among workers exposed to kaolin were attributed to possible contamination of the kaolin by crystalline silica. Before 1991, the ACGIH TLV for kaolin was that for a nuisance dust, namely, 10 mg/m^3 TWA. However, in 1991, ACGIH reviewed the available information and issued a notice of intended change (157). The ACGIH cited a number of case reports and epidemiological studies of workers who were exposed to kaolin during mining and processing in Georgia. For the most part, Georgia kaolinite contains little or no crystalline silica. In workers who were exposed to kaolin dust during the milling and bagging of kaolin, there was an increased prevalence of pneumoconiosis. The prevalence of pneumoconiosis was correlated with both the intensity and duration of exposure. Pneumoconiosis incidence was not increased in open pit miners, who were exposed to significantly lower dust concentrations than workers involved in milling, bagging, and loading. As with many epidemiological studies of the effects of respiratory particulate matter, quantitative data on past exposure for these workers were of poor quality, but exposure levels in the past were unquestionably very high.

There are no reports to suggest that workers exposed to kaolin free silica have a history of malignant respiratory diseases. The carcinogenic potential of kaolin has not been systematically studied in either experimental animals or exposed workers, however. Based on the available evidence that kaolin induces pneumoconiosis.
7.5 Standards, Regulations, or Guidelines
NIOSH has a recommended exposure limit of 10 mg/m^3 (total); 5 mg/m^3 (resp); OSHA has a standard of 15 mg/m^3 (total); 5 mg/m^3 (resp) (149). The ACGIH TLV standard is 2 mg/m^3 for matter containing no asbestos and <1% crystalline silica in the respirable fraction (157). It may be carcinogenic for humans but cannot be assessed conclusively because of lack of data. Pneumoconisis is the critical effect (155).

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8.0 Perlite
8.0.1 CAS Number:
[*130885-09-5*]
8.1 Chemical and Physical Properties
8.1.1 General Perlite is a natural glass formed by volcanic action. It is a sodium potassium aluminosilicate that has an amorphous structure. It possesses an unusual physical characteristic of expanding to about 20 times its original volume when heated to temperatures within the softening range, somewhere between 1400 and 2000°C. Expanded perlite is either a fluffy, highly porous

substance or a glassy-white particulate with low porosity, depending on how the material is heated. The bulk material has a density between 3 and 20 lb/ft^3.

8.1.2 Odor and Warning Properties The crystalline silica content of 16 samples of perlite ore collected from 19 deposits in 16 western states was quite low, < 2% in 15 and 3% in one sample (159). The crystalline silica content of typical expanded perlite ranged from 0 to 2% (160).
8.2 Production and Use
An estimated 517,000 tons of perlite was produced in the United States during 1988 (161). Most uses of perlite involve the expanded form. It is used in abrasives, acoustical plaster and tile, charcoal barbecue base, cleaner base, concrete aggregates, filter aids, fertilizer, metal foundries, insulation, and refractory products. It is used as a filler in numerous materials. Incorporation into construction materials accounts for about 70% of the domestic use of perlite.
8.3 Exposure Assessment
8.3.3 Workplace Methods The recommended methods for determining workplace exposures to perlite are NIOSH Method #0500 for total dust and #0600 for respirable dust (31).
8.4 Toxicity:
NA
8.5 Standards, Regulations, or Guidelines of Exposure
The NIOSH standard is 10 mg/m^3 for total dust and 5 mg/m^3 for respirable perlite. The OSHA standard is 15 mg/m^3 for total dust and 5 mg/m^3 for respirable perlite (149). The ACGIH TLV for perlite is 10 mg/m^3 for dust containing less than 1% crystalline silica and no asbestos (150).

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9.0 Pumice and Pumicite
9.0.1 CAS Number:
[*1332-09-8*]
9.1 Chemical and Physical Properties:
NA
9.2 Production and Use
Domestic production of pumice and pumicite was estimated at 400,000 tons in 1988 (162). About 70% of this came from mines in New Mexico and Idaho. Concrete admixtures and building blocks are the major uses for this material and account for 86% of the total production. A very finely groundform of pumice known as micronized pumice is used as an abrasive in toothpaste, polishes, and soaps. There is very little published information on potential occupational exposures to, and adverse health effects of, pumice.
9.5 Standards, Regulations, or Guidelines of Exposure
There are no hygienic standards or guidelines for controlling occupational exposure to these compounds. By default, pumice and pumicite containing no asbestos and less than 1% crystalline silica are considered inert or nuisance dusts for which the OSHA PEL is 15 mg/m^3 total dust or 5 mg/m^3 respirable dust TWA (151).

Silica and Silica Compounds
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10.0 Kyanite

10.0.1 CAS Number:
[*12183-80-1*]
10.1 Chemical and Physical Properties
10.1.1 General Kyanite, andalusite, and sillimanite are anhydrous aluminosilicate minerals that are closely related to several other aluminum silicate minerals such as topaz. Calcination of this mineral produces a refractory material that can be used to manufacture high-performance, high-alumina refractories (163).
10.2 Production and Use
It was estimated that in 1987, 90% of the kyanite produced in the United States was used in refractories, 55% of this for smelting and processing iron, 20% for smelting and processing nonferrous metals, and 15% for refractories in glassmaking and ceramics (163).
10.5 Standards, Regulations, or Guidelines of Exposure
As with pumice and pumicite, little is known about the occupational health and industrial hygiene aspects of this class of materials. There are no standards or guidelines for limiting occupational exposure to this material. By default, air concentrations are limited to those for inert or nuisance dusts according to OSHA policy (151).

Silica and Silica Compounds
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11.0 Mica
11.0.1 CAS Number:
[*12001-26-2*]
11.0.2 Synonyms:
Zimmwaldite, fluorophlogopite; margarite; silicates; soapstone, lipidolite; roscoelite
11.0.3 Trade Names:
Muscovite, Phlogopite; biotite
11.0.4 Molecular Weight:
Varies
11.1 Chemical and Physical Properties
11.1.1 General Nonflammable, nonfibrous, water insoluble

Color: Colorless, odorless flakes or sheets

11.2 Production and Use
Mica is a nonfibrous, natural silicate, found in plate form in nine different species. These materials are hydrous silicates, and the predominant minerals of commerce are muscovite, a hydrous aluminosilicate, and phlogophite, a magnesium silicate (164). Sheet forms of mica in the form of muscovite have historically been mined by hand from pegmatites. However, in the past decade, demand for sheet forms of mica have dropped dramatically as the electronics industry has switched to synthetic quartz to meet the traditional uses of this material. Most modern uses of mica involve ground material and almost all of this is derived as a by-product from mining lithium, feldspar, or kaolin. The state of North Carolina accounted for 75% of the domestic production of mica in 1988. The major uses of mica in 1988 were in wallboard joint cement, paint, rubber, and oil well drilling fluids. These uses totaled 95,000 tons (164).
11.5 Standards, Regulations or Guidelines of Exposure
The NIOSH recommended exposure limit is 3 mg/m^3, and OSHA's is 20 mppcf (149). ACGIH TLV has a TWA of 3 mg/m^3. This is the value for particulate matter containing no asbestos and < 1% crystalline silica. Pneumoconiosis is a critical effect (155).

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Manufactured Products Containing Silicon

Silica and Silica Compounds
Richard Lemen, Ph.D., Eula Bingham, Ph.D.

12.0 Portland Cement
12.0.1 CAS Number:
[*65997-15-1*]
12.0.2 Synonyms:
Silicate, cement; cement, portland, chemicals: cement kiln dust; kiln precipitator catch; portland cement kiln dust: portland cement plant kiln dust; waste kiln dust; hydraulic cement; portland cement silicate
12.1 Chemical and Physical Properties
12.1.1 General Although it is not a natural silicate mineral, portland cement resembles this family of minerals in its physical and chemical characteristics. Portland cement is the most common form of cement used throughout the world and was named because of its resemblance to a well-known English building stone from the Isle of Portland. It is manufactured by blending lime, alumina, silica, and iron oxide as tetracalcium aluminoferrate (with the theoretical formula $4CaO \cdot Al_2O_3 \cdot Fe_2O_3$), tricalcium aluminate ($3CaO \cdot Al_2O_3$), tricalcium silicate ($3CaO \cdot SiO_2$), and dicalcium silicate ($2CaO \cdot SiO_2$). Small amounts of magnesia (MgO), Na, K, and S are also present. Sand is added to make concrete. Modern cement may be augmented with a variety of natural or synthetic additives to impart specific physical properties. Natural or synthetic fibers may be added to impart specific physical properties and to improve strength or thermal resistance. Polymeric materials such as epoxy resins may be added to impart strength, flexibility, improved curing properties, or moisture resistance.

Portland cement is produced by grinding and mixing the starting materials and calcining this mixture in rotary kilns at about 1400°C. The cooled clinker that is formed is ground and mixed with additives such as gypsum to form the final cement. The cement may then be mixed with sand or gravel to make concrete. The quartz content of cement is usually less than 1%.
12.2 Production and Use
Because most portland cement is used in the construction of buildings, consumption parallels building trends. The total consumption of cement in the United States in 1988 was 84 million tons (165). This was similar to the consumption in the previous two years and considerably higher than the approximately 65 million tons consumed in 1982, a recession year. Occupational exposure to portland cement occurs during its manufacture and use and is limited primarily to inhalation of, or dermal contact with, the dry material. The majority of the cement used in construction is mixed with sand and gravel and water at a central plant and trucked wet to the construction site. Thus there is little opportunity for exposure of workers at the site to cement dust. Nevertheless, many construction workers may be exposed to cement dust when small amounts are mixed on site or when cement or concrete materials are cut or ground.
12.3 Exposure Assessment
12.3.3 Workplace Method The recommended method for determining workplace exposures to Portland cement is NIOSH Method #0500 (31).

12.4 Toxicity
The potential adverse health effects of portland cement have not been extensively studied. The available evidence suggests that it has a low degree of toxic hazard. There does not appear to be any evidence that pneumoconiosis is associated with exposure to portland cement dust if that exposure is not accompanied by exposure to other fibrogenic dusts such as crystalline silica. Deposition of portland cement in the eye can result in alkali burns from calcium oxide (CaO) in the cement if the material is not washed out (166).
12.5 Standards, Regulations, or Guidelines of Exposure
The OSHA PEL TWA for exposure to portland cement dust is 10 mg/m^3 for total dust and 5 mg/m^3 for respirable dust (151). The NIOSH REL is the same (152). The ACGIH TLV TWA is 10 mg/m^3. This value is for particulate matter containing no asbestos and < 1% crystalline silica. It causes irritation and dermatitis (155).

Silica and Silica Compounds
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13.0 Silicon Carbide
13.0.1 CAS Number:
[*409-21-2*]
13.0.2 Synonyms:
Carborundum; carbolon; silicon monocarbide; silicon carbide, 98.8%
13.0.3 Trade Name:
NA
13.0.4 Molecular Weight:
40.097
13.0.5 Molecular Formula:
SiC
13.1 Chemical and Physical Properties
In recent years, a crystalline form of silicon carbide, known as silicon carbide whiskers, has become an important industrial material. A silicon carbide whisker is a single crystal of silicon carbide that has a cylindrical shape, an aspect ratio of greater than 3, and a diameter of less than 5 mm (167).

Color: Yellow to green to bluish black iridescent crystals (149).

13.2 Production and Use
Silicon carbide, also known by the trade name Carborundum, has been manufactured and used as an abrasive material for more than a century. It combines desirable properties of hardness and thermal resistance. It is produced by heating high-grade silica sand with finely ground carbon at 2400°C in an electric furnace (178). In its powdered or granular form, it has been used as the abrasive material in “empty” paper and wheels. It is used as an abrasive in sandblasting and engraving. It has been incorporated into ceramics and glass and especially into refractory ceramic materials.

In silicon carbide, whiskers are used to impart strength and increased thermal resistance to structural materials that are used at high temperatures. Composite ceramics containing silicon carbide whiskers have been used in manufacturing sandblasting nozzles, rocket motor nozzles, heat shields for reentry vehicles, and parts for nuclear reactor fuel assemblies.
13.3 Exposure Assessment
13.3.3 Workplace Method The recommended method for determining workplace exposures to silicon carbide is NIOSH Method #0500 for total dust and Method #0600 for respirable dust (31).
13.4 Toxicity

13.4.1 Experimental Studies 13.4.1.1 Chronic and Subchronic Toxicity Silicon carbide whiskers accumulated in a dose-related manner in lung tissue during the exposure period and resulted in a significant increase in lung weight for the rats in the highest exposure group compared to controls. The whiskers were most concentrated at the bifurcations of the alveolar ducts and respiratory bronchioles. Most whiskers were either engulfed by alveolar macrophages or located intracellularly in the interstitial tissues. Whiskers also accumulated in the bronchial and mediastinal lymph nodes. Whiskers were present in the interstitial lung tissue and lymph nodes after the 26-week recovery period. Histopathologically, there was evidence of inflammation in both the alveoli and in the lymph nodes. Bronchiolar, alveolar, and pleural thickening, focal pleural fibrosis, and reactive lymphoid hyperplasia were observed in treated rats, and the incidence and severity were dose-related. At the end of the 26-week recovery period, inflammation and lymph node hyperplasia regressed but there was an increased incidence of alveolar and pleural thickening accompanied by a dose-related incidence of adenomatous hyperplasia of the lungs. Despite the relatively short exposure period in this study, the changes seen are consistent with early pulmonary responses to fibrogenic and carcinogenic mineral fibers, such as asbestos, and some of these changes were not reversible. Lapin et al. also noted that no "no-effect level" was demonstrated in their study and that lower exposure levels would need to be examined to detect such a level (167).

In vitro and *in vivo* studies of silicon carbide whiskers deposited on the ciliated epithelium of the respiratory system indicated that the whiskers were swept to the nonciliated regions by ciliary action (143). There they penetrated the epithelial layers and caused cell damage and death. The cytotoxicity observed was similar to that of asbestos. Intrapleural injections of 20 mg of silicon carbide whiskers once a month for three months caused a 47.7% incidence of pleural mesotheliomas in rats compared to a 34.1% incidence in rats treated with UICC chrysolite asbestos (168).

13.4.1.2 Epidemiology Studies Silicon carbide dust has been considered relatively inert when inhaled. However, in recent years, a number of publications have appeared, suggesting that inhalation of silicon carbide during its manufacture or use as an abrasive may result in pneumoconiosis, Individual cases were described in reports by Funahashi et al. (169), De Vuyst et al. (170), and Hayashi and Kajita (171). Peters et al. (172) found radiographic abnormalities and altered pulmonary function in 171 men employed in the manufacture of silicon carbide. Osterman et al. (173) and Gauthier et al. (174) studied workers from this same plant and also reported decrements in pulmonary function, increased respiratory symptoms, and radiographic changes related to the duration of exposure. Elding et al. (175), on the other hand, found no increases in total mortality, cancer mortality, or mortality from nonmalignant respiratory diseases among 521 men who manufactured abrasive materials using silicon carbide. Interpretation of the results from the studies by Peters et al. (172) and Osterman et al. (173) is complicated by the fact that workers involved in the manufacture of silicon carbide are also exposed to sulfur dioxide and polycyclic aromatic hydrocarbons. Furthermore, the particulate matter to which they were exposed contained small quantities of quartz and cristobalite (176). Durand et al. (177) examined chest radiographs of 200 workers at a Quebec silicon carbide manufacturing plant. Twenty-eight had abnormal radiographs providing clinical evidence of pneumoconiosis, half of which were typical of pure silicosis. Examination of these workers over a seven-year period indicated that the condition did not progress. These same authors examined the particulate materials to which these workers were exposed and conducted experiments in sheep designed to identify the agent that might cause the conditions that were seen (178). They discovered that the particulate matter in the air of the plant contained silicon carbide in both particulate and fibrous form. In the sheep model, silicon carbide particles were no more active than inert materials such as latex beads and graphite powder. The silicon carbide fibers, on the other hand, had fibrogenic activity comparable to that of crocidolite and chrysotile asbestos fibers. They concluded that workers in silicon carbide manufacturing plants may be exposed to silicon carbide fibers, which can contribute to the induction of interstitial lung disease.

13.5 Standards, Regulations, or Guidelines of Exposure

NIOSH has a standard of 10 mg/m^3 (total); 5 mg/m^3 (resp). OSHA has a standard of 15 mg/m^3 total (<1% silica) and 5 mg/m^3 (resp) (149). These standards and guidelines reflect the traditional view of

this material as relatively innocuous. Silicon carbide whiskers in particular and perhaps silicon carbide dust also may be more biologically active than is reflected by these numbers. Occupational exposure should be minimized while additional information is being developed. The ACGIH TLV has a TWA of 10 mg/m^3 which is the value for particulate matter containing no asbestos and <1% crystalline silica. There is concern that it is carcinogenic for humans, but not enough data exists for a definite determination. The critical effect is on the lungs (155).

Silica and Silica Compounds
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14.0 Silicon Halides

	Silicon Tetrabromide	Silicon Tetrafluoride	Silicon Tetrachloride
14.0.1 CAS Number	[*7789-66-4*]	[*7783-61-1*]	[*10026-04-7*]
14.0.2 Synonyms	Silicon (IV) bromide; tetrabromo-silane	Silicon (IV) fluoride; tetrafluorosine	SIC-L (TM); silicon chloride; tetrachlorosilane; tetrachlorosilicon; silicon (IV) chloride
14.0.3 Trade Names	NA	NA	NA
14.0.4 Molecular Weight	347.40	104.080	169.90
14.0.5 Molecular Formula	$SiBr^4$	SiF^4	$SiCl^4$
14.1 Chemical and Physical Properties		Decomposes	
Color		Colorless gas	Colorless, mobile fuming liquid

14.1.1 General
Of the three silicon tetrahalides (also known as tetrahalosilanes), only two, the chloride and bromide, are of commercial significance, and silicon tetrachloride is of greatest importance. The tetrafluoride is a gas at room temperature whereas the tetrachloride and tetrabromide are fuming liquids. They are prepared by the direct halogenation of pure quartz or silicon carbide at elevated temperature and pressure.

The primary use of silicon tetrachloride is as the starting material for the manufacture of high-purity silicon, amorphous silica, and ethyl silicate. Silicon tetrafluoride is used as a starting material for fluorosilic acid (H_2SiF_6) for water fluoridation.

14.1.2 Odor and Warning Properties

Silicon tetrafluoride exhibits a very pungent odor. Silicon tetrachloride has a suffocating odor, is moisture sensitive.

14.4 Toxicity

Silicon tetrahalides are readily hydrolyzed to their corresponding hydrogen halides and silica upon contact with moisture. For this reason, all three silicon tetrahalides are highly toxic by either inhalation or ingestion and can cause severe irritation of the skin and mucous membranes. In this respect their occupational hazards are qualitatively similar to those associated with the hydrogen halides.

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15.0 Silanes

	Silicon Tetrahydride	Trisilane	Trichlorosilane	Hexachloro-disilane
15.0.1 CAS Number	[*7803-62-5*]	[*7783-26-8*]	[*10025-78-2*]	[*13465-77-5*]
15.0.2 Synonyms	Silane; silicone anhydride; Si-H; monosilane; silicon hydride; silane, C. P. grade; Silicon Tetrahydride (silane)		Silicochloroform; trichloromonosilane	
15.0.3 Trade Names	NA	NA	NA	NA
15.0.4 Molecular Weight	32.118	92.321	135.45	268.89
15.0.5 Molecular Formula	SiH^4	Si^3H^8	$HSiCl^3$	Si^2Cl^6
15.1 Chemical and Physical Properties	Insoluble in H^2O		Decomposes	
Color			Colorless liquid	

15.1.1 General

Silicon forms a large homologous series of silicon hydride compounds analogous to the alkane series of hydrocarbons. The simplest member of this series is silicon tetrahydride, better known as silane. Subsequent members of the series are disilane (Si_2H_6), trisilane (Si_3H_8), and so on. As with the

hydrocarbons, individual hydrogen atoms may be replaced by certain functional groups such as halogens, aliphatic hydrocarbons, and hydroxyl groups to form parallel series of compounds.

The silicon–hydrogen bond in silanes is much weaker than the corresponding carbon–hydrogen bond in aliphatic hydrocarbons. Therefore, these compounds are much more reactive and undergo spontaneous oxidation in air. They also are readily hydrolyzed to silicic acid and silica in the presence of water. They decompose upon heating to liberate hydrogen and free silicon.

15.1.2 Odor and Warning Properties

Silicon tetrahydride is a highly toxic gas with a repulsive odor. It is spontaneously flammable in air. Trichlorosilane has an acrid odor, fumes in air and supports combustion. It is a lachrymator and is moisture sensitive. Octamethyl tetrasilane is moisture sensitive.

15.4 Toxicity

Because of their reactivity and specialized usage, there is relatively little opportunity for significant occupational exposure to the silanes and their derivatives. Perhaps the most extensively used compounds are trichlorosilane and hexachlorodisilane. These compounds decompose upon contact with moisture to form hydrogen chloride. The primary hazard associated with chlorosilanes is their extreme flammability. Silane ignites spontaneously in air and trichlorosilane has a flash point of 7 ° F. Apart from their flammability, these compounds have a relatively low order of acute toxicity relative to other volatile inorganic hydrides. The LC_{50} of trichlorosilane for rats is 1000 ppm and the oral LD_{50} is 1030 mg/kg. Silane is less toxic than trichlorosilane.

15.5 Standards, Regulations, or Guidelines of Exposure

The OSHA PEL for silane (silicon tetrahydride) is 5 ppm (7 mg/m^3), but was vacated (151). The NIOSH recommended exposure limit is also 5 ppm (149), and the ACGIH TLV si 5 ppm (7 mg/m^3) (151).

Silica and Silica Compounds

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Asbestos

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1.0 Asbestos

Asbestos is a generic name given to six fibrous minerals that have been used in commercial products. The six types of asbestos are: chrysotile, the most widely used; crocidolite; amosite; anthophyllite asbestos; tremolite asbestos; and actinolite asbestos. The properties that make asbestos so versatile and cost-effective are high tensile strength, chemical and thermal stability, high flexibility, low electrical conductivity, and large surface area.

1.0.1 CAS Number

The CAS Numbers, mineral, and commercial names for the asbestos mineral group, and the chemical formulas are provided in Table 12.1.

Table 12.1. Asbestos Mineral Group

Mineral Name	Commercial Mineral Name for Asbestos	Mineral Group	CAS Number	Chemical Formula
Chrysotile	Chrysotile	Serpentine	[*12001-29-5*]	$Mg_3Si_2O_5(OH)_4$
Riebeckite	Crocidolite	Amphibole	[*12001-28-4*]	$Na_2(Fe^{2+},Mg)_3Fe^{3+}Si_8O_{22}(OH)_2$
Anthophyllite	Anthophyllite	Amphibole	[*17068-78-9*] or [*77536-78-*	$Mg_7Si_8O_{22}(OH)_2$

			9]	
Grunerite	Amosite	Amphibole	[*12172-73-5*]	$(Fe^{2+})_2(Fe^{2+},Mg)_5Si_8O_{22}(OH)_2$
Actinolite	Actinolite	Amphibole	[*13768-00-8*] or [*77536-67-5*]	$Ca_2Fe_5Si_8O_{22}(OH)_2$
Tremolite	Tremolite	Amphibole	[*14567-73-8*] or [*77536-68-6*]	$Ca_2Mg_5Si_8O_{22}(OH)_2$
Asbestos fiber	Asbestos		[*1332-21-4*]	

Asbestos

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Talc

Barbara Cohrssen, MS, CIH, Charles H. Powell, ScD, CIH

1.0 Talc

Talc is a natural mineral of the general chemical composition $Mg_3Si_4O_{10}(OH)_2$ (1). The composition varies widely from one geologic deposit to another and even within the same deposit. The main component, crystalline hydrated silicate of magnesium, is usually found as plates but rarely may also be found as fibers. In many talc deposits, other silicates such as the amphiboles, tremolite and anthophyllite, as well as serpentines, antigorite, lizardite, and even chrysotile, may be present. This chapter discusses only the health effects associated with talc that does not contain asbestiform fibers. However, a number of studies have been conducted to determine the health effects of talc in which the purity of the material was not known. The discussion of asbestos is covered in Chapter 12, Asbestos.

1.0.1 CAS Number:

[*14807-96-6*]

1.0.2 Synonyms:

Hydrous magnesium silicate; non abestiform talc; steatite talc

1.0.3 Trade Names for Talc

Synonyms for talc include the following: Agalite; Asbestine; B9 finntalc P40; B13; Beaver white 200; CP-10-40; CP 38-33; Crystalite; CR 6002; Desertalc 57; Emtal 500; Emtal 549; Emtal 596; Emtal 599; Fibrene C 400; French chalk; FW-XO; Hydrous magnesium silicate; HSDB 830; IT Extra; LMR 100; Microneeca K 1; Micro white 5000A; Microtalco IT extra; Mistron; MP 25-38; MP 40-27; MP 45-26; MST; MT 12-50; Mussolinite; nonfibrous talc; NCI CO6018; Nytal 200; Nytal 400; Pk-C; Pk-N; Polytal 4641; Polytal 4725; Potstone; Snowgoose; Soapstone; Steatite; Steawhite; Supreme; Supreme dense; Talcan PK-P; Talcron CP 44-31; Talcum (2).

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1.1 Chemical and Physical Properties
Talc has a hardness of 1 on the Mohs scale of hardness; a density of 2.58 to 2.83; is commonly composed of thin tabular crystals up to 1 cm wide and is usually massive, fine-grained, and compact. It is also found as foliated or fibrous masses or in globular stellate groups (3).

Talc is a natural single-phase mineral ideally composed of 31.88% magnesium oxide, 63.37% silicon dioxide and 4.75% water. Formation is said to have occurred by hydrothermal alteration of rocks rich in magnesium and iron and low grade thermal metamorphism of siliceous dolomites (4). It is an odorless, solid material that varies in color depending upon the minerals that are found with it. Talc may be pale green to dark green or greenish gray; brownish; translucent; white to grayish white; or pearly, greasy, or dull.

The term talc in the mineralogical connotation denotes a specific rock-forming mineral of the sheet silicate category. However, when talc is referenced in the industrial or commercial sense, it may represent a varied mixture of associated minerals that have physical properties similar to the mineral talc (5).

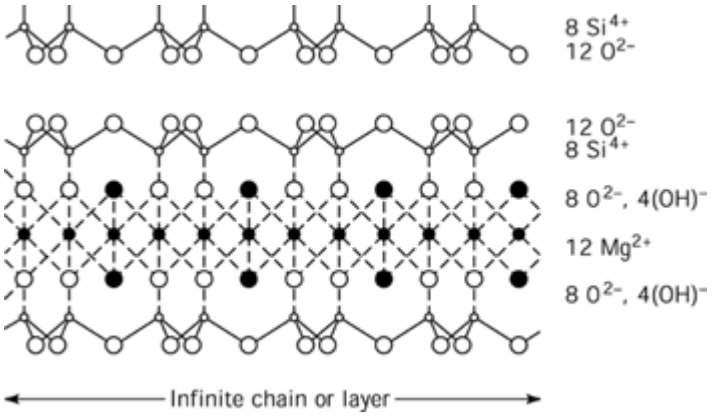

Figure 13.1. Molecular structure of pure talc mineral (1).

A number of minerals are commonly associated with talc deposits: calcite, dolomite, magnesite, tremolite, anthophyllite, antigorite, quartz, pyrophyllite, micas, and chlorites (5).

The most common type of talc is of ultramafic origin, formed by the alteration of serpentinite to talc-carbonate rock. It is common in Vermont, Quebec, and Finland. Talc of mafic origin, found in Virginia, North Carolina, and Georgia, is formed by hydration of mafic rock to serpentinite, followed by alteration of the serpentinite to talc-carbonate. It is usually contaminated with chlorite and silica. Talc of metasedimentary origin is formed by hydrothermal alteration of the dolomitic host rock by silica-containing fluid. This type of talc is commonly found in Montana and Australia. It is usually quite pure and quite white. The fourth type of talc is of metamorphic origin, where siliceous dolomite is first converted to tremolite or actinolite and then partially converted to talc. The New York and California deposits are of this type (1).

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1.2 Production and Use

Talc-containing rocks were first used in prehistoric times as utensils and ornaments. The term talc was first applied to this mineral in 869 AD. The abundance of talc, the ease with which it can be mined, and its properties have made it an important industrial mineral (6).

Talc is an extremely versatile mineral that has found a number of uses despite the relative impurity of most of the ores mined. Except for pure steatite grades, hand-picked, platy, cosmetic talcs and a few products from wet processing plants, industrial products are mixtures of many minerals. The principal uses are as an extender and filler pigment in the paint industry; for coating and filling paper; in ceramic products; and as a filler for plastics and roofing products. Miscellaneous uses of talc include binders and fillers in textiles; fillers in integral, foamed, latex rubber backings for carpets, rugs, and parquet hardwood floor panels; filler for upholstery fabric backing and draperies; lubricant in extreme temperature range greases; corrosion proofing composition; 10–15% in dry fire extinguishing powders; loading and bleaching materials such as cotton sacks, cordage, and rope string; cereal polishing; bleaching agents; food odor absorber; floor wax; water filtration; leather treatment; joint fillers and grouts; insecticides; shoe polishes; welding rod coatings; printing inks; encapsulant for acceleration testing artillery shells; coatings for iron ore pellets in direct reduction processes; source of magnesium in plant foods; pigment in white shoe polishes and white glove cleaners; dusting powder for salami; admixture for certain concretes; polishing medium for peanuts, gunpowder grains, and turned wooden articles; to prevent sticking of bottle, rubber and candy molds; and to impart a finish to wire nails and leather (7).

For example, much of the talc used by the ceramic industry is a mixture of platy talc and tremolite; most of the talc used by the rubber, plastic, and paper industry is at best about 90% talc and the balance is dolomite, calcite, serpentine, chlorite, actinolite, iron- and manganese-containing minerals, and carbonaceous material.

According to the U.S. Geological Survey, China was the largest producer in 1999 with 2.3 million metric tons, and the United States produced about 0.9 million metric tons. After these two countries, Finland, India, and Brazil are the next largest producers. In 1999, the total usage of talc totaled 796,000 metric tons. Consumption in decreasing order was in ceramics (31%), paper (21%), and paint (18%) (7a).

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1.3 Exposure Assessment

The NIOSH Method P&CAM #355 is recommended for determining workplace exposures to talc. This method involves drawing a known volume of air through a MCE filter. Then the sample is ashed and analyzed by X-ray diffraction (8). However, if the sample contains asbestos, several other methods are recommended. These include NIOSH Method 7400 that uses optical counting of asbestos fibers, NIOSH Method 7402 that uses transmission electron microscopy (TEM) for analysis of the sample, or NIOSH Method 9000 that uses X-ray diffraction for analysis. A method recommended for determining the presence of asbestos in talc is NIOSH Method 9002 that analyzes the sample by polarized light microscopy (PLM) (9).

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1.4 Toxic Effects
1.4.1 Experimental Studies
Inhalation Studies

Inhalation studies have had technical problems due to the lack of methods to determine accurately the amount of talc inhaled by exposed animals.

1.4.1.1 Acute Toxicity Rats exposed to a "very dense" cloud of talc, whose particle size was less than 5 mm, for 3 hours per day up to 12 days may have died because of suffocation (10).

1.4.1.2 Chronic and Subchronic Toxicity None of a group of rats exposed to 30–383 mg/m^3 of "technical/pharmaceutical grade" talc for 6 hours per day, six days a week for up to nine months died as a specific consequence of exposure. However, they developed chronic inflammatory changes, including thickening of the pulmonary artery walls and eventually emphysema (11).

Hamsters exposed by inhalation to 8 mg/m^3 respirable "baby talc" for up to 150 minutes per day, five days a week for 300 days showed no negative effects (12, 13). According to a study conducted by Hildick Smith, hamsters exposed to respirable cosmetic grade talc dust showed no difference in incidence, nature, or pathological lesions from those observed in a group of untreated animals (14).

Heavy dosing of rats by inhalation of talc caused severe dyspnea. However, no histological change was observed within 20 days, and talc particles were trapped by alveolar macrophages (10).

Minimal fibrosis was observed in rats exposed by inhalation to 10.8 mg/m^3 of Italian talc (grade 00000, ready milled, mean particle size 25 mm) for three months; this did not change during the postexposure period. The rats exposed for one year had minimal to slight fibrosis, whose degree had increased to moderate within one year after exposure ceased (15).

However, Syrian golden hamsters exposed to 8 mg/m^3 of talc aerosols for up to 150 minutes per day, five days per week for 30 days showed no histopathological change in the lungs, heart, liver, renal tissues, stomach, or uterus (12, 13, 16).

The National Toxicology Program (NTP) (17) conducted a lifetime study of talc in rats. This study consisted of groups of 49 or 50 male and 50 female rats exposed to aerosols of 0, 6, or 18 mg/m^3 of talc until mortality in any exposure group reached 80%. This occurred at 113 weeks for males and 122 weeks for females. These exposures were based on 4-week inhalation studies of terminal lung talc burden in F344/M rats; concentrations greater than 18 mg/m^3 were expected to overwhelm lung clearance mechanisms and impair lung function. These exposure concentrations provided a dose equivalent of 0, 2.8, or 8.4 mg/kg per day for male rats and 0, 3.2, or 9.6 mg/kg per day for female rats. The survival of male and female rats exposed to talc was similar to that of the controls. Mean body weights of rats exposed to 18 mg/m^3 were slightly lower than those of controls after week 65. No clinical findings were attributed to talc exposure.

In another study, conducted by the NTP (17), groups of 22 male and 22 female rats were similarly exposed and examined for interim pathology or pulmonary function after 6, 11, 18, and 24 months and for lung biochemistry and cytology after 24 months. Absolute and relative lung weights of male rats exposed to 18 mg/m^3 were significantly greater than those of controls at the 6, 11, and 18 month interim evaluations and at the end of the lifetime study, whereas those of female rats exposed to 18 mg/m^3 were significantly greater at the 11, 18, and 24 month interim evaluations and at the end of the lifetime study. Lung talc burdens of male and female rats exposed to 6 mg/m^3 were similar and increased progressively from 6 to 24 months. Lung talc burdens of females exposed to 18 mg/m^3 also increased progressively from 6 to 24 months, whereas those of males exposed to 18 mg/m^3

remained about the same after 18 months. Lung burdens were generally proportional to exposure concentrations at each interim evaluation. It was also noted that a concentration-related impairment of respiratory function increased in severity with increasing exposure duration. The impairment was characterized by reductions in lung volume, lung compliance, gas exchange efficiency and nonuniform intrapulmonary gas distribution.

The NTP (17) also conducted a 2-year study of exposure to talc by mice. Groups of 47 to 49 male and 48 to 50 female mice were exposed to an aerosol containing 0, 6, or 18 mg/m^3 talc for up to 104 weeks. These exposures were selected based on 4-week inhalation studies of the terminal lung talc burden in B6C3F$_1$ mice; concentrations greater than 18 mg/m^3 were expected to overwhelm lung clearance mechanisms and impair lung function. These exposure concentrations provided a dose equivalent of 0, 2, or 6 mg/kg per day for male mice and 0, 1.3, or 3.9 mg/kg for female mice. Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls. There were no clinical findings attributed to talc exposure.

In a special study by the NTP, additional groups of 39 or 40 male and 39 or 40 female mice similarly exposed, were examined for interim pathology, lung biochemistry, and cytology after 6, 12, and 18 months of exposure. Lung talc burdens of mice exposed to 6 mg/m^3 were similar between males and females and increased progressively from 6 to 24 months, except for males at 18 months. The lung talc burdens of mice exposed to 18 mg/m^3 were also similar between the sexes at each interim evaluation. Although the talc burdens of males and females increased substantially from 6 to 24 months, the values at 12 and 18 months were similar. Generally, lung burdens of mice exposed to 18 mg/m^3 were disproportionately greater than those of mice exposed to 6 mg/m^3, suggesting that clearance of talc from the lung was impaired or impaired to a greater extent in mice exposed to 18 mg/m^3 than in mice exposed to 6 mg/m^3 (17). Oberdörster comments on the study that analysis of the particle accumulation kinetics in lungs of the rats shows that lung overload had been reached at both the 6 and 18 mg/m^3 concentrations, resulting in increased talc accumulation of high lung burdens (18).

In a previous study, a group of 24 male and 24 female Wistar-derived rats, six to eight weeks of age, was exposed by inhalation to a mean respirable dust concentration of 10.8 mg/m^3 Italian talc (grade 00000; ready milled; mean particle size 25 mm; containing 92% talc, 3% chlorite, 1% carbonate minerals, and 0.5 to 1% quartz) for 7.5 hours per day, five days a week for six or twelve months. Ten days after the end of each exposure period, six rats in each group were killed; another four rats were killed in each group one year later. Within 28 months of the start of the study, another 12 animals in each group had died. No lung tumors were observed in rats exposed to talc for six months, whereas one lung adenoma occurred among those exposed for 12 months. No lung tumors were found in 24 male or 24 female controls (15).

Three groups of 50 male and 50 female Syrian golden hamsters, four weeks old, were exposed to an aerosol of talc baby powder, prepared from Vermont talc by flotation, for 3, 30, or 150 minutes per day, five days a week for 30 days. The mean total aerosol concentration was 37.1 mg/m^3 with a mean respirable fraction of 9.8 mg/m^3. Two other groups of hamsters, seven weeks old, were exposed to a talc aerosol concentration of 27.4 mg/m^3 with a mean respirable fraction of 8.1 mg/m^3. Two control groups of 25 males and 25 females were sham exposed. No primary neoplasms were found in the respiratory system of any hamster. The incidence of alveolar cell hyperplasis was 25% in the groups exposed to aerosols for 30 or 150 minutes per day for 300 days compared with 10% in the control group (13, 14).

Guinea pigs exposed for eight weeks to continuously circulating talcum dust were sacrificed at intervals after dust exposure, and sections of the lungs were examined histologically. Chronic inflammatory changes were noted in one animal sacrificed immediately after four weeks of

exposure. There was no nodule formation and no increase in connective tissue, although masses of dust particles had accumulated in the lungs. In another animal exposed to talc for four weeks and not sacrificed for six months, fewer inflammatory changes were found, and there was much less dust present (19).

Pickrell et al. studied the lung deposition and effects of inhalation exposure in F344/Crl rats and $B6C3F_1$ mice. The rats were exposed to aerosols containing 2.3, 4.3, or 17 mg/m^3 talc for 6 hours a day, 5 days a week for 4 weeks. The mice were similarly exposed to 2.2, 5.7, or 20.4 mg/m^3 talc. The animals were killed 24 hours after the last exposure. Talc accumulated in the lungs in a dose-dependent manner. The average talc lung burdens in rats ranged from 0 to 0.72 mg per gram of lung tissue and in mice from 0 to 1.0 mg per gram. No exposure-related lung lesions were seen other than slight diffuse increases in the number of free macrophages containing talc particles within the alveolar spaces of rats and mice exposed to the highest doses (20).

Ingestion

Groups of 25 male and 25 female Wistar rats, ten weeks old, received about 50 mg/kg body weight per day of commercial talc (characteristics unspecified) in their diets for life (average survival 649 days). No significant difference in tumor incidence was found compared with controls (21).

A group of 16 male and 16 female Wistar-derived rats, 21–26 weeks of age, was exposed to 100 mg of Italian talc (grade 00000, ready milled; mean particle size 25 mm; containing 92% talc, 3% chlorite, 1% carbonate minerals, and 0.5 to 1% quartz) per day per rat in the diet for five months and then maintained on a basal diet for life (average survival 614 days). A control group of 16 rats was fed a basal diet. No difference in tumor incidence was found between the two groups (15).

Rats fed 100 mg of talc for 101 days showed no significant depression of mean life span (15).

Phillips et al. studied the effects of tritium-labeled talc fed to male albino Wistar rats, female LACA mice, female guinea pigs and intravaginally instilled in large white female rabbits. In rats, 75% of the single dose was excreted in feces in 24 hours; after 96 hours, 95.8% of the dose had been eliminated. Kidneys of rats that received multiple doses had less than 0.02% radioactivity. In the guinea pigs, nearly all of the radioactive dose was excreted in 96 hours, and less than 0.2% was in the urine. For the mice, all of the radioactivity was found in the GI tract and feces, and none in other tissues. In rabbits, after 72 hours, radioactivity was found only at the site of a single installation and at the site of administration (22).

Intravenous

Guinea pigs that received two or three 25-mg intravenous injections of talc in saline showed significant mortality (23). Guinea pigs that received single 200-mg intraperitoneal injections of one of several industrial grade talcs (up to 52% talc, up to 82% tremolite, and traces of quartz) developed nodules consisting of macrophages and giant cells after 10 days on the ventral parietal surface which became smaller after a 15-month period. Fibroblastic proliferation was pronounced in the early phases (24).

In contrast, there were no treatment-related deaths of rabbits injected daily for two weeks with 100 mg of talc in saline (25), of rabbits that received 50-mg injections of talc two times a week for ten weeks, or of rats that received injections of talc over a nine week period, total dose 100 mg. (26). In another study, rabbits were observed to have transient convulsions after cisternal injection of 1 mL of a 1:9 or 1:4 suspension of talc in saline (27).

Rats that received a single 50-mg/mL intratracheal injection of talc in water suffered a 79% mortality rate. Subsequently, it was found the rats could tolerate the dose if they were given two 25-mg/0.5 mL

injections at weekly intervals (28). Rats injected intratracheally with 25 mg tremolitic talc/mL of water had a 40% mortality rate. In another study of rats, granulomas at the injection site were common, and one small pulmonary adenoma was observed two years after the injection of 20 mg of Italian talc into the right pleural cavity, but no other relevant pathology was observed in the lungs (15). Albino rats that received an intraperitoneal injection of approximately 400 mg of talcum powder of the type used on surgical gloves exhibited typical granulomas and numerous foreign body giant cells when laparotomized six months later (29). No acute toxicity was observed after a single 10-mg injection into the bursa of rats (30). Three of 11 rats died within one day following injection of 1400 mg/kg body weight of talc into the lower pole of the spleen (31). Hamilton et al. studied the effects of talc on the ovaries of Sprague–Dawley rats. Animals were sacrificed at 1, 3, 6, 12, and 18 months. They concluded that changes in the ovarian surface may be related to the direct effects of talc or may be due to the buildup of high concentrations of steroid hormones in the distended bursa (30).

Two out of 14 chinchillas given five 40-mg intratracheal injections of talc in saline died (32). Chinchillas that received a single or several 40-mg intratracheal injections of "purified" talc in saline exhibited chronic pulmonary irritation, proliferative pneumonia, giant cell granulomas, and adjacent metaplasia of the alveolar epithelium. The hyperplastic cells subsequently transformed into cuboid cells that formed a continuous lining of the affected alveoli and finally acquired an adenomatous appearance (32).

Mice injected with 10 mg of talc (containing asbestos fibers) into the pleural cavity produced granulomas, some of which were firmly attached to the surface of the lungs or other chest contents and occasionally to the lung lobes (33). No acute toxicity was observed after a suprascapular subcutaneous 600-mg injection into mice (34).

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Seven different types of talc were administered *in vitro* to mouse peritoneal macrophages. All of the talcs caused cytoxcity as determined by the release of lactate dehydrogenase and beta-glucuronidase. All of the talcs were of high purity, except for one talc that contained high amounts of chlorite (35).

Mice that received a sterile subcutaneous injection of talc were studied by measuring the incorporation of radioactive leucine and glucosamine into liver and plasma proteins and the talc granuloma at various intervals between 2 and 528 hours after injection. Incorporation into plasma proteins indicated a biphasic response with a marked increased incorporation into the perchloric acid insoluble fraction at 21 hours, a return to normal values at 45 hours, and a similar marked increase into the perchloric acid soluble fraction at 45 hours with a gradual return toward normal values. The response was dependent upon the amount of talc injected (36).

Using radioactive tracer techniques in rats, mice, guinea pigs, and hamsters, no intestinal absorption or translocation of ingested talc to the liver and kidneys was detected (37).

In hamsters, the deposition, translocation, and clearance of talc was followed by giving them a single nose-only inhalation exposure to 40–75 mg/m^3 neutron-activated talc for 2 hours. High cosmetic talc was used, consisting of 95% platy talc. Alveolar deposition was approximately 6 to 8% of the inhaled amount. The biological half-life of talc deposited in the alveoli was 7 to 10 days, and the alveolar clearance was basically complete four months after exposure. No translocation of talc to liver, kidneys, ovaries, or other parts of the body was found (12, 38).

Rats that were exposed to aerosols of Italian talc retained 2.5, 4.7, and 12.2 mg per rat following exposures for 3, 6, and 12 months, respectively. These levels were roughly proportional to the cumulative exposures (15). In rats exposed for 2.3, 4.3, and 17 mg/m^3 of respirable talc for 6 hours per day, five days a week for 4 weeks, the amounts retained in the lung at the end of exposure were 77,187, and 806 micrograms talc per gram of lung (39).

In the NTP two-year study conducted of exposure of rats to talc which was discussed earlier, male rats exposed to 6 mg/m^3 talc had a significant increase in beta-glucuronidase and polymorphonuclear leukocytes after 24 months. Males exposed to 18 mg/m^3 had significant increases in beta-glucuronidase, lactate dehydrogenase, alkaline phosphatase, and total protein in bronchoalveolar lavage fluid. All exposed females had significantly increased alpha-glucuronidase, lactate dehydrogenase, alkaline phosphatase, total protein, and polymorphonuclear leukocytes; females exposed to 18 mg/m^3 also had significantly increased glutathione reductase. Viability and phagocytic activity of macrophages recovered from lavage fluid were not affected by talc exposure. The total lung collagen was significantly increased in rats at both exposure concentrations after 24 months whereas collagenous peptides in lavage fluid and the percentages of newly synthesized protein from females, but not males, were also significantly increased at the 6 or 18 mg/m^3 levels. In addition, lung proteinase activity, primarily cathepsin D-like activity, was significantly greater in exposed males and females. Rats exposed to talc also had significant increases in collagenous peptides and acid proteinase in lung homogenates.

In the NTP study conducted of exposure of mice to talc which was discussed above, increases in total protein, beta-glucuronidase, lactate dehydrogenase, glutathione reductase, total nucleated cells and polymorphonuclear leukocytes in bronchoalveolar lavage fluid were observed primarily in mice exposed to 18 mg/m^3, although some parameters were also increased in mice exposed to 6 mg/m^3. The amount of collagenous peptides in lavage fluid and total lung collagen were increased in male and female mice exposed to 18 mg/m^3. Acid proteinase activity, principally cathepsin D-like activity of lung homogenate supernatant fluid was also significantly increased in mice at the 18 mg/m^3 exposure.

Guinea pigs given a single 200-mg intraperitoneal injection of one of seven commercial talc samples were examined at intervals up to 15 months. Talc particles were found mainly on the ventral parietal surface of the peritoneum within macrophages and giant cells (24).

1.4.1.4 Reproductive and Developmental Talc produced nonspecific abnormalities in chicken eggs at an incidence similar to that induced by thalidomide and sulphadimethoxine (40).

No teratolological effects were observed in hamsters, rats, mice, or rabbits after oral administration of the following doses of talc: 1600 mg/kg body weight to rats on days 6–15 of gestation, 1600 mg/kg body weight to mice on days 6–15 of gestation, 1200 mg/kg body weight to hamsters on days 6–10 of gestation, and 900–mg/kg body weight to rabbits on days 6–18 of gestation (41).

Talc was not mutagenic to *Salmonella typhimurium* TA 1530, *his* G46, or *Saccharomyces cerevisiae* D3 *in vitro* or in host-mediated assays in mice given 30 to 5000 mg/kg body weight (42).

In human W138 cells treated with talc at 2 to 200 mg/mL, chromosomal aberrations were not induced nor were dominant lethal mutations induced in rats following oral administration of 30–5000 mg/kg body weight of talc (42).

Single 20-mg intraperitoneal injections of talc plus 2 mg of particulate prednisolone acetate in saline into mice induced significant numbers of multinucleated giant cells within 48 hours. Neither compound alone induced this response. The multinucleated cells arose by cell fusion, and the resultant polykarions exhibited severe chromosomal abnormalities. Prednisone in combination with talc also elicited the formation of multinucleated giant cells. Polykarions were not observed when talc was injected in combination with cortexone acetate, cortisone, or testosterone isobutyrate (43).

1.4.1.5 Carcinogenesis Hamsters given 10- or 25-mg intrapleural injections of tremolitic talc and maintained for 600 days were studied for tumorigenic effects. No tumors were seen in animals

treated with talc (44).

The NTP conducted a 2-year inhalation study with talc in rats and mice. In this study, male and female F344/N rats were exposed to aerosols of 0, 6, or 18 mg of nonfibrous talc/m^3, free of SiO_2 and asbestiform minerals, for 6 hours per day, 5 days per week for up to 113 weeks (males) and 122 weeks (females). Groups of $B6C3F_1$ mice were exposed similarly for up to 104 weeks. These exposures resulted in concentration-related chronic inflammation, cell proliferation, and fibrosis in the lungs of both male and female rats, and 13 out of 50 of the female rats of the high-exposure group developed lung tumors. The mice showed only limited chronic inflammation and no increased cell proliferative, fibrotic, or tumorigenic responses in their lungs (17).

A four-week talc inhalation study on rats was also conducted by the NTP. This study determined that exposure concentrations in excess of 18 mg/m^3 overwhelmed the lung clearance mechanisms and impaired the lung function of the animals (18).

1.4.2 Human Experience

Pathology

In persons exposed to talc by inhalation, gross examination of the lungs may reveal diffuse pleural thickening and fibrous adhesions of pleural surfaces. In some cases, localized pleural plaques, located on the costal parietal pleura and diaphragmatic surfaces may calcify. According to J.F. Gamble and M. Kleinfeld (7, 45), pulmonary parenchymal lesions may be classified in three general groups:

1. Diffuse interstitial fibrosis with collagen deposition in the alveolar walls and dust laden macrophages both in the alveolar septa and free in the alveolar spaces. Bronchi and bronchioles may be distended and distorted, and normal lung architecture may be obliterated with dilated spaces lined with cuboidal metaplastic cells replacing the alveoli.
2. Lesions of widespread, poorly defined nodules which consist of stellate collections of macrophages and fibroblasts. There may be some fine reticulin, but little collagen is found in these lesions.
3. Foreign body granulomata consisting of epitheloid cells and foreign body giant cells. Granulomata may be found in association with nodular fibrosis or isolated in the alveolar interstitium with normal thin alveolar septa intravening.

Health effects found in workers who have inhaled talc vary, depending upon the composition of the dust inhaled. A significant increase in mortality was found for nonmalignant respiratory disease, especially pneumoconiosis and obstructive lung disease. When silica is significant, the lesions resemble those in silicosis. When fibrous materials such as tremolite are present, diffuse interstitial fibrosis resembling that of asbestosis may be found.

1.4.2.3 Epidemiology Studies Merewether was one of the first to observe that rubber tire workers exposed to French chalk showed “diffuse interstitial fibrosis” by chest X-ray and nothing more than “peribronchial increase in the fibrous tissue” after 30 years. Exposure ranged from 10 to 32 years (7).

In 1949, Hogue and Mallett reported on 20 rubber workers exposed to talc for 10 to 36 years. Exposure concentrations averaged 20 mppcf for six tube machine operators, 15 mppcf for three tube bookers, 15 mppcf for 10 tube curemen, and 50 mppcf for a liner reroller. None of them had dyspnea, cough, shortness of breath, cyanosis, or clubbing of the fingers. Chest X-rays were all normal, and their vital capacity range was 71 to 122% with a median of 105% (46).

A number of studies looked at the health effects of mining and milling of talc on workers. The most significant exposures occurred in milling talc. Table 13.1 (47–78) summarizes a number of these

studies and includes several studies of rubber workers.

Table 13.1. Epidemiological Studies

Occupation	Focus of study	Length of exposure	Exposure concentration	No. of people	Findings	Date
Mining and milling			17 to 1,672 mppcf of Georgia talc	66	Of 33 patients exposed to high concentrations of dust, 22 had pneumoconiosis of varying severity. Persons with low exposures showed no signs of pneumoconiosis.	
Mining and milling	Lung fibrosis	15 to >30 years	Tremolitic talc; 6 to 5,000 mppcf in mines; 20 to 215 mppcf in milling	221	Fibrosis was found in 32 people. All of them had been exposed for at least 10 yrs. The highest incidence, 40.6 %, occurred with those who had been exposed 15 to 19 yrs. Of the eight workers who had worked >30 yrs, six had fibrosis.	194
Rubber worker	Fatal pneumoconiosis	37 years	Norwegian or Canadian varieties of talc	1	At autopsy, both lungs were found to be moderately pneumoconiotic.	
	Respiratory disorder	28 years		1	X-ray revealed two, dense, homogeneous, opaque masses with round irregular contours in the upper portion of the pulmonary field.	
Millers	Talc pneumonoconiosis			32	Talc plaques observed in all but one case. Six of 11 electrocardiographic configurations were abnormal. Four persons died who ranged in age from 48 to 84.	

Miners	Mortality studies	10 mo to 27 years	8	Causes of death: five died of cor pulmonale or TB; one of congestive cardiac failure; one of nephritis with cardiac complications; and one unknown.
Soapstone workers	Pneumoconiosis	16 to 60 mo.	8	Extent of disease varied with the time of exposure. Clinical signs included cough, mucopurulent sputum with talc bodies, dypsnea on exertion, and weakness.
Rubber workers	Talcosis	19 years average	12,000	During TB screening, 16 cases of symmetrical, modular foci of the lungs w/o swelling of the hilar glands, nine cases of definite talcosis (19 yrs exposure) and seven cases of slight talcosis (12 yrs exposure)were found.
Lead casters	Talc pneumoconiosis	15 to 39 years	7	One death from cor pulmonale and talc pneuomoconiosis after 15 yrs. exposure. Chest X-rays of all patients showed the presence of scattered opacities thoughout the lungs which coalesced to form larger masses with indefinite margins and uneven density.
Miners		>20 years	60	All had pneumoconisis; those with greater exposure had more severe disease.
Miners	Pneumoconiosis	>12 years	260	First radiographic

					signs of pneumoconiosis appeared in 89% after 12 yrs; after 22 yrs. it was 100%.	
Grinders	Pneumoconiosis	10 to 20 years		25	Incidence of pneumoconiosis was 52% after 10 to 20 yrs.	
Rubber workers	Pneumoconiosis	Unknown		72	Exhibited linear pneumoconiosis in 11% of workers.	
	Pneumoconiosis	24 years average		6	The most frequent pathological change was diffuse fibrosis containing macrophages with absorbed dust particles. Also found were diffuse or localized emphysema and granulomatous formation made up of focal areas of epitheliod and foreign body giant cells.	
Miners/millers	Pulmonary function	23 years average	Talc admixed with tremolite, anthopyllite, and free silica: >50 mppcf	20	Changes in pulmonary function indicate a restrictive or obstructive breathing disorder. No consistent correlation exists between degree of functional lung impairment and clinical symptoms or X-ray findings.	196
	Pulmonary function	>10 years	62.3 mppcf	43	Predominant symptoms were dyspnea, cough, basilar crepitations, and clubbing. Poor correlation between impairment and clinical and X-ray results.	
Electrical fitter	Pulmonary talcosis	15 years	Pharmacy talc	1	Thoracic radiography revealed large nodular trabecular	

					images with fairly abundant rounded spots in both lungs.
Miners or millers	Mortality	>15 years	Talc mixed with serpentine and tremolite	91	Nine lung carcinomas, one fibrosarcoma of the pleura, two stomach cancers, one case each of colon, rectal, and pancreatic cancer; 25 cardiac arrests and 28 deaths from pneumoconiosis.
Rubber workers	Talcosis	20 to 40 years		5	Granular pneumoconiosis resulting from long-term or intense exposures.
Milling		<5 to >25 years	> MAC for talc	50	Sixteen cases of talc pneumoconiosis diagnosed.
		16.2 years	Commercial talc with tremolite and anthophyllite	39	One worker showed a chest X-ray consistent with pneumoconiosis. Talc containing tremolite and anthophyllite may be less fibrogenic than chrysotile or amosite at the same exposure levels.
	Mortality	>15 years		260	The overall proportional mortality due to carcinoma of the lung and pleura was four times that of the general population. The carcinogenic effect was significant in workers exposed 15 to 24 yrs.
Rubber workers	Respiratory function			80	Workers exposed below 20 mppcf showed a greater prevalence of productive cough and positive criteria for COPD than control workers.

					Workers with < 10 yrs. exposure showed decreased FEV_1. TWA exposures below 25 mg/m^3 are recommended.	
Rubber workers	Stomach cancer			17,000	There was an association between exposure to talc materials and 100 cases of stomach cancer.	
Miners/millers	Morbidity study		NY State talc	121	With <15 yrs., increased prevalence of cough and dyspnea; with >15 yrs. increased prevalence of pleural calcification. Radiographic findings occur primarily after 15 yrs.	
Talc miners	Mortality patterns			1,260	Death was due primarily to pneumoconiosis and tuberculosis.	
Talc millers	Mortality patterns	22 years	11 mppcf	218	Radiographic evidence of pneumoconiosis after 22 years of exposure but little cancer.	
Mining/milling	Mortality/morbidity	13 years	N.Y. State talc	398	Significant increase in mortality due to bronchogenic cancer, nonmalignant respiratory disease, and respiratory tuberculosis. Four of 10 bronchogenic cancer deaths occurred in individuals with less than 1 yr. of exposure.	197
Grinding(milling)	Interstitial lung disease		U.S., Australian, and French talc	6	Large amounts of talc and talc bodies were found in the BAL fluid of all of	

					the workers 21 yrs. after last exposure. The authors suggest that examination of BAL fluid can provide information about talc exposure.
Mining	Morbidity/mortality (cancer)	> 1 year (1944–1972)	Talc with < 1% quartz	94	27 deaths, with 15 cases of cancer; cancers were of the stomach, prostate, and lung.
Milling	Morbidity/mortality (cancer)	> 2 years (1935–1972)	Talc with <1% quartz	295	90 deaths, with 31 cases of cancer; cancers of the bladder and kidney were elevated.
Mining	Bronchiolitis	> 15 years	Before 1976: 86 mg/m^3; after 1976: 3.5 mg/m^3. Smoked 21 cigarettes/day for 21 yrs.	1	Pulmonary function testing revealed a restrictive ventilatory defect and impaired diffusing capacity. Open lung biopsy revealed bronchiolitis.
Talc factory	Respiratory health		1.87 mg/m^3 to 15 mg/m^3	139	Increased exposure decreased FVC and FEV_1
Latex glove mfg.	Respiratory function		7.7 mg/m^3 total dust; 1.9 mg/m^3 resp. dust	17	FVC and FEV_1 were lower in latex workers than controls.

As can be noted from Table 13.1, a number of studies looked at the rate of cancer among talc workers. There have been several individual case reports of cancer, including a lung adenocarcinoma following talc pleurodesis (79) and a pleural mesothelioma following occupational exposure to talc (80–82).

Talc mining is attributed to causing four cases of mesothelioma reported to the tumor registry of the Cancer Control Bureau, New York Department of Health. These mines contain high levels of fibrous tremolite (83).

1.4.2.3.7 Other Health Effects In 1995, a workshop on consumer uses of talc was organized and held under the joint sponsorship of the U.S. Food and Drug Administration (FDA), the Cosmetic, Toiletries and Fragrances Association (CFTA), and the International Society of Regulatory Toxicology and Pharmacology (ISRTP). One of the issues discussed was the association of perineal talc exposure with ovarian cancer. The attendees agreed that, although some weak association between talc exposure and ovarian tumors has been reported, so far there was insufficient evidence for concern. Although it is theoretically possible that talc could reach the ovaries, the actual access to or the presence of talc in ovarian tissue has not yet been documented (84).

Standards, Regulations, or Guidelines of Exposure

A number of countries have standards, regulations, and guidelines for regulating exposure to talc in the workplace. The exposure limits vary depending upon whether the talc contains asbestos or silica or if it is total dust or respirable dust only. Total dust exposures for talc are 10 mg/m^3 in Switzerland and the United Kingdom, 5 mg/m^3 in Finland, 2.5 mg/m^3 in Australia, and 2 mg/m^3 in Belgium and Germany. Respirable dust exposures for talc are 2 mg/m^3 in Bulgaria, Columbia, Jordan, Korea, New Zealand, Singapore, and Vietnam; and 1 mg/m^3 in the United Kingdom (85).

In the United States, the OSHA PEL for talc not containing asbestos and containing less than 1% quartz is 20 mppcf. For talc containing no asbestos but 1% or more of quartz, the OSHA PEL is calculated from the formula for silica. For talc containing asbestos, the asbestos limit is used (86). The ACGIH has a TLV of 2 mg/m^3 for talc dust containing no asbestos and a TLV of 0.1 f/cc for talc containing asbestos (87).

Talc

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Rock Wool and Refractory Ceramic Fibers
Carol Rice, Ph.D., CIH

1 Introduction

Man-made vitreous fibers (MMVF) is a generic descriptor for a group of fibrous materials made from melting inorganic substances such as sand, clay, glass, or slag. Synthetic vitreous fibers (SVF) or man-made synthetic vitreous fibers (MSVF) may also be used to describe these groups of materials. These terms have generally replaced earlier use of man-made mineral fibers (MMMF). MMVF are further classified by the raw material used in production; major categories include glass fibers (glass wool or continuous filament), mineral wool (rock or slag), and refractory ceramic fibers. The latter two types are covered in this chapter; glass fibers are described in Chapter. Within each category, a variety of commercial products have been produced and may be identified by manufacturer and product name and number. Each has a slightly different formulation and characteristics; therefore it is important where possible to identify the particular product number.

Dimension, durability, and dose delivered to the target organ are critical factors in the toxicity of MMVF. Fibers are generally distinguished from other particles by having a length to width ratio (aspect ratio) of at least 3:1. A maximum or minimum for one or more of the dimensions may also be specified. For example, a fiber meeting WHO (1) criterion has an aspect ratio of at least 3:1 and a diameter of 3 mm or less. MMVF counted in airborne exposure assessments in the United States are generally described as having an aspect ratio of at least 5:1, a diameter of 3 mm or less, and at least 5 mm long (2). Long fibers are thought to be more biologically active than shorter fibers (3).

MMVF are characterized by length (L) and diameter (D). The arithmetic mean or median of the observed distribution of lengths and diameters may be given as the count mean or median diameter (CMD) or length (CML). If the observed values are transformed by taking the natural logarithm of the measured parameters, the geometric mean (GM) of each dimension may be given with a geometric standard deviation (GSD). The size determinations may be made by either scanning (SEM) or transmission (TEM) electron microscopy. TEM has the lower limits of detection by which investigators can characterize fibers with diameters in the nanometer range. Dose by some routes of administration may be further described by the mass of material, for example, in implantation or single bolus injection studies. For inhalation studies, GM and GSD length and diameter are usually listed for the exposure aerosol, and often the number of fibers within specific size ranges are listed; for example, the number of WHO fibers or the number longer than 20 microns may be tabulated.

Following inhalation, fibers may be deposited on surfaces within the respiratory tract or exhaled. For the fibers that are deposited, the site of deposition (dose) depends upon the characteristics of the fiber and results from one of five mechanisms: impaction, interception, sedimentation, electrostatic precipitation, or diffusion. The majority of the deposition of MMVF is probably governed by the first three mechanisms. Impaction and interception occur when the fiber is removed from the airstream by physically contacting the surface of the airway or a bifurcation. Sedimentation occurs in the lower airways, where the velocity of the fiber becomes low enough for it to settle on the airway surface. Electrostatic precipitation results when the fiber carries a charge opposite to that of the airway surface; for mineral wool fibers, no reports have been found on surface charge measurements. Deposition due to diffusion requires that the air molecules collide with the fiber, resulting in movement toward the surface. This mechanism could contribute to deposition of very thin fibers, e.g., those with diameters substantially less than one-half micron, but few of them are expected in the work environment (4).

The clearance mechanism of the deposited fibers depends upon the characteristics of the fiber and the site of deposition. Fibers deposited in the tracheobronchial region are cleared with the mucous by the cilia and swallowed. This process is completed in a matter of days, during which little change in fiber dimensions would be anticipated. Fibers deposited lower in the respiratory tract are cleared more slowly. Here the fibers are cleared by translocation to another area of the lung or dissolve; translocation may be facilitated by partial dissolution of the fiber or breakage into particles of shorter length. When fibers recovered from the lung or other tissue are characterized by dimensions, comparison with the parent material provides information on deposition and distribution.

Solubility has been investigated as an indicator of durability. Guldberg et al. (5) noted that testing at pH 7.2 to 7.8 represents the neutral conditions of the lung; testing at an acidic pH of 4.5 to 5 represents the environment created by contact with the phagolysosomes. End points include 95% loss of leachable elements, 75% total mass loss, and mass lost in a specified number of days. Both pH values should be considered when evaluating biopersistence (6). The formulation of the test fluid for solubility studies also influences results (5, 7); however, for a given fluid, the rank order of dissolution rates is unchanged (5).

The interpretation of short-term bioassay results is still under study (8). Bernstein et al. (8a) suggested that the results of dissolution at neutral pH are correlated with *in vivo* biopersistence. Others report that the dissolution rates of MMVF that have high aluminum content are much greater in acidic environments (9). Evidence from animal studies shows that the macrophages may interact with long fibers and that multiple macrophages attach to a single fiber which can lead to dissolution (10–13).

Two reviews of animal studies should be consulted by the reader interested in contrasting the observations of effects among two or more MMVF (14, 15). The contribution of various types of studies to the overall assessment of the toxicity of MMVF was the focus of a 1994 workshop (16), and a 1995 review by De Vuyst et al. (17).

Rock Wool and Refractory Ceramic Fibers
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1.0 Mineral Wool
1.0.1 CAS Number:
none
1.0.2 Synonyms:
rock wool, slag wool

1.0.3 Trade Names
The major U.S. suppliers and product types include

American Rockwool, Inc.

- Rock/slag wool building insulation
- Rock/slag wool fire-accoustical thermal spray systems
- Rock/slag loose wool industrial and OEM fibers and insulation

Celotex Corporation

- Slag wool ceiling tile

Fibrex, Inc.

- Rock wool board, pipe and blanket insulation
- Slag blowing wool building insulation
- Rock wool roof insulation
- Rock wool marine insulation

Isolatek International

- Slag wool insulation (bulk)
- Slag wool fire protection (sprayed)
- Slag wool building insulation (sprayed)

MFS, Inc.

- Slag wool insulation (bulk)
- Slag wool fire protection (sprayed)
- Slag wool insulating cement (troweled, sprayed)

OCHT

- Rock wool pipe, board, and blanket insulation

Rock Wool Manufacturing Co.

- Slag wool building insulation
- Slag wool pipe and board insulation
- Slag wool commercial insulation

Roxul, Inc.

- Rock wool building insulation
- Rock wool pipe, board, and blanket insulation
- Rock wool roof insulation

Sloss Industries Corporation

- Slag wool insulation (bulk)
- Slag wool ceiling tile
- Slag blowing wool insulation

Thermafiber LLC

- Slag wool board and blanket insulation

Slag wool building insulation
Slag wool ceiling tile

USG Interiors, Inc.

Slag wool ceiling tile

Brand names are not given because a single supplier may have 200 products, each with a unique trade name.

(Source: North American Insulation Manufacturers Association, Washington, DC, 1999).

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2.0 Refractory Ceramic Fibers (RCF)
2.0.1 CAS Number:
[*142844-00-6*]
2.0.2 Synonyms:
NA
2.0.3 Trade Names
United States trade names:

Anchor Loc
Cerafiber
Cerawool
Cerafelt
Durablanket
Duraboard
Duraset
Fiberfrax
Kaowool
Kaoset
K-Lite
Pre Flex
Pre Mix
Pyro-blanket
Pyro-fold
Thermotect
Ultrafelt
Uni-Bloc
Z-Bloc

(Source: Refractory Ceramic Fiber Coalition, Washington, DC, 1999)
2.0.4 Molecular Weight
The molecular weight varies depending upon the raw materials used in the formulation.

Rock Wool and Refractory Ceramic Fibers

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54–61 (1997).

Fiberglass
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1.0 Fiberglass
1.0.1 CAS Number:
(none)
1.0.2 Synonyms:
Glass wool; Fiberglas®; Fiberglass insulation; boron silicate glass fibre; Saint Gobain; JM 100; JM 102; JM 104; JM 110; TEL
1.1 Chemical and Physical Properties
1.1.1 General Physical properties are listed in Table 15.1.

Table 15.1. Physical Properties of Fiberglass[a]

Glass Type	Form	Fiber Diameter Range (mm)	Specific Gravity (g/cm^3)	Refractive Index
I	Textiles	6–9.5	2.596	1.548
II	Mats	10–15	2.540	1.541
	Textiles	6–9.5		
III	Wood (coarse)	7.5–15	2.605	1.549
IV	Packs (coarse)	115–250	2.465	1.512
V	Wool, fine	0.75–5	2.568	1.537
	Ultrafine	0.25–0.75		
VI	Textile	6–9.5	4.3	—

[a] NIOSH (4) and taken from IARC (5).

Relative density of fiberglass is 2.5–2.6 (water = 1). It is not soluble in water. Components are listed below.

Continuous Glass Filament[a]		Glass Wool[ab] (Mohr and Rowe, Ref. 1)	% by Weight
Component	**% by Weight**		

SiO_2	52–56	63
CaO	16–25	7
Al_2O_3	12–16	(+Fe_2O_3)6
B_2O_3	8–13	6
MgO	0–6	3
Na_2O	0–3	14
K_2O	0–3	1
TiO_2	0–0.4	—
Fe_2O_3	0.05–0.4	—
F_2	—	0.7

[a] Ref. 2.
[b] Glass wool is an amorphous silicate manufactured from glass and may contain a binder and an oil for dust suppression (3).

1.1.2 Odor and Warning Properties Fiberglass can irritate the eyes, skin and the respiratory tract (3). It can also cause an itch called fiberglass itch (6).
1.2 Production and Use
Fiberglass is produced as a glass wool or glass filament by drawing, centrifuging, or blowing molten glass into fibers of certain predetermined widths and lengths or by continuously drawing or extruding glass filaments from molten glass (5).

Glass fiber production is in the 100s of million kg per year and continues to grow (5.
1.3 Exposure Assessment
1.3.1 Air: NA

1.3.2 Background Levels Fiber concentrations in the atmosphere have been generally low and range from undetectable to 0.00004 to 0.009 fiber/cm^3 (5).

1.3.3 Workplace Methods Fiberglass can be sampled by using a filter (0.45 to 1.2 mm cellulose ester membrane, 25-mm; conductive cowl on cassette) and measured by the light microscope, phase contrast technique. This allows a manual count of all fibers. If used for detecting one fiber type it will not be successful because other fibers with similar diameters and lengths will interfere. The working range is between 0.04 to 0.5 fibers/cc for a 1000-L air sample. The limit of detection depends on sample volume and the quantity of interfering dust, but in the absence of such interferences, the quantitative concentration goes down to <0.01 fiber/cc (7). NIOSH recommends alternate counting rules for non-asbestos fibers that include “B” rules given in NIOSH Method 7400. NIOSH further recommends the use of the 3 : 1 aspect ratio in counting fibers. Other methods are outlined by the IARC (5) and WHO (2). However, the phase contrast method described by NIOSH (7) is the most commonly used method and NIOSH recommends it be used in conjunction with the NIOSH electron microscopy method 7402. Optical and scanning electron microscopy are improving with time and can add to the level of quantification. Scanning electron microscopy is the method of choice for identifying fiber type and for accurate sizing. With a magnification of 5000×, it can detect fibers as small as about 0.5 mm in diameter.

1.3.4 Community Methods The same sampling methods apply to the community as for the workplace.

1.4 Toxic Effects
1.4.1 Experimental Studies 1.4.1.1 Acute Toxicity Inhalation can result in sore throats, hoarseness, coughs, and labored breathing. Skin contact can result in itching and redness; and eye contact can cause redness, pain, and itching (3).

1.4.1.2 Chronic and Subchronic Toxicity Studies of hamsters revealed hemorrhagic and edematous lungs after intratracheal instillation of 0.1 mm diameter fiber but not in animals given thicker fibers (median diameter, 2.3–4.1 mm). Gross et al. (1956) reported similar findings in rats. Other findings included pulmonary inflammation in rats, phagocytosis of short, thin fibers from the lungs by macrophages, as well as other cellular reactions to the fibers once in the lung (8–13). Other effects included filling of the alveoli of rats and hamsters with granular material that caused a condition of alveolar lipoproteinosis (14, 15). The asbestos fiber amosite did not cause alveolar lipoproteinosis.

Fibrosis tends to be related to the fiber length. Davis (16) found that finely ground material was much less effective in producing fibrosis than dusts containing long fibers.

1.4.1.3 Pharmacokinetics, Metabolism, and Mechansims [4]Deposition, retention, and clearance depend clearly on a large number of factors including, but not limited to, the fiber size (length and width); velocity; and aerodynamic properties. An excellent discussion of each these factors and others are found in IARC (5).

1.4.1.4 Reproductive and Developmental: NA

1.4.1.5 Carcinogenesis The IARC has concluded that there is sufficient evidence of the carcinogenicity of glass wool in experimental animals (5). The NTP has listed glass wool (respirable size), first in the Seventh, and now in the Eighth Report on Carcinogens as reasonably anticipated to be a human carcinogen (17, 18).

These conclusions are based on the findings of numerous animals studies supporting the carcinogenic potential of fiberglass. Excellent reviews of these studies can be found in IARC (5), WHO (2), and Infante et al. (19). Basically these reviews found that after intratracheal instillation, statistically significant incidences of lung tumors occurred in rats and that significantly increased incidences of thoracic tumors (lung tumors and sarcomas) and mesotheliomas were found in hamsters. The fiber diameters were generally less than 0.3 mm.

Intrapleural implanation and injection in rats caused incidences of pleural tumors (mesothelioma) which varied with fiber size, but not with physicochemical properties.

Injection of glass wool into the peritoneal cavity of rats caused mesotheliomas and sarcomas, and the incidence depended upon fiber size and dose. Leaching of fibers with hydrochloric acid in two of the studies reduced the number of tumors, whereas treatment of fibers with sodium hydroxide did not. One study of Fisher 344 rats inoculated intrapleurally with a single 20-mg dose of JM-100 fibrous glass (mean length 2.2 mm and width 0.15 mm; within respirable range) found that 3/25 developed mesothelioma, but because the authors observed such a spectrum of pleural mesothelial histopathological changes they concluded that there may be a gradual progression from mesothelial hyperplasia or dysplasia to mesothelioma (20).

Inhalation studies reviewed by both the IARC and NTP were insufficient to determine fiberglass carcinogenicity. However, as explained in the NTP report, those differences in particle deposition and retention in rodents are considerably different from those in humans and thus particles that may be important in inducing human disease may never reach the target tissues with sufficient quantities in rodents. Therefore, inhalation studies may well be less sensitive than tests by other routes. IARC indicates that it is often necessary to use other routes of administration when testing the carcinogenicity of mineral fibers (5).

Some inhalation studies have found that special application of 475 fiberglass can induce pulmonary fibrosis and pleural mesothelioma in hamsters as does amosite asbestos (21).

1.4.1.6 Genetic and Related Cellular Effects Studies Glass wool reportedly induced numerical and structural chromosomal alterations in mammalian cell *in vitro* and caused morphological transformation in rodent cells *in vitro*. The transformation depended on fiber diameter and length. Neither sister chromatid exchanges *in vitro* nor mutations in bacteria were induced by glass wool (5). It is reported that glass fiber-induced cell transformation could be the result of activating the H-ras, K-ras, c-myc, and c-fos proto-oncogenes and/or inactivating the p53 tumor suppressor gene as a result of gene amplification and/or point mutations, and that multiple mutations might be the result of genomic instability from chromosomal alterations induced by glass fibers (22).

1.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization

1.4.2 Human Experience 1.4.2.1 General Information Excellent summaries of human experience are found in IARC (5), WHO (2), and Infante et al. (19).

1.4.2.2 Clinical Cases 1.4.2.2.1 Acute Toxicity Inhalation can cause sore throats, hoarseness, coughs, and labored breathing (3). Skin contact can result in fiberglass itch and redness (3, 6) dermal effects reported have been as high as 61% in a worker population (23), but most other studies have reported lower incidences. Sometimes the irritant effects of dermal exposure can result in inducing eczematous reactions that mimic allergic responses, and allergic reactions to resins applied on the fibers can occur (24).

Irritation of the cornea was reported by Longley and Jones (25) after exposure to manmade mineral fibers (MMMF).

1.4.2.2.2 Chronic and Subchronic Toxicity There have been no consistent findings of pulmonary effects among workers exposed to fiberglass. However, some findings of pulmonary abnormalities have been reported. Radiological abnormalities have been reported among workers in the glass fiber manufacturing industry (26–28). Others who found radiological abnormalities have been unable to associate them clearly with exposure to fiberglass either because of a history of smoking or lack of correlation with duration or intensity of exposure (29–32).

1.4.2.3 Epidemiology 1.4.2.3.1 Acute Toxicity: NA

1.4.2.3.2 Chronic and Subchronic Toxicity: NA

1.4.2.3.3 Pharmacokinetics, Metabolism, and Mechanisms: NA

1.4.2.3.4 Reproductive and Developmental: NA

1.4.2.3.5 Carcinogenesis In 1988, the IARC concluded that there was inadequate evidence of the carcinogenicity of glass wool and glass filaments in humans, but that glass wool was possibly carcinogenic to humans, placing it in its Group 2B (5). Infante et al. (19) reviewed the studies evaluated by IARC and additional epidemiological studies (33–37) and concluded that when all studies were taken together, they were sufficient to conclude that respirable glass wool is carcinogenic and that when placed in combination with the experimental carcinogenic findings the data were sufficient to include fibrous glass in the category of a likely human carcinogen. These same data were reviewed by the NTP which concluded that glass wool (respirable size) is reasonably anticipated to be a human carcinogen (17). Chiazze et al. (38) reported a statistically significant lung cancer odds ratio of 23.4 (95% CI 32–172.9) in a case-control study among a group of fiberglass workers drawn from a historical cohort mortality study conducted on behalf of the Thermal Insulation Manufactures Association (TIMA). On further analysis, again using a case-control design,

it was reported that a history of cigarette smoking and not exposure to respirable glass was the most important variable for the increased lung cancer (39). New data continue to emerge evaluating fibrous glass and carcinogenicity. However, the evidence is still compelling enough given both the experimental data and the epidemiological data that neither IARC nor NTP have reversed their conclusions that glass wool can reasonably be anticipated to be a human carcinogen (17) or that glass wool is possibly carcinogenic to humans (5).

1.5 Standards, Regulations, or Guidelines of Exposure

OSHA regulates fibrous glass dust at a PEL of 15 mg/m^3 (total) and 5 mg/m^3 (respirable), and NIOSH recommends an REL of 3 fibers/cm^3 (fibers ~3.5 mm in diameter and ~10 mm in long) or 5 mg/m^3 (total dust) (40). The ACGIH recommends a TLV of 1 fiber/cc as a TWA (41).

Fiberglass

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Coal

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1.0 Coal

1.0.1 CAS Number:

NA

1.0.2 Synonyms:

Coal, anthracite, bituminous coal, lignite, brown coal.

1.0.3 Trade Names:

NA

1.0.4 Molecular Weight:

The molecular weight of coal *as mined* is indeterminate. Alkylated coal products have molecular weights from 500–2000 (low to high rank coal) (1).

1.1 Chemical and Physical Properties

1.1.1. General Coal is an organic, combustible, rock-like natural substance that occurs in various forms from hard and brittle anthracite to soft and friable lignite. Coal is sometimes classified into two types: hard coal and soft coal. These terms do not, however, have a standardized meaning. One definition calls anthracite hard coal and places all other coal types in the soft coal category. A more common convention is that of Speight (1), in which anthracite and bituminous coals are termed hard coal and lignite and brown coal are classified as soft coal. Research on the health effects of coal has been heavily concentrated on the more common anthracite and bituminous types. There, the results have shown more of a gradient in toxicological effect across coal types rather than any clear-cut divisions between types. Little research has been undertaken on lignite and other brown coals. This has prohibited drawing firm conclusions on its toxicity relative to its harder cousins. This lack of any obvious demarcation has led us to report on overall patterns of effect rather than to provide separate presentations by coal type. Where data are available, we draw attention to any findings especially

relevant to any particular coal type.

Coal varies considerably in composition and consists largely of carbon, hydrogen, and oxygen with smaller amounts of sulfur, nitrogen, trace elements, and metals. Coal originated from mostly organic material that was long ago buried by sediments. Heat and pressure converted the plant remains over geologic time to coal, the process thought to have led to peat, lignite, bituminous coal, and anthracite in turn. Coal, as extracted, contains many minerals in various proportions, including quartz, clays, carbonates, and sulfides. These minerals can be intrinsic to the coal, as in silica grains within the coal matrix, or may lie in pockets or layers. Although there are different methods for classifying coal—each developed for a specific geological or economic purpose—all tend to relate to the age of the coal. Older coals are purer, harder, more brittle, have less volatile matter, and have higher calorific value. They also contain higher amounts of fixed carbon. Fixed carbon is the basis of a commonly used classification index of coal—coal rank. High rank coals, such as anthracite, have the greatest amount of fixed carbon, whereas bituminous and subbituminous coals are defined as low rank. A rank-based system devised by the American Society for Testing and Materials (ASTM) divides coal into four main subtypes: anthracite, bituminous, subbituminous, and lignite (2). Each subtype is further divided, using fixed carbon, moist Btu, or other factors. For example, the main anthracite group is divided into meta-anthracite (98% or more fixed carbon), anthracite (92–98% fixed carbon), and semianthracite (80–92% fixed carbon). The lignite group is split into lignite and brown coal; the main distinction is whether the substance is consolidated (lignite) or not consolidated (brown coal).

Coal

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Wood Dust

John Dement

1.0 Softwoods and Hardwoods

Wood dust is any particle arising from processing or handling wood (1). Woods are classified into two broad botanical classifications; hardwood is the common name given to the botanical classification *Angiosperms*, and softwood is the common name given to the botanical classification *Gymnosperms*. *Gymnosperms* have exposed seeds whereas angiosperms have encapsulated seeds. Although there are more than 12,000 species of trees recorded, most species are deciduous trees or hardwoods, and only about 800 species are coniferous trees or softwoods (2). Table 17.1 summarizes nomenclature for the more typical softwoods and hardwoods.

Table 17.1. Nomenclature of Some Softwoods and Hardwoods

Genus and Species	Common Name
Softwood	
Abies	Fir
Chamaecyparis	Cedar
Cupressus	Cypress
Larix	Larch
Picea	Spruce
Pinus	Pine
Pseudotsuga menziesii	Douglas fir
Sequoia sempervirens	Redwood
Thuja	Thuja, arborvitae
Tsuga	Hemlock
Hardwood	
Acer	Maple
Alnus	Alder
Betula	Birch
Carya	Hickory
Carpinus	Hornbeam, white beech
Castanea	Chestnut
Fagus	Beech

Fraxinus	Ash
Juglans	Walnut
Platanus	Sycamore
Populus	Aspen, poplar
Prunus	Cherry
Salix	Willow
Quercus	Oak
Tilia	Lime, basswood
Ulmus	Elm
Tropical Hardwood	
Agathis australis	Kauri pine
Chlorophora excelsa	Iroko
Dacrydium cupressinum	Rimu, red pine
Dalbergia	Palisander
Dalbergia nigra	Brazilian rosewood
Diospyros	Ebony
Khaya	African mahogany
Mansonia	Mansonia, bete
Ochroma	Balsa
Palaquium hexandrum	Nyatoh
Pericopsis elata	Afrormosia
Shorea	Meranti
Tectona grandis	Teak
Terminalia superva	Limba, afara
Triplochiton schleroxylon	Obeche

Wood Dust

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Cotton and Other Textile Dusts
James A. Merchant, MD

1 Introduction

Byssinosis is a generic term applied to acute and chronic airway disease among those occupationally exposed to vegetable dust arising from the processing of cotton, flax, hemp, and possibly other textile fibers. Observations regarding respiratory disease attributable to these vegetable dusts date to the early eighteenth century (1).

Today the production of cotton products is commercially important to developed and developing countries alike. Processing of flax and hemp remains regionally important industries, which continue to provide traditional textile products. Thus several million workers are occupationally exposed to these vegetable dusts worldwide. In the United States more than 300,000 workers are directly

exposed to cotton dust, primarily in the textile industry, but also in cotton ginning, cotton warehousing and compressing, cotton classing offices, cottonseed oil and delinting mills, bedding and batting manufacturing, and utilization of waste cotton for a wide variety of products.

Two febrile syndromes characterized by fever, cough, and other constitutional symptoms including headache and malaise are also associated with byssinosis and textile manufacturing. These occur most frequently with exposure to low-grade, spotted cotton. Mattress-maker's fever and weaver's cough may be considered together because of their characteristically high attack rate and probable similar etiology. Mill fever, which is characterized by fever, malaise, myalgia, fatigue, and often cough, was a common complaint among workers first exposed to high levels of these vegetable dusts, with the prevailing cotton dust levels in the Western world it now rarely occurs. These febrile syndromes are similar to other febrile syndromes described among agricultural workers exposed to high levels of contaminated vegetable dusts. It is now also clear that symptoms typical of byssinosis are observed among others occupationally exposed to vegetable dusts. Many of those exposed are employed in agriculture, which typically involves daily exposure, rather than the cyclical workweek exposure of textile workers. It is also clear that exposure to organic dusts in textile and nontextile operations will often result in clinical asthma. This often results in self-selection or transfer of the affected worker out of dusty jobs or entirely out of the industry. There is also now evidence that exposure to textile dusts results in heightened airway reactivity and that atopy is a risk factor for the development of vegetable-dust-induced bronchoconstriction (2). These observations are likely to become more relevant with regulation of cotton dust to lower levels. This may allow toleration of lower exposure to cotton dust by many of those who were previously selected out of these industries because of asthma, thereby resulting in increased risk to the development of chronic airway disease.

1.1 Exposure Assessment

It is recommended that workplace exposures be determined using a vertical elutriator.

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2 Epidemiology

The term *byssinosis* was first used by Proust in 1877 to describe respiratory disease among textile workers (3). It arises from the Latin *byssus*, which means fine and valuable textile fiber known to the ancients, usually referring to flax, but also cotton, silk, and other natural textile fibers. While Ramazzini was the first to describe asthma and chronic respiratory disease arising from the processing of textiles, there are abundant important historical descriptions of respiratory disease among textile workers, which were variously described as tracheal phthisis, spinner's phthisis, cotton pneumonia, stripper's asthma, or stripper's and grinder's asthma.

Mortality studies began with the collection of data on those exposed to cotton dust found in the Decennial Supplements to the Annual Report of the Registrar General of Births, Deaths, and Marriages in England and Wales between the years 1880 and 1932. Caminita et al. (4) reviewed these data and found a “marked excess” of deaths in higher age groups, particularly from bronchitis and pneumonia. Later reports emphasized that excess mortality from respiratory disease occurred chiefly among card room and blowing room operators, strippers, and grinders, rather than among other cotton workers. These observations were reconfirmed by Schilling and Goodman (5, 6), who showed that a substantial proportion of cardiovascular deaths should have been classified as respiratory deaths because cardiovascular disease was traditionally given priority in multiple certifications prior to 1939.

Barbero and Flores (7) studied 100 consecutive deaths among hemp workers and compared the results with 100 consecutive deaths among farm workers from the same region of Spain for the years 1938–1943. The mean age of death for hemp workers was 39.6 years; that for farm workers, 67.6

years. Cardiorespiratory disease was listed as the cause of death twice as often among hemp workers.

Contemporary studies of cotton textile workers' mortality have not revealed consistent excesses in overall mortality. Assessment of respiratory mortality has been difficult because of a lack of adequate work history data and lack of smoking histories. Enterline and Kendrick (8) studied 6281 white male cotton textile workers employed in Georgia mills. They found an overall mortality similar to that of asbestos building product and asbestos friction material workers but less than that of asbestos textile workers. There was no evidence of excess respiratory deaths among all cotton workers when cause-specific rates were compared to U.S. white male mortality rates. There was, however, an increase in cardiovascular and all causes of death with increasing duration of exposure. Of interest was a deficit in lung cancer deaths that led Enterline to suggest that there may be a cancer inhibitor, possibly endotoxin, in cotton dust (9). Recent studies of lung cancer in China have confirmed significantly less lung cancer among cotton textile workers after controlling for smoking (10). While methodologic factors were considered, these authors concluded that their findings are consistent with Enterline's hypothesis that some tumor-inhibiting factor(s) may be present in dusts from cotton and other vegetable fibers.

Daum investigated a South Carolina cohort exposed primarily to cotton processing and employed between 1943 and 1949 (11). In this small cohort, moderate increases in respiratory deaths were found among male carders with 10–20 years' exposure, and from respiratory and cardiovascular disease among female spinning room workers with greater than 20 years' exposure. A study of two North Carolina mills assessing exposure between 1936 and 1970 found no increase in respiratory mortality, but did report a trend towards increased respiratory mortality with increasing duration of exposure (12). Excesses in cardiovascular mortality were also observed and accounted for a high proportion of deaths. A proportionate mortality study of Rhode Island male textile workers who died during the period 1968–1978 reported a statistically significant increase in nonmalignant respiratory mortality that appeared to be consistent with cotton dust exposure (13). Prospective evaluation of mortality among Finnish women cotton workers hired between 1950 and 1971 found no excess in respiratory disease mortality but did report a fourfold excess in disability from respiratory disease (14). Mortality from cardiovascular diseases was lower than expected, and mortality from specific cancers did not differ from that expected. All these mortality studies suffer from the selection biases of the healthy worker effect, which becomes more pronounced with years of followup (12, 15). However, in a recent prospective mortality study of a cohort British textile workers, initially enrolled between 1968 and 1970, both the overall mortality and the respiratory disease mortality of the whole cohort were less than expected. However, there was an excess mortality from respiratory disease in those initially reporting byssinotic symptoms.

Early morbidity studies of cotton and flax workers found an unusually high prevalence of respiratory disease, particularly among those working in high dust exposure areas (16–18). In Great Britain, byssinosis was made a compensable disease in 1942 and, on the basis of the number of cases compensated, was thought to be a disappearing disease. Schilling and Goodman rediscovered byssinosis when they studied Lancashire mills to investigate an apparent increase in cardiovascular mortality (5, 6). In a series of studies extending over a 10-year period, Schilling contributed significantly to our understanding of the epidemiology of respiratory diseases among textile workers. He developed, and tested for reliability and validity, a series of questions that were added to the British Medical Research Council (BMRC) respiratory questionnaire, which provided the basis for his byssinosis grading scheme (19):

Grade O. No symptoms of chest tightness or breathlessness on Mondays

Grade 1/2. Occasional chest tightness on Mondays, or mild symptoms such as irritation (cough) of the respiratory tract on Mondays

Grade 1. Chest tightness and/or breathlessness on Mondays only

Grade 2. Chest tightness and/or breathlessness on Mondays and other workdays

Schilling's questionnaire and grading scheme has been the standard for worldwide epidemiologic studies of workers exposed to textile and other vegetable dusts. To validate the grading scheme, he demonstrated that cotton workers with increasing grades of byssinosis have corresponding increases in airway obstruction. Together with Roach, he was the first to quantify a strong linear dose–response relationship between total and respirable cotton dust and the prevalence of byssinosis, which largely explained differences in prevalence in various mill work areas (19). He was also the first to report that smoking was an important risk factor in determining byssinosis prevalence (5, 19).

Since Schilling's publications, similar findings have been reported among textile workers from many countries around the world. Recent studies confirm the presence of byssinosis, but especially nonspecific respiratory symptoms and associated lung function abnormalities among Chinese cotton textile workers (20, 21). While byssinosis is now much less prevalent, it is still found among Lancashire cotton textile workers (22) and flax workers in Normandy, France (23). In addition to those exposed in primary textile mill operations, the disease has been reported among cotton ginners (24, 25), cotton seed oil and delinting workers (24, 26), workers in waste cotton operations (27), those in garneting (bedding and batting operations) (28), and those processing soft hemp (29, 30) and flax (30–33). Byssinosis has not been typically found among those processing “hard” fibers of sisal or jute (34, 35). However, one study reported typical byssinosis among Tanzanian sisal workers with very high dust exposure (36). In addition, symptoms consistent with byssinosis have been reported among workers exposed to herbal tea processing and among workers engaged in swine confinement housing operations (37, 38).

Several investigations (25, 32, 39–42) have now confirmed, with remarkable uniformity, Schilling's early dose-response findings, despite differences in dose–measurement technique, study population composition, and source of raw product. More recent studies have demonstrated that reliance on total dust measurement may provide a misleading indication of risk, as much of the mass may be composed of cotton lint (43).

In the United States measurement of inhalable dust (<15 mm in aerodynamic diameter) has proven to be a reliable and valid dust measurement for assessment of vegetable dust dose–response (44). Most of these studies have concentrated on preparation and yarn-production workers, with little attention given to weavers and others exposed to cotton dust. One study examined both preparation and yarn processors, who were found to have similar dose–response relationships, and weavers, who were found to have a quantitatively different dose–response relationship (44) (see Fig. 18.1). Studies of changes in lung function over a Monday working shift have provided objective data on dose-related declines in FEV_1, which were consistent with the dose–response relationships based on byssinosis prevalence (44). Based on these data, a permissible exposure limit for exposure to raw cotton dust has been promulgated by the U.S. Department of Labor (OSHA): for preparation and yarn operations, a time-weighted concentration of 0.2 mg/m^3 of air, and for weavers, 0.75 mg/m^3 of air (45).

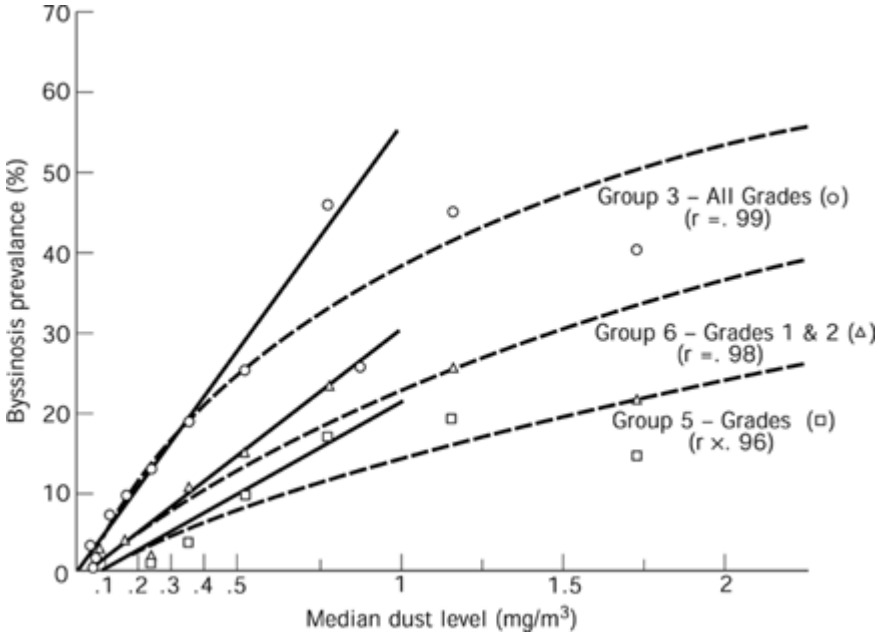

Figure 18.1. Byssinosis prevalence by grade and by median dust level among cotton preparation and yarn area workers: linear regressions and fitted probit dose–response curves.

Dose–response data are less available for cotton dust exposures outside the cotton textile industry, but there is evidence of a dose–response relationship for other cotton operations and for processing of flax and hemp (46, 47). Based on all available data, the World Health Organization has recommended exposure limits for several of these exposures (48).

Assessment of chronic cough and phlegm, as defined from the BMRC respiratory questionnaire (49), has been an integral part of most epidemiologic studies of cotton, hemp, and flax textile workers. While not a uniform observation, most surveys have reported increased rates of chronic cough and phlegm among those with heavy cotton dust exposure, especially among those with symptoms of byssinosis (50, 51). Similarly, indices of dyspnea, as assessed by the BMRC questionnaire, have been shown to be strongly associated with dustier exposures and have been found to be increased among those with more severe grades of byssinosis (29–31, 47). As with many other epidemiologic studies of respiratory disease, smoking has been found to be a powerful risk factor for chronic cough and phlegm and for measures of dyspnea (44, 52).

Two major effects of vegetable dust on lung function have been reported in epidemiologic studies. The first is a chronic effect characterized by airway obstruction and manifest by reductions in FEV_1, FVC, and FEV_1/FVC with increased dust concentration and duration of exposure. The second is an acute effect characterized by measures demonstrating bronchoconstriction over a working shift of exposure to cotton dust, especially after an absence from exposure for 2 or more days (Fig. 18.2) (41, 53). Spirometric evaluation, typically conducted prior to the Monday shift in Western countries, has confirmed Schilling's observation that those with symptoms of byssinosis, as a group, may be expected to have lower expiratory flow rates than comparable controls. Furthermore, those with chronic cough and phlegm, in addition to symptoms of chest tightness, have been found to have a further decrease in lung function (50–52, 54). In large cross-sectional studies, smoking has also been found to exert a significant additive decrease in preshift lung function (43, 44, 55). Recent studies by Schacter et al. suggest that smoking may be more related to abnormalities in maximum expiratory flows at 50% and 25%, whereas cotton dust appears to be either more important than or as important as the smoking effect on FVC and FEV_1 among cotton textile workers with long exposures (56).

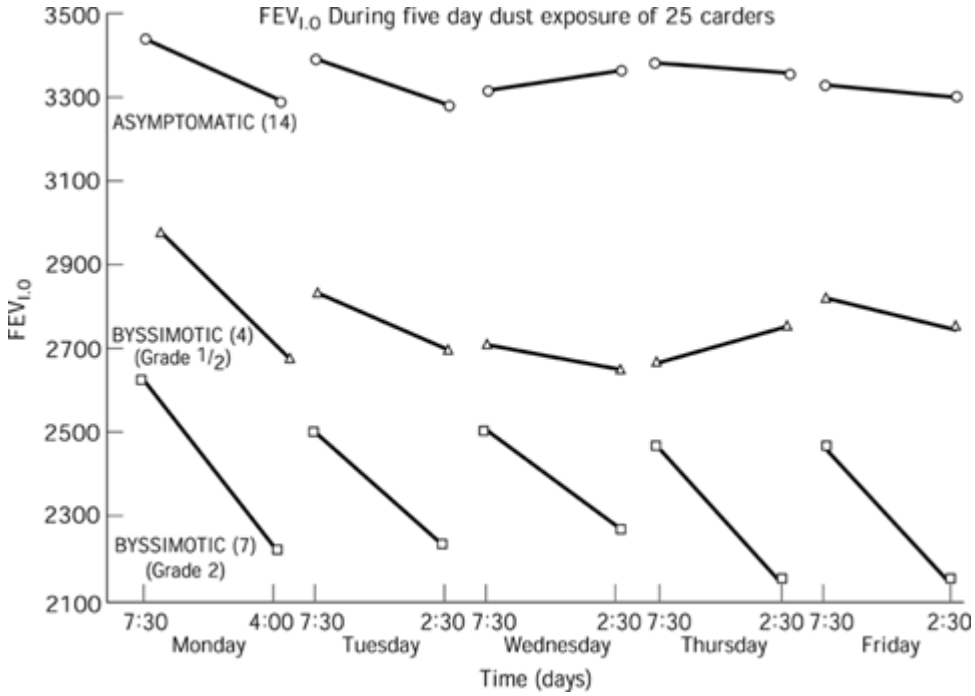

Figure 18.2. Pattern of response among 25 cardroom workers exposed to cotton dust.

McKerrow et al. (57) were the first to observe a reduction in expiratory flow rates over a work shift, a reduction that was most marked after an absence from exposure and especially among workers in areas with higher dust levels. From these observations they suggested that symptoms of Monday chest tightness and dyspnea might be explained by the reduction in expiratory flow rate. This hypothesis has been questioned, as many with symptoms of byssinosis do not exhibit work shift decrements and because the degree of reduction, although statistically significant in epidemiologic studies, is typically not considered clinically significant (decrement of 10% or more) (58).

It has been further observed that subjects with bronchitis and byssinosis tend to have greater cross-shift decrements in expiratory flow than those with byssinosis alone (50, 54). On the basis of the epidemiologic association between byssinosis grade and mean decrement in expiratory flow, Bouhuys et al. (59) proposed a functional grading scheme. Subsequent reports have shown that the relationship between a Monday decline in FEV_1 of 200 cm^3, as proposed by Bouhuys, is highly variable. An appreciable proportion of those without symptoms of byssinosis have a Monday decrement of greater than 200 cm^3 or 5%, whereas many with byssinosis symptoms do not show even a modest decline (50, 60). Nevertheless, because expiratory flow can be easily measured in untrained subjects and provides an objective indicator of biologic effect to vegetable dusts, spirometry before and following exposure has been widely used in epidemiologic studies. Those exposed to cotton, soft hemp, and flax dusts usually have greater decrements in expiratory flow than those exposed to similar dust levels from “hard fibers” (46, 47). Those exposed at higher dust levels have been found to show more marked decrements, and the dose–response relationship between respirable dust and decrement in flow rates approximates that for byssinosis symptoms (25, 28, 44).

In a series of experimental card room studies utilizing volunteer subjects exposed to a wide variety of cottons at different levels of dust exposure, Castellan et al. have demonstrated a stronger dose–response relationship between vertically elutriated endotoxin than vertically elutriated dust and have concluded that these observations strongly support the hypothesis that endotoxin plays a causative role in the acute pulmonary response to cotton dust (61, 62). As the volunteer subjects were not textile workers, these investigators were unable to assess the pattern of symptoms characteristic of byssinosis. Kennedy et al., in a dose–response study in Shanghai, reported a significant association with current endotoxin level and the prevalence of byssinosis and chronic bronchitis, but not with

dust alone (63). While smoking clearly affects baseline spirometric levels, there is conflicting evidence regarding the influence of smoking on acute changes in lung function (50, 53, 63). Cross-shift decline in FEV_1 remains a very useful epidemiologic tool, and despite its limitations in its application to individual workers, it has been incorporated as one feature of the medical surveillance examinations required by the U.S. Cotton Dust Standard (45).

Several studies have evaluated lung function prospectively (64–67). In each of these studies, conclusions were necessarily based upon survivor populations and include other selection biases, which usually tend to minimize occupational effects. Prospective assessments of decline in lung function have been carried out on workers exposed to high levels of cotton dust in Yugoslavia, India, and China, all of which demonstrated accelerated annual declines in FEV_1, which were associated with higher dust exposures that were several times higher than the U.S. Cotton Dust Standard (68–70). Berry et al. (65) reported roughly twice the annual decline in FEV_1 among cotton textile workers as among synthetic textile workers. The decline attributable to cotton dust was slightly greater, but similar in magnitude, to that attributable to smoking, and was somewhat greater among those working in dustier areas and among those exposed for shorter periods of time than longer periods. Merchant et al. (67), who studied a single cotton textile mill several times over a single year, found that those exposed to high levels of cotton dust (many of whom were new employees) had 10-month declines as high as 280 cm^3, and that smaller dose-related increased 10-month declines in FEV_1 occurred among workers in three other work areas with less dust exposure and longer tenure. A community study of active and retired older cotton textile workers found cotton textile workers to have a higher prevalence and attack rate of respiratory symptoms than controls, and that both men and women cotton textile workers had greater annual declines than did community controls. This study confirmed the cross-sectional assessment of this community and reported a significantly higher proportion of textile workers than nontextile worker controls to be severely impaired (55, 64).

In the first published prospective study of lung function among cotton textile workers exposed at or below the U.S. Cotton Dust Standard, Glindmeyer et al. (66) found no accelerated decline in FEV_1 among slashers and weavers exposed below the cotton dust standard and no accelerated decline among nonsmoking yarn-processing workers exposed at the cotton dust standard. However, smoking yarn-processing workers were found to have accelerated loss in annual FEV_1, even below the cotton dust standard of 0.2 mg/m^3; dose-related increases in decline in annual FEV_1 were observed among men and women smokers and nonsmokers, thereby unambiguously confirming the dose–response findings from the cross-sectional studies of byssinosis prevalence and cross-shift decline in FEV_1 on which the U.S. Cotton Dust Standard was based (40, 45). While these aggregate data support the hypothesis that those with increased acute responses are at increased risk for increased declines in lung function over time, as suggested by Bouhuys (30, 69), this question is not fully resolved.

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3 Clinical Evaluation
3.1 Signs and Symptoms
The hallmark of byssinosis is the characteristic symptom of chest tightness that typically occurs following a weekend away from exposure. Chest tightness is described by workers, often accompanied by placing a hand over their chest, as a heaviness on their chest, as chest congestion, as difficulty taking a deep breath, and sometimes as a bandlike feeling around their chest. The onset of chest tightness is variable in the British Home Office report (71), which described the symptoms in 100 card room workers: 93% described respiratory symptoms; of these 59% experienced their most

severe symptoms during the first half of the working shift, and 41% during the second half of the shift. In all workers symptoms were most severe on the first day of the working week. This time period is important as it distinguishes byssinosis from occupational asthma, which tends to increase in severity over the working week. Affected workers often compare the feeling of chest tightness to that of a chest cold. Frequently chest tightness is accompanied by a cough, which is more prominent on Monday. Indeed, a Monday cough may be the only symptom. A history of chronic productive cough is frequently obtained. Among older workers who have been exposed to cotton dust for many years, a history of exertional dyspnea is a common finding. Among those severely affected, chest tightness and dyspnea occur on all workdays, with relief coming only on weekends and holidays, if then.

All these symptoms become more severe if the period away from cotton dust exposure is prolonged; that is, the affected individual appears to lose exposure tolerance. Conversely, Monday symptoms do not occur if exposure occurs 7 days a week, as often occurs with cotton ginning. Symptoms are more severe and more frequent among smokers (42, 67). Occasionally, a worker with typical byssinosis will report that symptoms of Monday chest tightness disappeared when he or she stopped smoking without an apparent change in dust exposure (52).

There are no typical or characteristic signs found upon physical examination of workers with symptoms of byssinosis. While the symptomatic worker frequently exhibits a productive cough, on examination the chest is usually relatively quiet. Wheezing is not commonly found early in the course of the disease. Among those severely affected, all the physical findings of advanced chronic airflow limitation may be observed.

A number of nonspecific symptoms of occular and nasal irritation are often observed among those exposed to cotton dust, apart from byssinosis. Febrile syndromes that have been associated with cotton processing include mattress maker's fever and weaver's cough. These conditions occur among experienced workers and are characterized by a high attack rate, a clear-cut febrile episode, severe cough, and dyspnea. Most of these outbreaks have been attributed to mildewed yarn. These febrile syndromes are similar to those common among agricultural workers who are frequently exposed to high concentrations of moldy grain, hay, or silage (72–74). Because the clinical presentation is the same, and because the etiology of all these febrile syndromes is probably from microorganism toxins, the term organic dust toxic syndrome (ODTS) has recently been suggested in an attempt to codify this condition (75). It is likely that the febrile syndromes arising from high levels of cotton or grain dust are also attributable to endotoxins, which are now well-known constituents of these vegetable dusts.

Newly hired workers, and those who first go into dusty cotton-processing areas for a period of a few hours, may experience mill fever (76), which has also been called card room fever, dust chills, dust fever, cotton cold, cotton fever, weaver's fever, and, among flax workers, heckling fever (4). A similar syndrome has been described among those exposed to high concentrations of grain dust (75). Symptoms, which typically occur 8–12 h following heavy dust exposure, consist of chills, headache, thirst, malaise, sweating, nausea, which may be accompanied by vomiting, and a transient fever, followed by fatigue. Without further exposure, these symptoms subside spontaneously within a day or two, but the fatigue may continue for several days. With repeated exposure, such as that experienced by a newly hired textile worker, these symptoms may occur for several days until the worker is “seasoned” or develops a tolerance (77). This “seasoning” is well recognized by workers exposed to high dust concentrations.

Another common complaint of new workers or visitors to mills with high exposures to cotton dust is tobacco intolerance (52). Also a common finding among mill visitors who have a history of asthma, and who may not have had an asthma attack for years, is immediate onset of clinical asthma, which may be severe and often requires medical intervention (78). With the improved dust control achieved through implementation of the Cotton Dust Standard, mill fever and tobacco intolerance are now infrequent observations. However, it has been suggested that better dust control may allow many

more workers with airway hyperreactivity to remain in vegetable dust-processing operations and that these workers may constitute a high-risk group for future development of airway obstruction (79).

3.2 Lung Function

A series of studies of volunteer textile and nontextile workers in experimental card rooms have provided a good understanding of lung function abnormalities with cotton dust exposure (2, 41, 77, 80–82). These studies have documented a linear decline in expiratory flow over the period of exposure, which is most consistently and significantly discriminated by the FEV_1 (41). Measures of expiratory flow rates have been found to be more sensitive indicators, but increased variance in flow rate measurements decrease their discrimination. Closing capacity and total lung capacity have been found to increase and oxygen tension decrease, but not significantly, with exposure. Body plethysmography before and following exposure suggests that those who exhibit decreased expiratory flow with exposure have increased resistance primarily in peripheral airways, while increased resistance among those who do not have an expiratory flow response occurs primarily in central airways (77). Helium–oxygen spirometry in these subjects found significant decrements in specific airways conductance and found that smokers had greater spirometric responses than nonsmokers (82).

A temporal association between a peripheral leucocytosis and recruitment of leucocytes to the nasal mucosa and decline in FEV_1 has been noted with heavy dust exposure (41). Evaluation of a selected population of nonasthmatic volunteers demonstrated that atopy, defined as positive prick tests to at least two allergens, and cross-shift decline in FEV_1 were independent. However, those with atopy had significantly greater long-term declines in FEV_1, and the degree of atopy, as measured by the number of positive skin tests, was significantly associated with cotton-induced decrements in FEV_1 (2). It was suggested that this finding may reflect airways hyperresponsiveness described in nonasthmatic, atopic individuals. Studies by Boehlecke et al. (personal communication) now suggest that exposure to cotton dust heightens airways hyperreactivity, as has been previously reported with other organic dust exposures (83).

Only one detailed physiologic study has been done of an asthmatic with exposure to cotton dust (68). This followed an unexpected asthma attack triggered by cotton dust exposure in an investigator who had not had asthma since childhood. Highly significant declines in FEV_1 accompanied by marked declines in oxygen tension occurred within 15 min of exposure. Both FEV_1 and PaO_2 remained depressed following exposure and over 3 more days of cotton dust exposure. No significant change was noted in temperature, leukocyte, or eosinophil count. FEV_1 and PaO_2 returned to baseline level, without bronchodilation, after 3 days away from dust exposure.

Assessment of lung function in those with byssinosis and cotton textile workers with long-duration exposure has usually demonstrated a pattern of mild to moderate airways obstruction, but occasionally this may be severe (84, 85). A very significant proportion of older cotton textile workers (50% of men and 37% of women) have been found to have some lung function abnormality (85). One study of women with byssinosis assessed transfer capacity for carbon monoxide (TLCO) and found that smokers had significantly lower TLCO, despite shorter cotton dust exposure, while nonsmoking women had normal levels of TLCO. The authors concluded these results support the hypothesis that emphysema among cotton textile workers is probably due to concomitant cigarette smoking and is not itself a feature of byssinosis (86).

3.3 Treatment

Research on medical treatment for byssinosis has been confined to acute events. Clinical trials have relied almost exclusively on changes in flow rates among active workers as the indicators of effect. While propranolol has been shown to increase bronchoconstriction with hemp dust exposure, antihistamines and ascorbic acid have been found to protect against this effect (87, 88). Similarly, inhaled bronchodilators (87–89). Finally, preexposure treatment with cromolyn sodium tends to block bronchoconstriction (87–89). Inhaled beclomethasone also appears to reduce the flow-rate

response to cotton dust exposure (89). It must be emphasized that these beneficial physiologic effects occur without similar documentation in regard to symptoms. Thus, while the bronchoconstricting effect of these organic dusts, which is usually not severe, may be blocked or reversed, there is no evidence that use of these drugs will necessarily suppress byssinosis symptoms or retard the progression of cotton-dust-induced obstructive airway disease. Therefore, these drugs cannot be considered preventive measures. Management of severe cases of byssinosis does not differ from that for chronic bronchitis and emphysema.

3.4 Pathology

Schilling and Goodman reviewed pathologic observations on lungs of workers with long cotton dust exposure, as made by several early investigators, and concluded that the pulmonary pathology was that of chronic bronchitis and emphysema (6). In one report lungs were fixed in inflation from 10 autopsies of workers with over 20 years of cotton dust exposure. Nine of these cases were found to have chronic bronchitis and/or emphysema, which was more marked among those working in high dust exposure areas. These five and two others had evidence of right ventricular hypertrophy, and four of these cases were judged to have died of cor pulmonale. Gough and Woodcock described lungs of cotton textile workers with histories of byssinosis as having inflammation of the bronchi with squamous metaplasia and generalized emphysema, which was somewhat more prominent in proximity to dust deposits (6).

Three more recent studies of lung pathology in cotton textile workers have been reported (90–92). Edwards et al. (90) studied lungs from 43 patients who had long exposures to cotton dust and had been receiving industrial benefits for byssinosis. The lungs were distended with formalin at necropsy. Gross examination revealed 27 (63%) with no significant emphysema, 10 (23%) with varying degrees of centrilobular emphysema, and 6 (14%) with panacinar emphysema. Most cases showed heavy black dust pigmentation, often associated with centrilobular dilation of distal airspaces. There was, however, significantly more mucous gland hyperplasia and hypertrophy of smooth muscle in the upper and lower lobar bronchi and significantly less connective tissue and cartilage in cases than in controls. While the authors suggested that both smoking (17 cases) and air pollution from living in the Lancashire region could have contributed to these pathologic lesions, this study did not assess these possible risk factors.

Pratt and colleagues (92) studied lungs fixed in inflation from 44 textile workers and 521 nontextile workers. Their study had the advantage of using lungs properly prepared for evaluation of emphysema and knowledge of smoking status. It was limited, however, by lack of documentation of cotton dust exposure, the extent of that exposure, and the small numbers of nonsmoking textile workers (8 cases). Nevertheless, significantly more mucous gland hyperplasia and goblet cell metaplasia was found among textile workers. Centrilobular emphysema was slightly, but insignificantly, increased among textile workers. Moran (91), who conducted a study of cotton textile workers over an 18-year period, reported an odds ratio of 2.2 for emphysema among active and highly exposed cotton textile workers compared to a group of noncotton workers. The results of this study suggested that there may be a shift to an earlier age of onset of emphysema among certain exposed cotton textile workers, but details regarding specific cotton dust and smoking exposures were not available. Of relevance to the question of emphysema among cotton textile workers is a recent animal model of intratracheally instilled cotton dust endotoxin in hamsters, which revealed both functional and morphologic evidence of mild emphysematous lesions (63, 93).

In summary, the available pathologic data consistently find evidence of considerably more airway disease (both large and small airway lesions of chronic bronchitis), while the data regarding emphysema are incomplete. There appears to be historical evidence for the existence of emphysema and some recent clinical and animal morphologic evidence for an increase in emphysema among those with heavy cotton dust exposure. An autopsy study of a larger number of cotton textile workers with well-documented occupational and smoking histories is needed to resolve this issue.

3.5 Prevention

Given our current state of knowledge regarding the etiology of byssinosis and the lack of practical biological assays, risk assessment depends on measurement of dust concentrations, and prevention

depends largely on dust control in the workplace (94). Significant improvements in exhaust ventilation and in dust control technology and application have resulted in reduced risk in most areas of textile mills in the United States. A second control technology, which appears promising in experimental studies, is cotton washing (53). Although this preprocessing has been found to reduce symptoms and functional changes among experimentally exposed subjects (largely through removal of fine dust), it is not yet clear whether cotton washing will be technically feasible prior to spinning. It is recognized to be efficacious for certain cotton products (medicinal cotton and cotton batting) that do not require spinning and is so recognized by the U.S. Cotton Dust Standard (45).

While dust control is the foundation of a respiratory disease prevention program in the cotton-processing industries, medical surveillance and employee education also play important roles. Smoking, and the interaction between smoking and cotton dust exposure, are clearly important risk factors in byssinosis and chronic lung disease arising from cotton dust exposure. Therefore, it is essential that information regarding the adverse effects of smoking, and the combined effects of smoking and cotton dust exposure, be made available to workers through employee education and smoking cessation programs. Workers who continue to smoke should be placed in low dust exposure areas (44, 66). It is also essential to stress the use of appropriate work practices to reduce dust exposure. Periodic medical examinations designed to detect those acutely affected and those with chronic lung disease are important and can be effective (66). Through the use of a standard questionnaire, it is possible to ascertain a sound occupational and smoking history and to screen for byssinosis, bronchitis, dyspnea, and other common medical conditions. Simple, routine spirometry will identify many of those acutely affected and should detect all with significant impairment.

All these prevention provisions—allowable dust concentrations, work practices, and medical surveillance—are detailed in the Department of Labor Cotton Dust Standard promulgated in 1978 (45). With the 4-year grace period given to the industry to implement all provisions, this standard has now been in place for 10 years. Evaluation of the efficacy of the standard has been examined by Glindmeyer et al. (66), who found that the standard provided protection from progressive declines in lung function for all those working in slashing and weaving areas and for all yarn-processing workers, except for smokers, who still showed progressive losses in lung function below the 0.2 mg/m^3 standard. This finding, which is consistent with previous cross-sectional and prospective studies of smoking cotton textile workers, points up the importance of medical surveillance and appropriate placement of smoking textile workers, but raises the possibility that dust levels may need to be further controlled to protect this sector of the workforce.

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4 Summary
Byssinosis is the term given to the acute and chronic respiratory disease arising from occupational exposure to textile vegetable dusts. It is characterized by chest tightness following an absence from regular exposure to dust. Symptoms of chest tightness have also been observed with a variety of other organic dusts, but this finding has not been referred to as byssinosis in nontextile processing settings. Also observed with exposure to textile vegetable dusts is an increased prevalence of nonspecific airway symptoms, modest cross-shift declines in spirometry, and progressive declines in lung function that may result in significant lung impairment among those with long exposure to these dusts. Linear dose–response relationships have been observed between byssinosis prevalence, cross-shift decline in FEV_1, and concentration of inhalable cotton dust. Similar findings for various dust fractions have been observed in other industries. These findings have led to regulation of cotton dust in the United States and in several other countries. While dust control is the hallmark of prevention of lung disease among textile workers, placement of smokers in low dust areas, periodic medical

surveillance, and appropriate work practices are essential components of an overall program to prevent lung disease among textile workers.

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1 Introduction
Airborne contaminants in the workplace can include chemical, physical, and biological agents. Although the primary focus of the industrial hygienist and toxicologist in the past has been on the health effects of chemical and physical contaminants, there is renewed interest in the science of "aerobiology"—the study of airborne particles of biological origin.

Millions of workers in hundreds of occupations are exposed to potential health hazards in their workplace because of substances they breathe in the air. Every year, an estimated 65,000 U.S. workers develop respiratory disease related to their jobs, and an estimated 25,000 persons die from occupational lung disease (1–3). Respiratory illness causes an estimated 657 million person-days of restricted activity and 324 million person-days of lost work (4). Occupational exposure to airborne particles (aerosols) is very common and may pose a potential hazard to human health because microbial cells are particulate matter, studies that deal with airborne microorganisms are concerned with aerosols. Many of the physical and chemical processes that describe aerosol behavior also apply to bioaerosols.

The term bioaerosol is used to describe a colloidal suspension of liquid droplets or solid particles in air, that contain or have attached to them one or more living or dead organisms, certain products of bacterial and fungal metabolism, or other biological material. Bioaerosols are ubiquitous indoors and outdoors and may contain cell fragments, dust mites, animal dander, skin scales, and a wide variety of microscopic organisms, including bacteria, viruses, fungi, algae, amoebae, and protozoa. Other nonliving biological substances (e.g., cotton dust, pollen, hemp, jute, sugarcane) also produce respiratory illness in workers. These are not considered in this chapter but have been reviewed elsewhere (5). This chapter focuses on those bioaerosols most likely to be related to the workplace, although nonoccupational sources can be prevalent. Bioaerosols such as house dust mites, animal dander, or cockroach products that are very important in inducing diseases like asthma may be referred to but are not discussed in detail because of their strong association with the home environment. Attention is given to infectious agents (and their products) because many working conditions are conducive to transmitting of such agents.

Although bioaerosols generally represent fewer hazards than those of a physical or chemical nature, there are certain occupations where the risk of such exposures may be more prevalent. Occupational settings of concern include agriculture, saw mills, textile manufacturing, meat and other food processing, biotechnology, research laboratories, waste disposal, construction, and health-care

institutions (6–8).

The extent of health problems caused by bioaerosols in the workplace is difficult to estimate partly because of the wide array of agents that evoke a variety of human responses. The workplace atmosphere may contain hundreds of different kinds of biological particles, both pathogens and nonpathogens, and today's technology cannot quantify all of them. The complexity is even greater because of the broad range of different types of industrial environments and because exposures are not often recognized until the workers experience illness. Understanding the cause and effect relationship associated with exposure to bioaerosols is a most difficult and vexing problem. Despite uncertainty about the magnitude of the health risk caused by exposure, the impact is appreciable and has been considered the largest single cause of morbidity (9, 10).

This chapter is intended primarily for those occupational health professionals who seek to understand the potential health risk of airborne biological agents in the workplace. It presents an overview of the basic concepts and methodologies useful in assessing the health effects of bioaerosols, including the (1) types and properties of bioaerosols; (2) sources of bioaerosols; (3) transmission, infections, and disease; (4) interaction with environmental and physiological factors; (5) health effects from the inhalation of bioaerosols; (6) sampling and identifying airborne microbial contaminates; (7) assessment of risk; and (8) control and prevention of airborne infectious disease.

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2 Types and Properties of Bioaerosols

Bioaerosols differ from other air pollutants because they have complex and varied organic structures and may be capable of reproducing, thereby causing infections. This section presents an overview of the different types and properties of agents associated with bioaerosols. For those who desire more details and further explanation, there are numerous excellent texts on microbiology, aerobiology, and the toxicology of airborne contaminants (11–14).

2.1 Bacteria

Bacteria are free-living, unicellular organisms that can self-perpetuate without the aid of a host cell. Their chemical composition is not greatly different from that of other living materials. They are composed of water, proteins, fats, carbohydrates, and various inorganic compounds such as sulfur, phosphorus, and salts. Nearly all bacteria are encased in porous but rigid cell walls that protect them from osmotic rupture and give different types of bacteria characteristic shapes. They occur in three general shapes: spherical (coccus), rod-shaped (bacillus), and spiral (spirochete, spirillum, and vibrio). They also differ in size. Cocci range from 0.15 to 2.0 mm in diameter. The smallest bacillus is about 0.5 mm long and 0.2 mm in diameter, and the largest pathogenic bacillus may approach 1 mm in diameter and 3 mm in length. The spirilla are usually 1 to 14 mm long. An important fact associated with bacterial cells is that the ratio of surface area to volume is extremely high. This high surface area provides a good opportunity for direct contact with the surface tissue of susceptible host cells. Typically pulmonary diseases resulting from bacterial infections include pneumonia, brucellosis, Legionnaires' disease, tuberculosis, meningitis, and anthrax.

A mucilaginous capsule surrounds many pathogenic bacteria. The presence of a capsule may increase the virulence of an organism by protecting it against certain host defenses. Most unencapsulated microorganisms are readily destroyed after being engulfed by local phagocytes. As an example, unencapsulated *Streptococcus pneumoniae* are generally considered avirulent, whereas encapsulated strains can produce pneumonia. Some airborne bacilli form resistant structures, known as spores. In a spore state, the organism has a relatively high degree of resistance to all sorts of injurious environmental influences such as high temperatures, germicidal chemicals, dryness, etc. When spores are brought under conditions favorable for growth, they germinate; the spore becomes

a vegetative form of the bacillus, which then multiplies and behaves in the usual manner.

2.2 Viruses

The large and heterogeneous group of microorganisms called viruses are alike in that they are all obligate intracellular parasites that live in cells of their selected hosts. Viruses, the smallest parasites (0.02 to 0.3 mm), are intracellular molecular particles, in some instances crystallizable. The virus particle consists of a central core of a nucleic acid for its reproduction. The nucleic acid core may be made up of either RNA (ribonucleic acid) or DNA (deoxyribonucleic acid), which represents the basic infectious material. When viruses invade a host cell, the genetic material takes over the host cell's own reproduction process and causes the cell to produce more viruses. Viruses cannot replicate themselves in the extracellular state and are highly specific in selecting cells that they will infect. Some viruses replicate within the cytoplasm of the host cells, and others replicate within the nucleus of the cell. Viruses can be released from the host cell when the cell ruptures, a process which is lethal to the host cell. Other viruses are released from the host cell gradually through a “budding-off” process. In this process, each newly formed virus particle released is surrounded by a host-derived membrane called an envelope. This process does not result in the death of the cell. The severity of the disease caused by viruses varies considerably in terms of their effect on susceptible individuals. Pulmonary diseases caused by viruses include influenza, the common cold, and bronchiolitis.

2.3 Fungi

Fungi are a diverse group of saprophytes that occur in many forms, inhabit air, soil, water, and vegetation, and also live on the bodies of humans and animals. It has been estimated that there are more than 50,000 species of fungi, but fortunately only about 50 are associated with human disease. Fungi are considered one of the most common forms of life on earth. They vary in shape and size from a single-celled microbe to giant multicellular mushrooms. Fungi reproduce by a variety of methods, including budding, fission, and spore formation. Pathogenic fungi generally produce no toxins. All fungi are heterotropic, requiring organic nutrients for existence, and most are obligate aerobes. Within the protoplasm of fungi are enzymes which, when diffused into the surrounding environment, change complex substances into simpler substances useful as nutrients for the cell. Human disease caused by fungi can vary from superficial infections of the skin to severe diseases that involve the respiratory system and other internal tissues and organs. The pulmonary diseases associated with fungal infection include asthma, aspergillosis, coccidioidomycosis, histoplasmosis, and various types of hypersensitivity pneumonitis. Fungi have a special tendency to cause infections in people with compromised immune systems. Fungal pneumonia may be dormant in the host respiratory system for months or years and cause disease only when the host's defenses are compromised.

Yeasts are filamentous, unicellular forms of fungi that are usually 3 to 5 mm in diameter. In view of the ubiquitous distribution of yeast in air, dust, and soil and also on surfaces of the body, it is not surprising that these forms have been associated with a variety of pathological processes. Morphologically they are oval or ellipsoidal and rarely form long filaments. Yeast cells are, on average, larger than bacteria and may have a volume thousands of time that of some bacteria. Yeast can be frequently found inhabiting the throats of healthy individuals. Many types of yeast infections are superficial, but serious systemic diseases may occur.

Molds are multicellular fungi found practically everywhere. The term mold is a general one which is used to describe the woolly, cobweb-like, cottony or powdery, black, green, yellowish, or white growths, seen on a variety of surfaces. Molds are very conspicuous in nature and are recognized by their filamentous and branching structures and macroscopic size. Molds have branching tubular structures that can be 2 to 10 mm in diameter and are associated with nutrition and reproduction. Molds produce enzymes that cause rapid fermentation, proteolysis, and other biochemical changes in a variety of substances. Some allergic diseases caused by the inhalation of molds include farmer's lung disease from the inhalation of moldy hay, bagassosis from dried stalks of sugarcane, grain fever from handling grain in all stages of production from harvest to storage, sequoiosis from moldy sawdust, and coffee worker's lung from coffee bean dust (5, 15).

2.4 Rickettsias

Rickettsias are closely related to viruses. They are smaller than bacteria, and their growth occurs

within the cytoplasm (e.g., typhus) or in the nucleus of the infected cell (e.g., Rocky Mountain spotted fever). These organisms have a diameter of about 0.3 mm and lengths seldom exceeding 2.0 mm. They are pleomorphic and may be found singly, in pairs, in chains, or in long filaments. No spores are produced. The normal natural reservoir and primary hosts of these organisms are a variety of infected insects (lice, fleas) or arachnids (ticks and mites). When these organism invade the human, they attack the reticuloendothelial system and colonize in the lining of the blood vessel walls. With such infection, there is hyperplasia of endothelial cells and a localized thrombus formation that leads to obstruction of blood flow and results in the escape of red blood cells into the surrounding tissue. The rickettsia that causes Q fever is resistant to drying and can survive in the dust for months until it becomes airborne and infects an individual.

2.5 Nonliving Contaminants of Biological Origin

The products of microbial metabolism are complex and numerous. Chemically, they can consist of a wide variety of proteins, lipoproteins, and mucopolysaccharides. The amounts of these materials produced are determined by the particular substrate available to the organism and the environmental conditions (i.e., temperature, humidity). Exotoxins are proteins produced within the cell and excreted into the surrounding environment and may be fatal in quantities of micrograms or less by causing diseases such as botulism, tetanus, gas gangrene, and food poisoning. Bacteria may also liberate endotoxins, which are lipolysarcharides intimately associated with the cell wall of certain gram-negative bacteria that can produce diseases such as typhoid fever, cholera, and brucellosis. They are not released until the cell disintegrates. Endotoxins are usually water soluble, relatively heat-stable but less potent than the exotoxins, and less specific in their action. Certain fungi may also produce toxins that may have health effects in sufficient doses. For example, the Aspergillus organism elaborates aflatoxins that can cause hepatic necrosis, liver cancer, and immunotoxic effects.

Microorganisms such as bacteria, actinomycetes, and fungi may also produce a variety of volatile organic compounds (VOCs) and semi-VOCs during metabolism. VOC metabolites such as higher alcohols, ketones, and organic acids are responsible for the odor often associated with the growth of these microbes.

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3 Sources of Bioaerosols

Microorganisms are the most versatile and most widely distributed kind of living thing and occur nearly everywhere in the environment. As such, they may be capable of replicating themselves or merely surviving in habitats that are extremely diverse. Any place that maintains viable microorganisms represents a reservoir from which they may be dispersed. Although certain organisms are known for their infectivity and are commonly referred to as pathogens, all organisms are potential pathogens under certain host conditions, especially in an immunocompromised individual.

The air does not constitute a normal bacterial habitat. Air is not a medium in which microorganisms can grow, rather it is a carrier of particulate matter, dust, and droplets that may be laden with microbes. The microbial flora of air are both transient and variable. Only those species resistant to desiccation and exposure to the conditions in the air can persist long in this medium.

The number and types of microbes that contaminate the air are determined by the source of contamination. The environment is laden with reservoirs of microorganisms that may become airborne when disturbed. Once airborne, success in reaching a susceptible host depends on the number of organisms present, the particle size, the force with which they are propelled into the environment, the resistance to drying, the temperature and humidity of the air, the presence of air currents, and the distance to the host. There are numerous processes and activities in industry that

may generate microbial aerosols. A few examples include facilities such as slaughter houses, textile mills, animal-waste rendering plants, hospitals, nursing homes, and various research and diagnostic laboratories. Biomedical researchers in hospitals, universities, and research institutions are at risk of infections with a wide variety of microorganisms. Workers may become infected because their occupation puts them in direct contact with animals, their secretions, and their by-products. Some of the animals used in research may harbor pathogens of human disease.

Although most of the microbial contaminants identified in the work environment are similar to those microbes found outdoors, the air within the workplace may actually become more heavily contaminated, even under normal working conditions, and may potentially place workers at greater risk (16). An enclosed work environment tends to confine aerosols under temperate conditions and may actually allow them to increase in numbers. Certain bacteria and fungi can flourish in improperly maintained air ducts, air conditioners, humidifiers, dehumidifiers, air-cleaning filters, carpets, and improperly ventilated places where moisture is likely to collect (17, 18). Fan coil units are potential sources of bioaerosols in health-care facilities and in certain offices. Ventilation systems can pick up contaminated air, distribute, and transport infectious microorganisms to other parts of the building and to susceptible individuals (19, 20). A good example is *Legionella pneumophila* which becomes airborne from contaminated cooling system water and is responsible for Legionnaires' disease (21, 22).

Bioaerosols are also produced as sprays in liquid droplets from nozzles in agricultural applications, spray from manufacturing processes, bursting bubbles from wastewater treatment plants, and spray drift from nuclear cooling towers or as dry particles from urban vehicular activity and rural agricultural practices.

Although progress in occupational health and safety has led to the disappearance of some occupational diseases, technological development has brought new challenges (15, 23, 24). New hazards could arise from the introduction of new products and technologies through biotechnology and genetic engineering. Genetic engineering technology can be used to alter the genetic material of living cells, allowing changes to be made to the inherited characteristics of plants, animals, and microorganisms. The methodology used ranges from traditional techniques such as natural mating methods for selective breeding to advanced recombinant DNA techniques where genetic material is altered and manipulated directly. The ability to produce organic materials with new characteristics offers many potentially useful products for the production of pharmaceutical products, food processing, agriculture advances (plant breeding and biological pesticides), mineral leaching and recovery, enhanced oil recovery, and pollution control. A major concern has been the fear of releasing such genetically engineered microbes into the environment. The metabolites produced by such organisms may be toxic and may even persist in the environment. For example, a potential concern regarding a microorganism being used to biodegrade toxic chemicals is the buildup of intermediary metabolites that could be more toxic, more mobile, or more resistant than the original chemicals. In addition, once such organisms are developed in the laboratory, it becomes necessary to test these organisms in the field. Such field testing can inevitably result in the use of large volumes of microorganism with possible decreased control of the exposure and a potentially increased health risk. This emerging threat results from microbes that develop new pathways, new proteins, and new strategies for survival. Microorganisms, even of different species, are known to exchange genetic material, including the gene for drug resistance.

Even in a outer space, numerous microorganisms have been identified in the spacecraft environment and may pose a potential health hazard for astronauts who work in space (25). The primary source of microorganisms in spacecraft habitats is the crew. The risk of infection among crew members has been well documented from previous missions, and the incidence of infections can be expected to increase as space missions lengthen (26). The potential health risk from airborne contaminants within the spacecraft is unique due to microgravity conditions, which affects the dispersion and transmission of airborne particles, including microorganisms. On earth, large droplets produced by coughs and sneezes settle to the floor quickly. For example, a spherical particle 100 mm in diameter

falls 3 m (the height of an average room) in 10 seconds, 40 mm particles take 1 minute, and 20-mm particles require 17 minutes to settle out. In the microgravity environment of space, atmospheric particles would possibly remain airborne indefinitely and continue to contaminate the breathing air regardless of their size (26, 27).

Microbial contaminants have been found in increasing levels in recent years because of the attempts to make buildings more airtight for energy conservation. This action reduces the rate of air exchange between outside (fresh air) and the inside environment. For example, older buildings may have air exchange rates that are 7–10 times greater than those in newer buildings. With this reduction, the levels of airborne particles, including microorganisms, can be higher than the concentration of these same materials outdoors. *Sick building syndrome* (SBS) is a term used to describe workers' discomfort and medical symptoms believed related to the accumulation of airborne contaminants indoors. Complaints include respiratory tract infections, irritation of the eyes, nose and throat, lethargy, and other flu-like symptoms (28). The range and severity of the symptoms vary greatly, depending on the sensitivity of the exposed individual. It has been proposed that the problems associated with SBS can be attributed to poorly designed and functioning ventilation systems, inadequate filtration, improper drain lines, and inadequate maintenance that result in subsequent increased levels of microbiological contamination and/or indoor pollution sources such as tobacco smoke and volatile organic compounds from building material and cleaning products (20, 29–32). The availability of moisture, increased CO_2, and the temperature have been factors that amplify microbial agents within this environment.

All forms of life harbor microorganisms in and on their bodies. Generally, the agents of infectious diseases are transmitted from one species to another or from one individual of a species to another member of the same species. Certain individuals may be carriers who harbor pathogenic agents in their bodies but show no signs of illness, that is, the carrier is infected but is asymptomatic. Human carriers play an important role in the spread of diphtheria, epidemic meningitis, hepatitis B, streptococcal infections, and pneumonia, and such individuals can be considered living reservoirs from which microbes can be dispersed. Consequently, many normal human activities generate airborne microbes during sneezing, coughing, talking, shedding of skin flakes, surgical and dental processes, and activities such as cleaning and sweeping (20, 27, 33). It has been estimated that a healthy individual maintains about 10^{12} bacteria on the skin, 10^{10} in the mouth, and 10^{14} in the alimentary canal (34). Microbes are being shed continuously from the skin. Humans shed about 10^{10} skin scales every 24 hours, including about 4.0×10^7 bacteria that are shed with these desquamated skin scales (17, 34, 35). Diseases spread from person to person by direct contact include tuberculosis, diphtheria, measles, pneumonia, scarlet fever, the common cold, smallpox, and epidemic meningitis.

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4 Transmission, Infection, and Disease
4.1 Transmission
Although bacteria exist in the air only as accidental contaminants, the air provides an effective means of disseminating the organisms. Once organisms are introduced into the air, they may be transported a few feet or many miles, some organisms die in a matter of seconds; others survive for an extended time. The ultimate fate of airborne microorganisms is governed by a complex set of circumstances. Their survival and hence their numbers is influenced by the environmental conditions of the air that transports them. Those that survive best have some resistance to heat, UV light, drying, and chemical agents. Some organisms can survive for months and attain survival as highly resistant spores. The simple presence of a microorganism in the air is insufficient evidence that it

will cause disease. The microorganisms must be transmitted to a host and have attributes that enable them to infect the susceptible host.

Transmission depends on the size of the particle, which may range from a single microorganism to large droplets containing agglomerations and/or rafts of microorganisms, often attached to various airborne particles. Liquid droplets may change in size due to evaporation (or condensation) and leave an aeroplanktonic residue of nonvolatile solute, particle matter, and/or viable or nonviable microorganisms.

The size of the bioaerosol is important for transmitting the organism and also is directly associated with the organism's ability to produce disease. Large particles (10 to 50 mm in aerodynamic diameter) are predominately deposited in the nasal passages. Particles less than 5 mm in diameter are considered respirable and are the most effective in establishing airborne infections. They can remain suspended in air for long periods and are most likely to be carried by air currents in a building's ventilation system. Particles <5 mm have a large deposition fraction in the alveoli, whereas particles between about 5 and 10 to 15 mm are predominately deposited in the tracheobroncheal region. Lung deposition can be influenced by the level of breathing and whether or not the breathing is through the mouth or nose.

4.2 Infection

It is important to understand the difference between infection and disease. Infection implies that a microbe has taken up residence in a host and may be capable of multiplying within the host—perhaps with no outward signs of disease. Thus, it is possible to be infected but not have the disease symptoms commonly associated with the agent, although disease may develop later.

At rest, the average adult breathes about 15 kg (10,000 to 20,000 liters) of air each day. When one compares this amount with the daily intake of food (1.5 kg) and water (2.0 kg), the potential exposure through inhalation becomes significant. During a lifetime, breathing brings approximately 300 million liters of air and airborne substances into contact with the respiratory surfaces (36). The lung also has nearly four times the total surface area (70 m^2) interfacing with the environment as the total combined surface area of the gastrointestinal tract and the skin. When comparing the potential exposure via inhalation to other routes of exposure, the seriousness and importance of bioaerosols becomes evident. This makes the respiratory tract the main portal of entry into the body and the lung the prime target organ for infection. In addition, the unique morphology of the conducting airways and the minute separation between the airspaces and the capillary circulatory system to the rest of the body highly suit the pulmonary milieu for microbial contamination.

The process of establishing an infection is complex and requires several steps. To initiate a respiratory infection, a sufficient number of organisms must escape from the existing reservoir, become airborne, enter the host's environment, be transmitted (directly or indirectly) to a susceptible host, and enter the host through the respiratory portal of entry. If there is a delay between these events, the organism must be able to survive in an unfavorable environment. Once the organisms have been deposited at a particular site in the host, the organism must enter into a relationship with the host (i.e., host–parasite relationship). After entry, the organisms must have been deposited on or be transported to a susceptible tissue particularly suitable for its multiplication and have the ability to remain viable and virulent during this process. The epithelial surfaces of the respiratory tract provide an appropriate medium for many microorganisms.

Elaborate defense mechanisms have evolved that enable the lung to protect itself from such microbial attacks (37–39). In spite of the vast exposure to many viable microorganisms, the normal respiratory system is efficient in clearing the lung of unwanted substances and in maintaining pulmonary health. Particles deposited in the tracheobronchial region may be transported out of the upper airways within a few hours by the mucociliary escalator system. The most effective defense of the alveolar region is provided by resident macrophages that can inactivate and kill microorganisms within a few hours of exposure. When normal pulmonary defenses are compromised by inhaled

substances, an individual's risk of disease can be significantly enhanced.

Once an organism has survived transport through the environment and has infected a susceptible host, several features of the bacteria are important in establishing disease. The term virulence is used as a quantitative expression of the disease-producing potential of a pathogenic organism. Measurement of the virulence of a microbe largely reflects the invasive properties of the organism. Certain organisms produce infections because they can invade tissue rapidly, spread throughout the body, and multiply extensively in susceptible tissue (40). A part of the invasiveness of microorganisms may also be attributed to certain surface components that protect the organism from normal host defenses, such as engulfment by phagocytic cells. Such surface substances may be polysaccharide capsules (e.g., pneumococci, *Klebsiella pneumoniae, Hemophilus influenza*), hyaluronic acid capsules, and surface "M" proteins (beta-hemolytic streptococci), or a surface polypeptide (anthrax bacillus). The pathogenicity of some organisms results from their ability to secrete complex toxins and extracelluar enzymes that aid in establishing infection and in spreading the organism through the tissue (41). Examples of factors and types of organisms that produce these factors include coagulase (staphlococci), hyaluronidase (staphlococcus, streptococcus, pneumococci), streptokinase or fibrinolysin (hemolytic streptococcus), hemolysins and leukocydins (streptococcus, staphlococcus), lecithinase, collagenase, exotoxins, endotoxins, and proteases (streptococcus).

Other factors that can influence exposure and the process of infection include specific occupational activities, as well as a various other factors related to age, drug use, alcohol consumption, smoking, hygienic habits, institutionalization (nurseries, day care, rest homes), and certain socioeconomic levels.

4.3 Disease

Once the host is infected, a number of factors influence the susceptibility of the host and the severity of the disease. The factors that function to prevent infection of a host can be divided into two categories: nonspecific and specific or acquired. Nonspecific or innate factors operate against a wide variety of organisms and include the body's natural physiological barriers at the portal of entry, inflammatory response, and phagocytic cells that engulf and destroy inhaled microbes. Certain specific defenses (immunological) are directed against specific organisms and are characterized by antigen-specific processes. An adverse change in the structure and functioning of these defense systems after exposure to a foreign substance is defined as an immunotoxic effect. Such immunotoxicity can be manifested in the host as an immunosupression, hypersensitivity, or an autoimmunite effect. Individuals particularly vulnerable to airborne infections are those whose normal pulmonary defenses are suppressed. Immunosuppression can be caused by inherited diseases, aging, alcoholism, HIV infections, radiation treatment, pregnancy, medication, and other concurrent infections (10, 42). Microbes that take advantage of a person's weakened state are called opportunistic organisms.

Individual susceptibility to airborne infections and the severity of the disease is also associated with the route of exposure (portal of entry), the duration of exposure, concomitant exposure to other pulmonary toxicants (tobacco smoke, air pollutants), age at the onset of infection, medication for treatment of other diseases, and nutritional status.

Race does not usually influence the infection process if exposure is equal, but the severity of the infection may vary, such as seen in Blacks with tuberculosis. However, there is overwhelming evidence that the conditions and the prevalence of health and disease may vary enormously among and within the regions of the world. The strikingly higher rates of mortality and morbidity in the less developed countries compared with the more highly developed countries are generally explained by a serious shortage of food, medical care, and extensive poverty due to socioeconomic conditions.

5 Contributing Environmental and Physiological Factors

In the natural environment, healthy individuals exist in equilibrium with a mass of potentially pathogenic microorganisms. The presence of microbes in humans and animals may be considered the normal state, and the process of disease is merely a disturbance of the equilibrium between the host, the parasite, and the environment. In addition to considering the virulence of the agent and the susceptibility of the host, attention must be given to a variety of environmental and physiological factors that might also influence the course of the disease. For this reason, a person exposed to a combination of stresses, such as those of a physical or chemical nature, may be more susceptible to certain biological agents and thus may be at a greater risk of contracting disease.

There is a need to learn more about the quantitative impact of a variety of physiological changes that may alter an individual's susceptibility to biological agents. The special conditions of the workplace may need to be taken into account in accurately assessing and characterizing the health risk associated with such exposures.

The nature, severity and likelihood of toxicity from bioaerosols are influenced by the total dose that ultimately reaches the sensitive target tissue. A number of generic factors significantly influence the dose of microbes reaching the lung. Ventilation is important because (1) the physics of airflow influences deposition and (2) the rate and depth of breathing influences the volume of air and hence the mass or number of infectious agents that enter the respiratory tract and the total surface area over which deposition will occur (43). An important element is the route of breathing (oral, nasal, or oronasal). This influences the efficiency of filtering inhaled materials in the nose and thus impacts the dose of infectious agents delivered to the respiratory system. Although most adults are nasal or oronasal breathers at rest, they often resort to oral breathing under certain work conditions or exercise that result in increased penetration of larger particles into the lung. Increased fatigue from a variety of stress factors (e.g., noise, vibration, temperature) may alter the homeostatic state of people and make them more susceptible to pulmonary disease.

A wide variety of gaseous and particulate airborne pollutants that may be present in the workplace can adversely affect the normal functioning of the host's defenses. Although the lung has an array of effective defense mechanisms available to kill, detoxify, and remove inhaled substances, numerous inhaled metals (e.g., Ni, Cd, Pb, V, and Mn), gaseous pollutants (e.g., NO_2, O_3, SO_2, phosgene, benzene, toluene, HCHO), particles (e.g., H_2 SO_4), and complex mixtures (e.g., auto exhaust, cigarette and wood smoke, and fly ash) can impair the functioning of these mechanisms which may significantly increase the susceptibility of the individual to infectious disease (37, 43–46). Infections have occurred in the workplace when uniquely sensitized workers were exposed to an airborne pathogen. Examples are *Acinetobacter pneumonia* in foundry workers and silicotuberculosis in workers with tuberculosis who are exposed to silica dust (47, 48).

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6 The Health Effects of Bioaerosols in the Workplace

Of the many diseases that have been associated with airborne contaminants in the workplace, the contribution of biological agents to total illness is presumed to be large. But to date, the attributable risk is not known with certainty. The frequency and severity of such diseases vary, depending on the particular work environment, types of organisms present, and the individual's susceptibility to the agent. Experimental and epidemiological studies have been used to evaluate the health effects of

bioaerosols. Respiratory infections, it has been estimated, cause 50–60% of all acquired illnesses (49). In the United States about two million people get pneumonia each year. It ranks sixth among all disease categories as a cause of death and is the most frequent lethal hospital-acquired infection (14). The economic impact from the standpoint of health-care cost and loss of productivity in the workplace is in the millions of dollars. A few examples of infectious diseases that are transmitted via inhalation are discussed later. This section addresses the potential for workplace exposure to biological agents, provides examples illustrating various mechanisms of action of different microbes, and identifies the great variety of illnesses that are associated with a broad range of diverse biological agents. Rather than attempt to list and discuss all organisms that might pose a threat within the workplace environment, this section uses a few examples to illustrate the principles involved in airborne infectious diseases. A broad base of understanding the basic concepts of the potential health risk of airborne microbes can aid in preventing and controlling such diseases. Excellent texts and handbooks on infectious diseases are readily available in most research and medical libraries for a more detailed discussion of specific types of organisms and the pathogenesis of their disease (4, 37, 50, 51).

6.1 Bacteria

6.1.1 Bacillus Anthracis As a disease of great antiquity, anthrax occupies an important place in the history of infectious diseases because it was the first human disease attributed to a specific pathogen (52). This organism is a large rod-shaped microbe that occurs frequently in chains. The bacterium can maintain itself in a spore state under severe adverse environmental conditions for many years. Anthrax is primarily a disease of farm animals (e.g., sheep, goats, cattle, and horses). The infected animal becomes a living reservoir from which the pathogens are dispersed. Human pulmonary anthrax, also called “woolsorter's disease” is rare but can be deadly. It is primarily an occupational disease among workers who come in contact with infected animals and/or their products (e.g., hides, hair, or meat) (53). It occurs occasionally in textile mills where imported animal products (goat, camel, sheep hair) are incorporated into fabrics. Such an occurrence can call for an immediate shutdown and disinfection of the entire plant, which is difficult and expensive. Pulmonary anthrax develops after aerosolized cells, usually spores, gain entry into the body through the respiratory system. The virulence of this organism results from the production of an exotoxin which allows this organism to spread rapidly through the circulation, and death can occur suddenly, usually as a result of cardiac failure (52, 54, 55).

Anthrax is a major military threat facing the armed forces and a biological agent that could be used in a terrorist attack. It has been estimated by the Department of Defense that more than ten countries may possess or are suspected of having anthrax as a biological warfare agent. The Department of Defense has plans to vaccinate more than 2.4 million military members against this organism by the year 2005.

6.1.2 Brucella The Brucella organisms are obligate parasites that can persist intracellularly in an infected host. Infected animals, typically cattle, swine, and goats are the reservoirs from which humans acquire brucellosis. In naturally acquired brucellosis, the organism usually enters the body through broken skin, the conjunctivae, or via the gastrointestinal tract. However, the organism may also enter the body via inhalation when contaminated dust becomes airborne. The symptoms are quite nonspecific, and the diagnosis may be overlooked unless a high degree of suspicion exist. Brucellosis has been associated with farm workers, packing house employees, livestock workers, and veterinarians and has been identified as one of the bacteria most infectious to laboratory personnel, probably by aerosols. In some developing countries, brucellosis is a reemerging communicable disease (56–58).

6.1.3 Klebsiella Pneumoniae This bacillus belongs to an enteric group of organisms whose natural habitat is the intestinal tract. The organism was initially described in 1882 by Friedländer who believed that it was the exclusive cause of pneumonia. These organisms are nonspore forming and are closely related to coliform bacilli. *Klebsiella pneumonia* can be found in the nose, mouth, and intestinal tract of healthy persons and is the etiologic agent responsible for about 5% of bacterial pneumonias. These pneumonias are usually very serious and are characterized by the production of

sputum and frequently the formation of lung abscesses which can be highly fatal. *Klebsiella* has a large mucoid capsule that surrounds the organism and is effective in protecting it against phagocytosis. It can be a secondary invader in the lungs of patients with bronchiectosis or chronic pulmonary diseases. Health-care workers are at risk of infection with these agents from daily exposure to patients who are admitted with this illness. It accounts for a significant proportion of pneumonias acquired in hospitals (59, 60).

6.1.4 Legionella Pneumophila The outbreak of this respiratory illness at the 1976 American Legion convention in Philadelphia focused attention on a common source of exposure to a bacterium later classified as *Legionella pneumophila*. Although morbidity rates are generally less than 5% for exposed individuals, the mortality rates may approach 10–15% (61). *Legionella* infections are not transmitted by respiratory droplets from one infected person to another but instead result from inhaling contaminated water droplets from sink outlets, shower sprays, humidifiers, water cooling towers, and air conditioners. Ingestion of contaminated water has not been implicated. The initial symptoms of the disease include malaise, headache, fever, chills, cough, and changes in mental status. At least 23 different species of Legionella have been implicated in human disease. This microorganism is very difficult to recover from air and usually detection depends on collecting and analyzing of water specimens (62–65).

6.1.5 Mycobacterium Tuberculosis Tuberculosis (TB) is caused by a rod-shaped bacterium and is a highly contagious disease easily passed from one person to another in the airborne droplets formed when a person with active tuberculosis sneezes or coughs. The causative agent (*Mycobacterium tuberculosis*) usually persists in the body long after the primary infection is over but can be reactivated, especially if immunosuppression occurs. Tuberculosis is a significant hazard to hospital personnel, medical students, and physicians who have two to three times the incidence of infection compared to nonmedical personnel. The AIDS epidemic has increased the likelihood that health-care workers will come in contact with active pulmonary tuberculosis because this organism is often one of the opportunistic infections seen in patients with AIDS. The TB incidence rate among people infected with HIV is nearly 500 times the rate for the general population. After a decline in rates of TB during the last several decades, the United States is experiencing a disturbing increase in such infections. The number of cases has gone from 22,200 in 1985 to more than 26,000 in 1991 or 10.4 per 100,000 population (7). Even more alarming is the rise of multidrug-resistant strains (14). Because of the importance of this highly communicable disease, a separate chapter (Chapter 21) has been dedicated to it (66–68).

6.1.6 Mycoplasma Pneumoniae These organisms are the smallest known free-living bacteria that, unlike most bacteria, do not possess cell walls. Mycoplasma are widespread in nature, commonly in pooled water and soils. This organism is associated with primary atypical pneumonia, an acute, febrile disease that usually begins in the upper respiratory tract and spreads to the lungs. The manifestations of the disease, including fever, cough, headache and malaise, can be fairly severe. Although the disease is transmitted by oral or nasal secretions, it is generally not considered very contagious. *Mycoplasma pneumoniae* can be recovered from sputum or pharyngeal swabbing. This disease typically occurs in young adults and children and also in institutions and among military personnel (69–71).

6.1.7 Neisseria Meningitis This organism causes meningococcus meningitis. Meningitis is a general term for inflammation of the meninges (membranes covering the brain and spinal cord). The cells may be either kidney-shaped or spherical, about 0.6 to 1.0 mm in diameter. They are nonmotile and nonspore forming. Early symptoms are excessive nasal secretions, sore throat, headache, fever, neck and back pain, and loss of mental alertness. Like most respiratory infections, the meningococcus organism is disseminated by direct contact through droplet infections from secretions of the nose, mouth, and throat. Some persons are temporary carriers, whereas others may discharge the organism continuously or sporadically. After being deposited in the nasopharynx, the organism directly invades the blood stream. This bacteremia is followed by the onset of acute purulent meningitis. The virulence of this organism is related, in part, to the antiphagocytic properties of its capsule. In

addition, these organisms produce an endotoxin that can cause extensive vascular damage. These organisms can withstand drying and other adverse physical conditions. Epidemics of meningoccus meningitis are prone to occur in military populations probably related to reduced overall resistance of the individual due to conditions of military life, fatigue, and exposure to inclement weather. It seems that with the relatively high carrier rate and the rather low rate of morbidity, there must be a high degree of normal resistance to this organism in the general population (72, 73).

6.1.8 Streptococcus Infections This organism is the commonest cause of community-acquired bacterial pneumonia and is also responsible for sore throats, bronchitis, meningitis, sinusitis, otitis, scarlet fever, rheumatic fever, and septicemia (55, 74). Streptococcal infection of the upper respiratory tract does not usually progress to involve the lungs. The various disease-causing strains of *Streptococcus* are grouped by their behavior, chemistry, and appearance. Group A streptococci are the most virulent species for humans. The ultimate source of these infections is usually a person who harbors these organisms. Such an individual may have a demonstrable or subclinical infection or may be a carrier. Nasal discharges of the organism are the most dangerous source of transmission of this disease. Although all streptococci are similar in cellular morphology, these organisms are extremely variable in pathogenicity. The high virulence of this organism is associated with its ability to produce several kinds of extracellular products, such as hemolysins, hyaluronidase, leukocidin, streptokinase, streptodornase, and erythrogenic toxins. Many of these products aid in spreading the organism within the host. The most virulent streptococci (beta-streptococci) produce hemolysins capable of destroying red blood cells. The less virulent organisms (alpha-streptococci) may also produce hemolysins but are characterized by their lack of complete lysis of the red blood cells. Of special concern is that a “new” form of highly virulent streptococcus has been identified (10, 75). The British tabloids have coined the term “flesh-eating bacteria” to describe this invasive, necrotizing infection. This new strain, like other streptococci, is transmitted by inhalation. However, the resulting infection is especially insidious. Its early symptoms are easily mistaken for signs of the flu. The infection is extremely difficult to treat even with massive doses of antibiotics, and there is no treatment for the deadly toxin produced which actually causes the pneumonia. Resistance against the streptococci is type-specific. Thus, a host who has recovered from infection by one Group A type is fully susceptible to infections by another type. Epidemics can occur in workplaces and institutions where large numbers of people are close together. Certain irritants (i.e., SO_2, NO_2, phosgene, and NH_3) in the workplace can increase the risk and incidence of this bacterial infection.

6.3 Fungi

A fungus infection is known as a mycosis. Environmental factors that can influence fungal growth in the workplace include outdoor air concentrations, type and rate of ventilation, and indoor moisture levels. Many of the diseases caused by these organisms occur in agricultural workers and workers exposed to contaminated air handling systems and open water spray chambers. The fungi that cause systemic mycoses are generally saprophytes in soil. Inhalation of these spores initiates the infection in humans. The spores germinate and develop vegetative organisms that initiate a localized infection. The earliest pulmonary infections are usually acute, consisting of self-limited pneumonitis that can be often overlooked or ascribed to a bacterial or viral disease. The infection subsequently begins to spread progressively to other tissues and often results in the development of granulomatous lesions that clinically resemble tuberculosis. Many fungi can spread by way of the bloodstream and can attack almost any tissue in the body. Because these organisms are not transmitted from human to human, they are not contagious. The organisms appear in infected tissue as small, oval cells (1–5 mm in diameter) frequently located within macrophages and/or reticuloendothelial cells. Miliary lesions appear throughout lung parenchyma, and the lymph nodes become enlarged. The disease may occur either in an acute or chronic state and may be localized or disseminated. Workers without adequate respiratory protection, who are exposed to atmospheres that have been contaminated with quantities of bird or bat droppings, are especially at risk of these types of respiratory diseases. The full range of health effects due to fungal exposure include allergic disease (e.g., allergic rhinitis, asthma, and hypersensitivity pneumonitis) and infectious diseases (e.g., histoplasmosis, blastomycosis, aspergillosis, coccidioidomycosis, and acute toxicosis). Fungi that cause these diseases are frequently opportunistic organisms that produce disease in compromised hosts, such as

those with reduced pulmonary defenses (e.g., from corticosteroids, X irradiation, medication), some concurrent disease, or a coexposure with some other air pollutants (76–79).

Of the more than 100,000 fungal species in our environment, only about 150 are pathogenic and of these only about 40 affect the lung. Of these, the two most pathogenic are *Histoplasma capsulatum* and *Coccidioides immitis*.

6.3.1 Histoplasma Capsulatum Histoplasmosis, sometimes called *Darling's disease*, is an infection resulting from inhalation of the fungus *Histoplasma capsulatum*. It was discovered in 1906 by Darling who observed it in sections of tissue taken from post-mortem cases. *H. capsulatum* is the most common endemic fungal disease in the United States, and it has been estimated that about 500,000 new cases of histoplasmosis occur each year (80). About 90–95% of these cases represent asymptomatic, self-limited pulmonary infections. The remaining 5–10% of patients may develop an acute pulmonary form, a disseminated form or a chronic pulmonary form of the disease (80).

Histoplasma capsulatum has been isolated from soil in more than 50 countries. In the United States, the most heavily endemic area includes Ohio, Kentucky, Indiana, Illinois, Tennessee, Arkansas, and Missouri. In these areas, up to 75% of the population has had primary pulmonary histoplasma infection before the age of 20, based on positive skin tests for the organism (80). Like other fungi that cause systemic mycoses, these organisms can be found as saprophytes in soil. Soil constitutes the reservoir from which infections with *H. Capsulatum* occur. These organisms are commonly found in areas heavily contaminated with the droppings of chickens and keratonaceous material, as well as in the soil beneath areas where pigeons, starlings, and other birds nest (80). Bats are implicated as carriers, and outbreaks of this disease have been traced to the inhalation of dust from bat guano found in caves. In these cases, the disease has been referred to as “cave fever” or “speleonosis.” Another source of soil contamination comes from decaying bodies of small rodents and excreta from a variety of wild and domesticated animals (81). Besides man, a variety of domesticated and wild animals are naturally infected (e.g., cats, fox, opossum; and dogs). Although chickens are heavily exposed, they do not develop the disease, nor do other birds, presumably because the fungus does not thrive at their high body temperature. No intermediate host has been identified, and the disease is not transmitted directly from one human to another or from an animal to a person.

Workers other than farmers who may be at risk include construction crews, operators of heavy equipment, such as bulldozers and graders, and maintenance workers. Any type of industrial activity that results in disturbing contaminated soil can disperse and scatter the infectious spores into the air, which then can be carried by prevailing winds to residents of adjacent areas who may also be at risk (81). Outbreaks of histoplasmosis have been associated with excavation of infected soil for construction of buildings and roads, working in soil fertilized by chicken manure, and breathing dust from silo towers or derelict houses where starlings have congregated or in caves inhabited by bats (82). Like all highly pathogenic fungi, these organisms are dimorphic, capable of changing their growth characteristic from a mycelial form normally found in nature and in laboratory culture, to a budding, oval, yeast-like structure found in infected tissue.

The pathogenesis of *H. capsulatum* has been clearly established. When soil or other contaminated matter is disturbed, aerosolized fungal spores called conidia are inhaled and they are transformed within the respiratory system, into yeast forms by the heat of the body. Most often, the infection remains localized within the lungs perhaps producing patchy areas of interstitial pneumonitis, but it is usually self-limiting (83). The host response to this infection varies with the dose of inoculum and the age and immunologic status of the host (84–86). In the lung, the spores are engulfed by macrophages and multiply intracellularly in the yeast phase with a generation time of about 4 h. The draining lymph nodes become quickly involved, and hematogenous spread of the organisms occurs. This fungemia is generally self-limited but results in seeding of reticuloenothelial organs throughout the body with this organism. Specific lymphocyte-mediated cellular immunity develops in 7–14 days that results in rapid limitation of the infection both in the lung and at distant sites with necrosis and

granuloma formation in involved areas. The lymphocytes of patients with healthy immune systems produce cytokines that activate macrophages and induce formation of granulomas. In a small number of individuals, an effective cell-mediated immune response may not develop, the infection becomes progressive and widely disseminated, and lesions occur in practically all tissues and organs. Ulcerating lesions may be found in the nose, tongue, and mouth. Fever, wasting, and enlargement of liver, spleen, and lymph nodes may occur, and the disease may closely simulate miliary tuberculosis. Histoplasmosis is also occasionally seen as a chronic pulmonary disease with cavitation that simulates chronic pulmonary tuberculosis.

Factors that may increase one's susceptibility to this infection include aggressive immunosuppressive therapy in organ transplant recipients and in AIDs patients and the presence of chronic debilitating diseases such as cancer, diabetes, Hodgkins disease, leukemia, and tuberculosis (83). Because this is an “opportunistic” organism, children and old and debilitated patients are also predisposed.

A provisional diagnosis of histoplasmosis is based upon clinical manifestations, serological tests, and a positive skin response to histoplasmin. The latter has virtually no value in those localities where the fungus is so prevalent that most persons have positive reactions to histoplasmin.

No treatment is needed for most patients with acute mild pneumonitis, but treatment is recommended for patients with severe, persistent, or progressive disease and for immunosuppressed patients. Amphotericin B remains the drug of choice (85).

6.3.2 Coccidioides Immitis This fungus causes the second most common endemic infection in the United States and is the cause of coccidioidomycosis (84). *Coccidioides immitis* was first observed in Argentina in 1892 when the causative agent was thought to be a protozoan but later was cultured and shown to be a fungus. This disease also goes by names of “valley fever,” “Joaquin fever,” or “desert rheumatism.” Approximately 100,000 cases occur annually in the United States and about 70 of these cases per year are fatal (84).

The fungus has a predilection for growth in desert soils and occurs endemically in the southwestern United States, especially in the San Joaquin Valley of California, and in areas around Tucson and Phoenix and western Texas, where the soil is arid and alkaline and the ambient temperature is usually higher than 26°C (84). In these areas, the majority of residents give evidence of past infection by a positive skin test. Both man and animals (e.g., wild rodents, dogs, and cattle) are infected by the inhalation of airborne spores contained in dust (82). The disease is not communicable, and there is no evidence that infected animals contribute directly to the spread of this disease.

In these endemic areas, the people who are particularly at risk include those individuals who work in agriculture and allied pursuits as well as oil field workers, highway maintenance and construction crews, operators of graders, bulldozers, and other heavy equipment, and occasionally train crews who pass through. Repair workers, mechanics, and those involved with handling the organism in a laboratory may also be exposed (81, 87). A high incidence has also been found in American Indian tribes who live in reservations in these dusty, desert areas (85).

Like other pathogenic fungi, *C. immitis* is dimorphic, that is, the infective stage within the tissue is morphologically different from that observed in nature and in culture. In body exudates and in histological sections, the organism appears as spherules or a mixture of spherules and hyphae (84, 88). The spherules are thick-walled structures as small as 5 mm in diameter but at maturity may be 20–60 mm. They are filled with hundreds of irregularly shaped endospores varying from 2 to 5 mm in diameter. These large spherules eventually rupture, and the endospores are released and develop into new spherules. In culture, growth is rapid, and fluffy white mycelia appear within about 5 days. A characteristic feature of the hyphae is the cast-shaped arthrospores, which alternate with smaller clear hyphal cells. When the hyphae fragment, they release huge numbers of arthrospores, which are easily airborne and highly infectious.

Coccidioides immitis can be both an acute, benign respiratory infection or a chronic disease, fatal if untreated. In about 60% of infected persons, the disease is not clinically apparent; infection is revealed only by the acquisition of delay-typed hypersensitivity (positive coccidioidin skin test reaction) in about three weeks. The rest of the individuals may develop a spectrum of symptoms ranging from a flu-like syndrome to frank pneumonia following an incubation period of 1–4 weeks. Symptoms include cough, fever, headache, chest pain, dyspnea, and malaise, often with pleurisy and skin eruptions. About 5% of infected persons ultimately develop chronic pulmonary cavitary disease resembling pulmonary TB. Dissemination occurs in less than 1% of the infected persons, producing infected granulomatous lesions that are indistinguishable from tuberculosis, unless spherules can be detected in numerous organs (84, 85). Death from disseminated coccidioidomycosis is usually attributed to meningitis (58%) or pulmonary disease.

Host factors associated with high risk of disseminated infection include race, sex, age, pregnancy, and immunosuppression. Dissemination occurs ten times more frequently in dark-skinned than light-skinned individuals. Men are 1.5 to 6 times more susceptible to disseminated infection than nonpregnant females. Pregnant females are more susceptible, especially during the second and third trimesters (84, 85). In endemic areas, this fungus is the third most frequent opportunistic infection of HIV-infected individuals. Many of these cases probably result from reactivation of latent infection rather than a recent primary infection.

Diagnosis is made by finding the fungi in the lesions. The organism can be found by direct microscopic examination of pus, sputum, gastric washings, spinal fluid, and biopsy specimens. The cocidioidin test, a test of skin sensitivity to an extract of the organism, is of value; however, cross reactions with other fungal infections such as histoplasmosis and blastomycosis may occur.

In endemic areas, infection can be diminished by dust control measures. Repeated spraying with oil has been used to reduce the incidence of *C. immitis* infections in very arid, dusty environments (81). No treatment is needed for most patients with acute pulmonary *Coccidioides immitis* but amphotericin B is the drug of choice for chronic or cavitary disease (85).

6.4 Viruses

Several hundred different viruses may infect humans. Examples of viruses found in indoors include rhinoviruses, influenza, parainfluenza, variola, adenoviruses, varicella zoster, paramyxoviruses, poliovirus, and cytomegalovirus (10, 23). The viruses that occur primarily in humans are transmitted chiefly by humans, mainly via the respiratory route. Diseases caused by viruses vary considerably in their effects on susceptible individuals, mild or moderate in some cases and extremely dangerous in others. Epidemics caused by viruses present formidable challenges to public health officials responsible for preventing and controlling the spread of such diseases. Infectious diseases caused by viruses are many and varied. This discussion focuses on viral infections such as influenza and the common cold that are associated with crowded working conditions.

6.4.1 Influenza Virus The 1918–1919 influenza pandemic is recognized as one of the most serious and devastating outbreaks of an infectious disease known. It was estimated that more than 20 million people died of this disease during that period (7, 78). Later, in the pandemics of 1957 and 1968, it was estimated that influenza killed 90,000 people in the United States alone and the direct cost of medical care exceeded $3.4 billion. Outbreaks have been associated with crowded working conditions and military posts. Influenza is an acute infection that enters the respiratory tract by direct contact with the mucus of an infected person. The virus can persist for hours in dry mucus. It is an RNA virus that possesses an unusual degree of genetic variability. As a result of this property, the virus frequently undergoes major antigenic shifts, and new variants emerge. Thus, individuals with immunity to prior strains have limited protection to the newly emerged strains. The infectious strain enters the body through the mouth and nose and replicates in the upper respiratory tract. Normally, the disease is self-limiting. However, serious effects may occur when the virus destroys the cells of the respiratory tract and secondary bacterial infection develops. The incubation period is short, only 1–2 days. The symptoms of infection include chill, fever, malaise, muscular aches, cough, and

general respiratory symptoms. Individuals with immunosuppression or chronic respiratory diseases have the greatest risk (89).

6.4.2 Common Cold The common cold is aptly named because it is one of the most common human maladies; it has been recognized since earliest recorded history. There are more than 200 agents that are etiologically responsible for clinical syndromes associated with pharyngitis or the common cold. These include certain bacteria and a wide host of viral agents, including respiratory syncytial virus, rhinovirus, adenovirus, influenza, parainfluenza virus, and certain echo- and coxsackieviruses. About 90% of colds stem from viral infections. Serological testing or viral isolation is necessary to establish the specific etiologic agent. Most colds develop in the nose and throat but then can spread to the trachea and larynx (laryngitis), the sinuses (sinusitis), or the lungs (bronchitis). Colds account for more time lost from work than any other cause. Although self-limiting, colds can lead to secondary infections. Health-care workers are at risk from these agents due to frequent exposure to infected individuals. Infection may be facilitated by excess fatigue, allergic nasopharyngeal disorders, or inhalation of certain noxious fumes in the workplace (90, 91).

6.5 Rickesttsial and Chlamydial Infections

Both chlamydia and rickesttsiae rely on host cells to compensate for their own metabolic deficiencies; thus they are obligate intracellular parasites. Although rickettsial infections in humans usually begin in the vascular system following the bite of an infected arthropod, an important rickettsial disease is acquired by inhaling contaminated dust particles, resulting in Q fever. Q fever is an acute febrile illness that affects veterinarians, farmers, dairy workers, and abattoir employees. Animals shed the organism (*Coxiella burnetii*) in their nasal and salivary secretions, and it can be inhaled by individuals who work in this environment. The organism remains viable in a dried state for long periods of time (92, 93).

Chlamydial infections are occupational diseases in the poultry industry. However, veterinarians, workers in pet bird industries, and bird owners may be infected. Psittacosis or ornithosis is the term used for human infections. At highest risk are workers engaged in plucking and eviscerating chickens and turkeys. Most infections are transmitted through inhalation. Because the symptoms resemble the “flu,” misdiagnoses are common (94).

6.6 Hypersensitivity Diseases

Microorganisms in the workplace may also affect the immune system. Allergic respiratory diseases may develop in response to inhaling aerosols of both viable and nonviable organisms and their antigens, as well as microbial products such as glucans, endotoxins, and mycotoxins. Fragments of microbial cells, including cell wall segments, flagella, genetic material, and by-products of metabolism that are transported as bioaerosols can cause health problems (95). Such allergic respiratory illnesses produce acute symptoms, including malaise, fever, chills, shortness of breath, and coughing. They can often be serious diseases possibly leading to permanent lung dysfunction. Individuals can become hypersensitive to the inhalation of thermophilic actinomycetes in heating, ventilating, and air conditioning systems (19, 96).

Potential allergens include dust mite wastes, mold spores, fungal hyphal fragments, and macromolecular organic dust deposited on floors and surfaces. Exposure to such allergens is an important cause of asthma and chronic allergic rhinitis in certain occupations. Worldwide, the incidence of asthma is increasing, and occupational asthma has become more prevalent. Various factors have been suggested to explain this increase, including increased exposure to allergens, possible adjuvant effects of environmental chemicals, and improved diagnoses. Occupational asthma, a common respiratory ailment, may be defined as a disease characterized by variable airflow limitations and/or hyperresponsiveness due to conditions in an occupational environment and not to certain stimuli outside the workplace. Symptoms include recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. About 200 agents have been implicated in causing workplace asthma (97). Examples include baker's asthma in workers exposed to *Aspergillus and Alternaria*, workers exposed to mites found in grain dusts, handlers of animal, workers involved in the manufacture of detergents where certain proteolytic enzymes are added; and workers exposed to wood dusts, especially red cedar.

6.7 Diseases Related to Bacterial Toxins
Microorganisms that cause disease may produce certain toxins. Airborne endotoxins are ubiquitous in nature and may be distributed throughout the workplace. Given appropriate moisture content and temperature, organic substrates furnish the necessary nutrients to promote the growth and reproduction of a wide variety of microorganisms (gram-negative) capable of producing endotoxins. Adverse human reactions to these endotoxins have been associated with a number of occupational settings including agriculture (e.g., swine/poultry shelters, composting, rice hulling and silo unloading, animal feed), manufacturing (e.g., machining oils, bioengineering, and mattress making), and textile production (e.g., cotton spinning mills, flax and textile processing, cotton garnetting, and carpet weaving). Although most of the settings in which high aerosol levels of endotoxins may occur are occupational, bacterial endotoxins have also been implicated in nonoccupational exposures as well. Endotoxin exposure is a possible cause of humidifier fever and is related to SBS (20, 98–100). A very important type of reservoir for such organisms is recirculated water-based fluids that are found in many home and office humidifier systems and possibly in areas where humans live downwind from sewage outfalls, solid waste processing centers, or wastewater treatment plants (98, 99). Endotoxin inhalation may cause an acute illness with fever, sweating, muscle aches, and headaches; sometimes rhinitis, asthma, and breathlessness may occur. Symptoms usually start within hours after exposure and may resolve in a day; however, they can reappear again with repeated exposures.

Mycotoxins, such as aflatoxins, are products of fungal metabolism that can lead to respiratory distress and severe systemic toxicosis. Some mycotoxins may be immunosuppressive and increase the likelihood of opportunistic and secondary bacterial infections. Inhalation of such toxin-containing spores may lead to “pulmonary mycotoxicosis” due to the absorption of toxin through the mucous membranes of the respiratory tract (100).

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7 Sampling and Identifying Airborne Microbial Contaminants
Before commencing extensive sampling for the presence of airborne microorganisms, medical evidence should suggest the occurrence of infectious or allergic disease among the workers that appears to be related to the workplace. Significant exposure to aerosolized infectious agents in the workplace can be suspected when there are (1) several important sources or reservoirs, (2) amplifiers or conditions favoring microbial survival, (3) highly susceptible individuals or known carriers, (4) complaints or epidemics of disease, and (5) a microbiological laboratory report of positive cultures. Of special concern are those environments with high occupant density possibly resulting in increased risk of the airborne transmission of infectious agents between individuals. An on-site inspection may aid in uncovering the potential source of biological contamination, which can be confirmed using standard microbiological techniques. The ventilating system should be examined for appropriate design, operation, and maintenance. Evidence of microbial growth in cooling coils and on wet surfaces can indicate a source of biological contamination and a possible microbial reservoir. In some cases, bioaerosol sampling may not be necessary if there is substantial evidence of visible microbial growth. With evidence of microbial growth on floors, walls, or ceilings, or in the ventilation systems, sampling for bioaerosols and appropriate remediation should be considered. Sampling for microorganisms should be undertaken, especially when medical evidence suggests the occurrence of disease. A careful on-site inspection can be of significant value in designing appropriate air sampling methods. Once the purpose or the goal of bioaerosol sampling is determined, appropriate sampling method(s) should be chosen. Sampling for bioaerosols in the workplace can provide useful information necessary to characterize the exposure conditions, determine whether the contamination represents a potential or real hazard, and establish the need for control measures.

Bioaerosol monitoring is a rapidly emerging area of industrial hygiene. Airborne sampling for bioaerosols is complex, expensive, and may include measuring bacteria, viruses, fungal spores, endotoxins, allergenic and toxic substances of plant and animal origin, and protein aerosols (3). The airborne concentration may be expressed in different ways, depending on the type of particle. Bacteria and fungal spores, for example, may be expressed in terms of the number of bacteria entities of a given type per unit volume of air (i.e., number per m^3 of air). On the other hand, viable particles may be expressed in terms of their ability to reproduce—that is, the number of "colony-forming units" per unit of volume of air (i.e., cfu per m^3 of air). For endotoxin and allergenic materials, it is appropriate to express concentration in terms of the mass of the active component per unit volume of air (i.e., mg per m^3 of air) Such diversity presents many difficulties in sampling and measurement methodology for exposure assessment.

Although there are no standard methods for sampling and analysis of microbiological agents in air, the same principles that apply to measuring and collecting any particulate aerosol also govern air sampling for microorganisms (101). The sampling methods most commonly used to collect airborne microbes are described in detail elsewhere (101–103). Methods commonly used include glass impingers, cascade impactors, sedimentation, and real-time samplers. A recent comprehensive review compares the various experimental, theoretical, and physical characteristics of the commonly used bioaerosol samplers (104).

The selection of the sampling methods and subsequent laboratory analyses are determined by the medium to be sampled (air, water, surface) and the type of agent to be detected (6). Samplers used to isolate viable microbes in the air must be capable of collecting the aerosol with high efficiency, must minimize injury to the organism during the collection process, and must maintain the culturability of the collected microorganisms. In monitoring viable microorganisms, only culturable microorganisms are enumerated and identified, thus possibly leading to an underestimation of bioaerosol concentrations.

Aeroallergens (pollen and fungi) may be sampled without culturing the microorganisms. This can be done using passive aerobiological monitors that rely on gravity collection on an appropriate medium or on some collection surface. Then the collected microorganisms can be enumerated and identified using microscopy, classical microbiology, molecular biology, or immunochemical techniques. With this method, large particles are collected more effectively than small particles. These passive monitors can be used either as area or personal monitors, but they provide only semiquantitative information because only particles of certain dimensions will settle onto the surface in a given time and there is no way of knowing the volume of air that is being sampled.

In sampling culturable bacteria and fungi, the bioaerosol is generally collected by impaction onto the surface of a solid medium (agar), filtration through a membrane filter, or impingement into an isotonic liquid medium. Such an air sampler consists of a pump that draws a known quantity of air over or through a collection surface that contains appropriate growth or collection medium for the organism suspected of being present.

After impaction onto a medium surface and incubation, the organisms may be transferred onto selective or differential media and incubated at different temperatures for identification and enumeration of the microbes (105). When using collection fluids, the sample can be placed directly on agar or serially diluted and plated, or the entire volume of fluid can be filtered through a membrane filter. The membrane filter is then placed on an appropriate growth medium. Microbes may be identified by using microscopy, classical microbiology, or molecular biology techniques such as restriction fragment length polymorphic (RFLP) analysis. Classical microbiology techniques include observation of growth characteristics, cellular or spore morphology, simple and differential staining, and biochemical, physiological, and nutritional tests for bacteria. DNA analytical techniques which may be applied to both nonviable and viable microorganisms include polymerase

chain reaction and enzyme-linked immunosorbent assay. Such methods may be used to identify specific microorganisms and to locate areas of contamination. Concentrations of endotoxin determined by using the *Limulus* amebocyte lysate assay method have been correlated with patient symptoms in some studies (105).

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8 Assessment of Risk
Remarkable changes have occurred in the way human health and environmental risks have been assessed and regulated during the past few decades. The passage of many federal, state, and local governmental regulations and statutes enacted to protect the health of workers and general public from occupational and environmental exposure and consumer products have provided a major stimulus to develop a formalized approach for assessing human health risk from exposure to radiation, physical and chemical agents, and other conditions that may pose human health or environmental hazards. The National Academy of Science/National Research Council has provided a structured approach to the risk assessment process that has become increasingly accepted (106). This method has been widely used by several governmental agencies, including the U.S. EPA, for assessing the risk of cancer and other health effects that result from exposure to chemical agents. Much has been written about the risk assessment process as it relates to chemical exposure (107–112). Such quantitative risk assessment has been widely used for (1) assessing human effects from exposure to chemicals, (2) developing regulatory standards, and (3) conducting risk/benefit analysis used to inform major policy decisions. A complete risk assessment approach that emerged in the 1980s involved four interrelated components but conceptually distinct steps: (1) hazard identification (the potential of the source for releasing a risk agent); (2) exposure characterization (the intensity, frequency, and duration of exposure and the nature of the population that might be exposed); (3) exposure–response characterization (the relationship between exposure and the resulting health consequences); and (4) risk characterization (the combined influence of these three factors on risk will provide estimates of the magnitudes of possible adverse health effects, including a characterization of the probabilities, uncertainties, and degree of confidence associated with these estimates).

With increase awareness of the potential for disease from exposure to microorganisms in our working and living environment, there has been an interest in developing similar risk assessment models to evaluate the likelihood of adverse human health effects from exposure to infectious microorganisms. Currently, the process being used to assess risk from exposure to pathogens uses the conceptual framework developed to assess risks of chemical exposures.

However, there are several reasons that these methods presently being used for chemicals may not be appropriate for assessing the risk of exposure to microorganisms. Issues that must be considered that are unique to assessing risks of the infectious disease process include an assessment of pathogen/host interaction, consideration of secondary spread, the possibility of short- and long-term protective immunity, and an assessment of those conditions that might allow the microorganism to propagate.

The development of a pathogenic risk assessment process is complex and may consist of several interrelated components but conceptually distinct steps (113).
8.1 Phase One
The initial phase is a systematic planning step that identifies the goals, breadth, and focus of the risk assessment. A critical component of this problem formulation phase is to determine the purpose of the risk assessment and to identify those specific questions that the assessment analysis is to answer. A risk assessment may be initiated for a number of reasons. For example, if it is known that microorganisms are present in air, food, or water without a recognized outbreak of the disease, it

may be desirable to assess the potential for human risk of exposure to the organism. Conversely, a risk assessment may be initiated as the consequence of an infectious outbreak but where the specific pathogen or the vehicle of infection (medium of concern) is unknown. Such analysis can be useful in determining critical points for control, such as reducing airborne contamination, activating specific water treatment processes, or initiating certain food handling activities.

8.2 Phase Two

The second phase consists of a number of technical evaluations of the existing database to gain a better understanding of the potential for exposure and consequential health effects. In characterizing the exposure, one attempts to determine the properties of the organism that are expected to influence its ability to be transmitted to the host, to infect, and to cause disease. The properties of the pathogen to be considered include virulence, host specificity, ability to survive in the environment, portal of entry, and mode of transmission. Characterization of the expected occurrence, distribution, and physical state of the microorganism can aid in determining the expected concentration of the organism in the environment and the sources of the microbes. Data gathered from this phase should provide useful information about relevant factors pertaining to the occurrence and distribution of the organism.

Included in this second phase is an exposure analysis step that characterizes the source and temporal nature of human exposure. This includes identifying and elucidating the vehicle of transmission, such as air, drinking water, food, as well as the size and demographics of the potentially exposed population. Such exposure analysis may aid in identifying whether a single airborne exposure to a certain organism with high transmission potential may have substantially different consequences than multiple exposures to pathogens with low transmission and virulence potential. The route of exposure and the transmission potential can in turn be influenced by the behavioral characteristics of the individuals exposed.

From this evaluation, an exposure profile can be developed to provide a qualitative and/or quantitative description of the magnitude, frequency, and patterns of exposure focused on those scenarios developed during the problem formulation phase. The exposure profile draws heavily on information obtained from the characterization and occurrence of the pathogen and the exposure analysis phase. The exposure profile should include an assessment of the various assumptions, modifying factors, and uncertainties that are included in the analysis, providing insight into the strengths and weaknesses of the assessment process.

The final task in this second phase is to characterize the human effects from exposure to the microorganisms. To meet these needs, one collects data necessary to adequately characterize the host. Host characterization involves evaluating the nature and characteristics of the population that might be exposed and the susceptibility to a particular pathogen. High-risk groups may develop severe symptomatic illness, whereas low-risk groups may develop asymptomatic infections or mild illnesses. Many other factors can influence susceptibility and severity, but not all are important for all microorganisms. The outcome of host characterization is the identification of factors that influence susceptibility and severity and the identification of susceptible subpopulations.

In the analysis of the health effects from exposure to the microorganism, the clinical illnesses need to be characterized. This should include characterizing the whole spectrum of clinical manifestations, including symptomatic and asymptomatic infections, duration of clinical illnesses, mortality, and sequelae. In most cases, the assessment of health effects usually relies on epidemiological and clinical information, but animal studies can provide useful information.

Dose–response analysis can be valuable in evaluating the relationship between dose, infectivity, and the manifestation of clinical illness. This relationship is complex, and in many cases a complete understanding of this relationship may not be possible. Often only crude indirect measures for dose–response assessment can be made because an actual dose of the microorganism is not available. When this phase is successfully completed, it provides valuable insight into the host–pathogen profile that provides qualitative and/or quantitative descriptions of the nature of the illness a

quantitative dose–response analysis for the scenarios developed during problem formulation, and serves as input for risk characterization.

8.3 Phase Three

The final step of the pathogenic risk assessment is the risk characterization phase. This consists of combining information from the other phases and provides estimates of the magnitude of the adverse health effect. This includes an estimated number of people who experienced health impacts of various severaties over time, a measurement that indicates the nature and magnitude of adverse consequences to the exposure, and the likelihood that adverse human health effects will occur. The degree of confidence in these risk estimates should be expressed in the risk description and should include consideration of the sufficiency, defensibility, quality, and uncertainties of the database and the evidence of causality.

The use of such risk assessment models can aid significantly in integrating our existing knowledge, identifying data gaps, and improving our planning and designing of future research to fill those gaps. Although the current methodology used in risk assessment has significant limitations and shortcomings, it still provides a useful short-term approach for addressing health, safety, and environmental risks and for providing a logical and effective means for analyzing and evaluating limited information to understand specific risk. In developing risk assessment processes for infectious diseases, the emphasis should be on the dynamic and iterative nature of the risk assessment process in providing individuals with a variety of options for planning and conducting risk analysis under a variety of diverse conditions often found in occupational environments (113).

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9 Control and Prevention of Airborne Infectious Disease

The fundamental aim of occupational hygiene is to protect the health of individuals by preventing or reducing risk from exposure to chemical, biological, or physical agents in the workplace. In controlling and preventing infectious diseases, the ultimate aim must be to quickly identify the causative agent and to establish reliable approaches for prevention and control. A well-designed, well-implemented surveillance program can detect unusual clusters of disease, document an outbreak, estimate the magnitude of the problem, and identify factors responsible for its emergence. Although specific guidelines for each industry are obviously beyond the scope of this chapter, there are certain practices that can significantly reduce the incidence of illness (114). Employing the control and prevention measures listed here will aid in (1) eliminating the reservoir of the microorganism, (2) interrupting the transmission of the infection, and/or (3) providing increased resistance of the individuals to the microorganism.

- Personal hygiene will lessen the spread of disease.
- The elimination and control of the source of the hazard is preferable to relying on personal protection, but in some work environments, the use of personal protective equipment, (e.g., clothing, gloves, face mask, and respirators) may be necessary for an acceptable level of protection.
- Cleanliness in the workplace, conforming to appropriate standards (e.g., refuse removal, hosing down abattoirs, disinfection of surfaces and articles in day-care centers and medical practices) is always indicated.
- Proper disposal of wastes, especially those suspected of microbial contamination, and proper cleaning of contaminated articles is critical.
- Special attention should be paid to the design and construction of buildings to avoid bioaerosol contamination. For example, the structure should consist of nondeteriorating material, so as not to offer a substrate for microbial growth. Control of moisture (i.e., maintaining relative humidity at

levels less than 70%) is an important factor in minimizing fungal growth. Proper maintenance, repair, and cleaning of air handling equipment (HVAC) is a cost-effective means of controlling contamination. Removal of pollutants from air can be accomplished by increasing effective ventilation and by air cleaning.

- Special care is necessary in the case of immunocompromised and particularly sensitive or susceptible employees.
- Prevention can occur through immunization or allergic desensitization. In certain professions where there is a high risk of exposure (e.g., veterinarians, researchers, animal handlers, and medical care personnel), immunization can be provided to maintain a high level of protection.
- Education and training helps workers to recognize conditions (e.g., sources, reservoirs) that contribute to bioaerosols. Individuals can use such information to reduce their exposure and to remove themselves from contaminated areas.

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1 Human Immunodeficiency Virus 1

On June 5, 1981, the CDC reported several cases of *Pneumocystis carinii* pneumonia in young male homosexuals (7). Several weeks later, Kaposi[apos]s sarcoma was reported in 26 male homosexuals, some of whom also were diagnosed with *P. carinii* pneumonia (8). These reports represented the first recognized cases of what is now defined as acquired immunodeficiency syndrome (AIDS). Seventeen years later, in June 1998, over 657,077 AIDS cases had been reported to the CDC among persons of all ages in the United States (9, 10), with an estimated 50 million infected throughout the world.

Within 3 years of the recognized syndrome, the virus causing AIDS was isolated and found to be a new human retrovirus (11–13). Retroviruses had been studied primarily in animal diseases and were

found to be a cause of a human disease in 1980 by Poiesz et al. (14). Although the virus was originally called *human T-cell lymphotropic retrovirus III* (HTLV-III) by Gallo, and lymphadenopathy-associated virus (LAV) by Montagnier, the virus has subsequently been termed *human immunodeficiency virus 1* (HIV-1) by committee (15).

1.1 Biological Characteristics

Certain biological characteristics of HIV-1 are important to the epidemiological and clinical aspects of the virus, and contribute to the risk involved with viral transmission. These include (16):

1. HIV-1 belongs to a group of RNA viruses known as *human retroviruses* named for the novel reverse transcriptase (RT) enzyme. The RT enzyme allows a DNA chain to be copied from the viral RNA. The double-stranded DNA material from the viral template is then incorporated into the host cell genome. This step is important epidemiologically, because the retroviruses are able to exist in a latent period for years to decades before disease develops. More specifically, HIV-1 belongs to the lentivirus group (*lenti-* = "slow"). It is estimated that the average incubation period between HIV-1 infection and the development of the disease, AIDS, for both homosexual men and adults with transfusion-associated HIV infection via transfusion is 8 years (17), and may be extended with treatment with antivirals or protease inhibitors.
2. The reverse transcriptase enzyme is a natural target for antiviral agents. For example, azidothymidine (AZT) inhibits HIV-1 replication by blocking reverse transcriptase activity. Such agents can block further transmission of HIV to other cells, but cannot eliminate the HIV provirus from reservoirs in cellular DNA.
3. Since reverse transcriptase activity is specific for replication of retroviruses, its detection provides an excellent indicator of retroviral activity in laboratory tests.
4. The polymerase enzyme of HIV that is involved in transcription is error-prone, contributing to the antigenic hypervariability on the viral envelope. This complicates the development of a universal vaccine and perhaps influences the virulence of the different strains of virus.
5. Surrounding the RNA viral core and viral enzymes, the lipoprotein envelope contains several important glycoproteins that help bind the virus to host cell receptors and are the focus of several vaccine studies. Evidence of antibodies to glycoproteins GP120, GP160, and GP41 is essential to laboratory testing for infection with HIV-1 (18).
6. Retroviruses, like other enveloped viruses, are rapidly destroyed by common laboratory disinfectants and detergents (19).
7. The HIV-1 viruses replicate intracellularly in the host. The major target cells are those that possess the CD4 protein receptor, primarily the T4 lymphocytes. The T4 cell is lysed or severely limited in function by viral replication, leading to eventual depletion of immunological capabilities. The monocyte–macrophage cell, another target cell for HIV-1, harbors the virus, but is more resistant to the cytopathic effects. The monocyte–macrophage cell serves as a reservoir for the latent viral state, a "Trojan horse" that transports the virus throughout the body, protecting it from host defenses. Evidence also indicates that the Langerhans cells of the skin may also harbor the virus (20).
8. The HIV-1 virus is found in body fluids as cell-associated as well as cell-free. The numbers of virally infected cells and infectious viruses in plasma vary with the stage of HIV-1 infection. For example, HIV p24 antigen, a marker of HIV-1 replication, has been demonstrated during the acute stage of HIV infection, and at the late stages of infection when CD4 lymphocytes decrease in number (21). Also, increased HIV-1 plasma titers are associated with the later stages of the disease (22). This higher "dose" of virus may be an important determinant of an increased risk of viral transmission.
9. The HIV-1 virus has been cultured from blood (12), semen (23), vaginal and cervical secretions (24, 25), saliva (26), breast milk (27), tears (28), urine (29), cerebrospinal fluid (30), alveolar fluid (31), and amniotic fluid (32); however, human transmission of the virus has occurred only via blood, bloody body fluids, semen, vaginal and cervical secretions, breast milk, or concentrated viral material. Proteins found in urine, tears, saliva, and mother[apos]s milk neutralize HIV and may explain why HIV is not transmitted via these fluids (33).

1.2 Inactivation Studies

Retroviruses are classified by Klein and Deforest (19) as protein and lipid viruses and, as such, are susceptible to many common disinfectants found in the laboratory. Since 1984, several studies have evaluated the inactivation of HIV-1 by a variety of physical and chemical means. The methods of testing for viability of HIV-1 after exposure to disinfectants or physical methods include the determination of reverse transcriptase activity and the ability of the treated virus to infect T-cell lines in tissue culture. The tissue culture assay appears to be more sensitive for small amounts of virus than the RT assay (34). It is yet unknown if the tissue culture assay is able to measure the critical human infectious dose. Therefore, the observed log reductions in virus titer and extrapolated decay rates using high concentrations of virus allow for inferences about effectiveness of the disinfectant or method of inactivation.

1.2.1 Environmental Stability Under experimental laboratory conditions and grown in high concentrations of 7–10 logs tissue culture infectious dose ($TCID_{50}$), HIV-1 demonstrates stability at room temperature in both dry and liquid forms. One $TCID_{50}$ is the amount of virus required to infect half of the cells in tissue culture. In aqueous suspensions of tissue culture fluid, the virus has remained viable after 1–2 weeks (34). Several authors have demonstrated the recovery of viable HIV-1 after 3–7 days in the dried state as a viral film on glass or a petri dish (34–36). Resnick et al. (34) and Prince et al. (36) calculated the amount of time required to reduce viral infectivity by 1 log or 90% (the D_{10} value) in a dried state at room temperature to be 8–9 h. It follows that a blood spill containing 1–3 logs of virus per milliliter (22) in a clinical or laboratory setting could potentially contain viable HIV-1 for over a day if allowed to dry. Prompt cleaning with appropriate disinfectants should be initiated to remedy this situation.

1.2.2 Heat Inactivation Although the HIV-1 appears stable at room temperature, it is very heat-labile. McDougal et al. (37) found that the virus follows first-order kinetics, and calculated the D_{10} values for a series of temperatures (see Table 20.1) (37–39). The study found little difference in the thermal decay rate when the virus was suspended in culture medium, serum, or liquid factor VIII, but found that the virus in the lyophilized state was somewhat resistant to heat.

Table 20.1. Environmental Survival of HIV-1

Condition	Temperature	Parameters	D_{10}[a]	Comments	Ref.
Heat	60°C	2 min	ND	Virus in factor VIII preparations	37
	60°C	2 h	ND	Lyophilized virus	37
	56°C	10 min	ND	—	38
	56°C	20 min	ND	50% serum	39
	56°C	10 min	2 min	—	37
	56°C	5 h	20 min	50% plasma	34
	50°C	—	24 min	—	37
	45°C	—	3.3 h	—	37
	37°C	—	4.8 days	—	37
	37°C	11 days	ND	50% plasma	34
	37°C	6 days	ND	Dried virus	36
Aqueous	RT[b]	15 days	—	—	34

solution	RT	>7 days	—	—	35
Dried virus	RT	>3 days	9 h	50% plasma	34
	RT	>7 days	—	In petri dish	35
	RT	>7 days	8 h	5% serum on glass	36

[a] D_{10} = amount of time required to reduce viral infectivity by 1 log or 90%.

[b] RT = room temperature (20–27°C).

Martin, as well as other authors (38, 39), reported inactivation of HIV-1 suspensions at 56°C within 10–20 min (D_{10} value = 2 min). Resnick et al. (34), however, found that heating at 56°C for 5 h was necessary, calculating a D_{10} value of 20 min. The reason for discrepancies in these studies is undetermined.

A 1988 survey of laboratories evaluating HIV-1 tests for CDC (40) reported that 3.9% of the laboratories heat-inactivated serum specimens at 56°C as a safety measure before testing. However, the heating process can cause false-positive results for enzyme immuno assay (EIA) and Western Blot tests (41, 42), changes in laboratory enzyme levels, and turbidity problems with plasma (43). The CDC recommended that heat inactivation of serum does not preclude the use of standard precautions and should *not* be used as a routine means of protection of laboratory workers (40).

The heating process has better applicability in the preparation of safe therapeutic blood products. Piszkiewicz (44) found that pasteurization of antithrombin III concentrate at 60°C for 7 min reduced HIV-1 to below detectable levels. Others have found alternative methods of inactivation of blood products, including exposure to tri- (*n*-butyl) phosphate and sodium cholate for 20 min at room temperature (45). A promising method that destroys HIV-1 but does not effect changes in hematological parameters is the "photodynamic method," a hematoporphyrin photosensitizer (46).

1.3 Epidemiology

Since the recognition and reporting of AIDS in 1981, more than 650,000 persons with AIDS have been reported to public health departments in the United States (9). In the United States, AIDS was the leading cause of death among those aged 25–44 years in 1993 (47), but dropped to the fifth leading cause in 1997 (48). Worldwide, at the end of 1997, approximately 30.6 million people were living with HIV infection, 20.8 million of them in sub-Saharan Africa (49).

Epidemiological information gathered since the early 1980s indicate that the modes of transmission of HIV-1 have remained the same. HIV-1 is transmitted through sexual contact, percutaneous or mucous membrane exposure to blood, birth, or breastfeeding from an infected mother, or transfusion of HIV-contaminated blood. However, trends of HIV infection for certain populations reflect the evolution of the epidemic. For example, in the United States, AIDS cases attributed to homosexual or bisexual behavior decreased from 65% of cases in 1984 to 48% in 1998. Heterosexual contact cases increased from 1.2% in 1984 to 10% in 1998 (50, 51).

The findings demonstrate a disproportionate increase in U.S. women and racial[sol]ethnic minorities. Women accounted for only 7% of AIDS cases in 1984 (50), 10% in 1987 (52), and increased to 16% in 1998 (51). The overall rate of AIDS per 100,000 population in 1998 was 34; however, the rate for African-Americans was 125 (51). Dr. Helene Gayle (53) noted that African-Americans make up 13% of the U.S. population, but accounted for 48% of all AIDS cases in 1998, and that higher annual infection rates are seen with young homosexual men, intravenous drug users, women, and minorities.

The annual incidence of AIDS cases associated with blood transfusions and therapeutics for hemophilia stabilized with about five cases per year after the serological screening of blood donations and heat-treatment of clotting factors was initiated in 1985. Currently (at the time of writing), it is estimated that the risk of any unit of blood being contaminated with HIV after the

screening process is 1:200,000–1:2,000,000 (54). The American Red Cross began testing donated blood units via nucleic acid testing (NAT) in June 1999 for early detection of viruses, such as HIV and hepatitis C virus (HCV) (55). Because NAT detects viral DNA or RNA, rather than the donor [apos]s antibodies, it can detect HIV virus within 6–10 days after exposures and HCV within about 41 days after exposure. This reduces the risk of transmission of undetected HIV or HCV via blood transfusions.

In 1998, 8% of all AIDS cases were assigned to a "no identified risk" (NIR) category, representing a large caseload of those recently diagnosed (51). For many of these cases, follow-up investigation is incomplete or the patient has died before an investigation could be performed. Historically, on investigation, 83% of the NIRs are classified into an identified risk category.

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2 Occupational HIV-1 Transmission
2.1 AIDS in Healthcare Workers
National surveillance data about AIDS in healthcare workers demonstrate that there is no high risk for working in the healthcare or laboratory setting. As of 1998, approximately 20,769 (5.1%) of reported AIDS cases whose work history was known had related a history of working in a healthcare or laboratory setting since 1978 (4). This percentage is comparable to the proportion of the U.S. population working in the healthcare area (56). The occupations of those healthcare workers with AIDS are as follows: 22% nurses, 21% health aides, 13% technicians, 8% physicians, 5% therapists, 2% dental workers, and 2% paramedics (4). Overall, 75% of the cases of AIDS in healthcare workers have died.
2.2 Prevalence Studies
More indirect evidence that the risk of transmission of HIV-1 in the healthcare setting is small is found in HIV prevalence studies conducted on cohorts of healthcare workers around the country, many of whom work in areas of high community seroprevalence. These studies have examined 7595 U.S. and European healthcare workers with reported HIV exposures and found nine seropositives (0.12%) in workers with no identified community risk (57–69). The prevalence of infection in healthcare workers does not appear to be any higher than that of the comparable population at large.

The lack of association of HIV transmission in the healthcare setting has also been demonstrated in a recent serosurvey of hospital-based surgeons in 21 hospitals in moderate to high AIDS incidence areas across the United States conducted by the CDC Serosurvey Study Group (70). This study also found a low prevalence of 0.14% (one seropositive in 740 surgeons with no community risk identified). This same finding is demonstrated in prevalence studies from Kinshasa, Zaire (71, 72), where community prevalence of HIV is high (6–8%), infection control practices are limited, and needles and syringes are usually washed by hand, sterilized, then reused. No higher rates of seropositivity were found in the hospital staff, nor were there any significant differences among the medical, administrative, and manual workers (6.5, 6.4, and 6%, respectively). These findings reaffirm the apparent low risk for occupational transmission of HIV.
2.3 Documented Case Studies
Occupational HIV infection following a specific exposure is the best indicator of the mode of HIV transmission in the healthcare setting. Although the risk of occupational HIV transmission appears to be low, case reports of healthcare workers infected with the virus through occupational exposure have been reported. Between 1981 and 1998, 54 healthcare workers in the United States have been documented as having seroconverted to HIV following occupational exposures. Twenty-five have developed AIDS. Individuals who seroconverted include 22 nurses, 19 laboratory workers (16 of whom were clinical laboratory workers), 6 physicians, 2 surgical technicians, 1 dialysis technician, 1 respiratory therapist, 1 health aide, 1 embalmer[sol]morgue technician, and 1 housekeeper[sol]

maintenance worker (4). The modes of transmission in these cases appear to be: 46 percutaneous (puncture[sol]cut injury) exposures, 5 mucocutaneous (mucous membrane and[sol]or skin) exposures to blood, 2 had both percutaneous and mucocutaneous exposure, and 1 unknown. Forty-nine exposures were to HIV-infected blood, 3 to concentrated virus in a laboratory, 1 to visibly bloody fluid, and 1 to an unspecified fluid.

Additionally, 133 other cases of HIV infection or AIDS have been reported among healthcare workers who were found to have no other social risk factors for HIV infection, but who experienced nondocumented occupational exposures to blood, body fluids, or laboratory levels of HIV. These include 33 nurses, 18 clinical laboratory workers, 17 physicians, 15 health aides, 12 paramedics, 10 housekeepers[sol]maintenance workers, 9 technicians, 7 dental workers, 3 dialysis technicians, 2 surgical technicians, 2 embalmers[sol]morgue technicians, 2 respiratory therapists, and 2 others (9).

Worldwide, including the United States, 94 documented and 170 possible occupational HIV infections have occurred among healthcare workers as of September 1997 (73). The United States accounted for 62.9% and Europe for 28.4% of documented and possible cases. Of the European countries, France had the highest number with 14.3% of cases. According to case descriptions, the majority of documented infections occurred among nurses or clinical laboratory workers (70.2%) after contact with infected blood (89.4%) from patients with AIDS (76.5%) by percutaneous exposure (88.3%) during a procedure involving placement of a device in an artery or vein (68%).

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3 Occupational Risk Assessment
Prevalence and epidemiological studies indicate that occupational HIV infection seldom occurs. Documented HIV seroconversion due to exposures demonstrate that an occupational risk of HIV transmission exists. Factors that may contribute to the magnitude of that risk include the type and extent of injury, the body fluid involved, the "dose" of inoculum, environmental factors, and recipient susceptibility. The interactions and additive effect of these factors on the individual laboratory worker are complex and unknown. However, some data are available that can help further define risks associated with several procedures or circumstances. The type, extent, and frequency of occupational HIV-1 exposure are summarized in Table 20.2.

Table 20.2. Summary of Published Prospective Studies of the Risk for Occupational HIV-1 Transmission in the Clinical Setting

Exposure Type	*N* Studies[a]	*N* Exposures	*N* Infected	Infection Rate (%)
Percutaneous	23	6202	20	0.32
Mucous membrane	13	1364	1	0.07
Cutaneous	1	5568	0	0
Routine patient care activities (no exposures)	3	929	0	0

[a] Refer to text for references (N = number of).

3.1 Route and Extent of Exposure
3.1.1 Parenteral Of the 54 occupationally acquired HIV infections reported, 46 (85%) have been

associated with parenteral exposure (needlesticks, cut with contaminated objects, or nonintact skin exposure to blood) (4). In 1995, a case control study described risk factors associated with occupational HIV infection after percutaneous exposures in cases reported from national surveillance systems in the United States, France, Italy, and the United Kingdom (74). The findings indicate an increased risk for occupational infections following a percutaneous exposure if it involved a larger quantity of blood, such as a device visibly contaminated with the patient's blood, or a procedure that involved a large-gauge, hollow-bore needle, particularly if used for vascular access. Other factors associated with increased risk include a source patient in the terminal stage of illness and lack of zidovudine prophylaxis of the healthcare worker (discussed in more detail later).

The best direct measure of risk of HIV transmission from a single exposure is accomplished through prospective cohort studies that document an HIV exposure event with follow-up serological monitoring of the exposed healthcare worker. In 23 prospective studies that have reported 6202 percutaneous exposures in healthcare workers, 20 instances of seroconversion have been documented, for an overall risk of transmission per percutaneous injury from an HIV-infected patient of 0.32% (66, 75–88). The risk of 0.3% is the average of all the types of percutaneous exposures to blood from patients in various stages of HIV infection. Certain factors, discussed below, contribute to a subset of exposures for which the risk is higher than 0.3%.

There have been two cases of HIV transmission from bites reported (89, 90). Both indicated that blood was involved. In one case (90), the biter died of AIDS 13 days after the bite.

3.1.2 Mucous Membrane Four mucous membrane exposures resulting in HIV infection have been reported in healthcare workers (91, 92, 92a), although in both instances, nonintact skin contact with blood could not be ruled out as a route of exposure. One of them was a laboratory worker whose face was splattered with blood when a vacutainer top flew off the tube while she collected blood from a patient. She also reported having acne (91).

Thirteen prospective studies have included mucous membrane exposures in their risk evaluations and have reported only one seroconversion from 1364 exposures (66, 75–77, 79–82, 84–87). Therefore, the risk of transmission of HIV via mucous membrane is extremely low (0.07%), much lower than that of a percutaneous injury: <0.3% per exposure.

3.1.3 Cutaneous The identification of the Langerhans' cell in the subepithelial tissue as a target cell for the HIV (20) has caused concern among some healthcare workers that cutaneous exposure to HIV may result in transmission of the virus via these cells into the body (93). Infection of the Langerhan's cells is usually a consequence of septic HIV infection (20). Enormous protection against all pathogens is provided by intact skin; however, penetration of the skin into the subepithelial tissues and subsequent inoculation of the Langerhan's cells might occur during a needlestick or cut injury, or other breaks in the skin (94).

One reported case of HIV transmission via skin contact has been reported in a mother caring for her HIV-infected child (95). Although no specific cuts, punctures, or splashes were noted, the mother reported that she used no barrier precautions such as gloves or gowns, and did not always wash her hands after caring for her child. She frequently handled blood and bloody body fluids. It is likely that tiny cuts on the skin may have actually been the route of transmission of the virus.

A report of a laboratory worker infected with a laboratory strain of HIV (60) considered the source of that exposure to be “contact of the individual's gloved hand with H9/HTLV-III$_B$ culture supernatant with inapparent and undetected exposure to skin.” The subject worked with concentrated HIV and reported wearing gowns and gloves routinely. The subject admitted episodes when pinholes or tears in gloves required that they be changed. The subject also related accounts of leakage of virus-positive culture fluid from equipment, and the subsequent decontamination efforts with a hand brush. The subject also recalled an episode of nonspecific dermatitis on the arm that was always

covered by a gown.

A subgroup of 98 other laboratory workers who also worked with concentrated HIV were seronegative. An incidence rate of 0.48 per 100 person-years of exposure has been calculated for prolonged laboratory exposure to *concentrated* virus, approximately the same magnitude of risk of infection as healthcare workers who experience a needlestick HIV exposure (60). Over a 45-year career, this rate would lead to a risk of 195 infections per 1000 exposed workers in research and production facilities.

Three prospective studies have reviewed the risk of HIV transmission as a result of routine patient care activities without a known percutaneous or mucous membrane exposure (66, 81, 96). None of the 929 healthcare workers studied has been infected. Henderson et al. (77) summarized a 6-year, ongoing study of the risk of HIV transmission to healthcare workers sustaining a variety of occupational exposures, including cutaneous exposure. Responding to a questionnaire, 149 National Institute of Health workers reported 5568 cutaneous exposures to blood or other body fluids from HIV-infected patients or their specimens and more than 10,000 cutaneous exposures to blood from all patients. No seroconversion occurred from these exposures despite the high frequency of occurrence, confirming the lack of evidence of any measureable risk of transmission of HIV by cutaneous exposure in a clinical setting.

3.1.4 Other Routes of Exposure There have been no documented cases of HIV transmission through the respiratory, ingestion, or vector route of exposure. Some have questioned the possibility of respiratory transmission of HIV (97), specifically with the research laboratory-acquired infection with no documented percutaneous exposure (60). It is well known that common laboratory procedures using blenders and centrifuges have been evaluated and shown to produce infectious aerosols. Prior to the CDC and NIH recommendations for biological containment in laboratories, agents such as rabies (98), which are not transmitted by aerosols in the community or clinical setting, were documented to cause infection under laboratory conditions when *concentrated* agents were aerosolized by blending or purification procedures. The reported laboratory worker infected with the laboratory strain of HIV may have been exposed to aerosols released during reported rotor-seal failures involving the continuous-flow zonal centrifuge.

However, an expert safety review team convened by the Director of NIH addressed this issue and agreed that the potential for direct contact transmission was much greater than for aerosol transmission (100). Procedures that generated aerosols were carried out in biological safety cabinets. They cite other instances involving overt aerosol exposure in laboratory and production facilities involving concentrated HIV that have not resulted in seroconversions in exposed workers (100). Nevertheless, the occurrence of infection through an unknown exposure emphasizes the need for laboratory workers, particularly in research or production facilities, to strictly adhere to published safety guidelines.

The potential for respiratory transmission of HIV in individuals performing aerosol-producing procedures in a clinical setting (e.g., surgery, dentistry) has also been raised (93, 97). No epidemiological information supports this theory. In fact, several studies have shown a low prevalence of HIV infection in dentists who are routinely exposed to aerosolized body fluids (64, 65, 68, 101, 102). Likewise, surgeons are not overrepresented in the reported AIDS cases compared with other healthcare workers (4).

Johnson and Robinson (97) demonstrated that HIV can remain viable in cool vapors and aerosols generated by common surgical power instruments, but not in the heated vapors produced from electrocautery. In a companion study, Heinsohn et al. (103) demonstrated that aerosols of nanometer and micrometer sizes are produced by the instruments. Questions remain as to whether any respirable-size particles generated contain viable HIV and if there exists an infectious dose required for aerosol transmission of HIV.

3.2 Other Factors

3.2.1 Viral Concentration The transmission of HIV and subsequent infection may also depend on the "dose" of the virus present at time of exposure. The dose is determined by the size of the inoculum or the concentration of virus in the inoculum. The dose of HIV required to infect humans is unknown. Fultz et al. (104) studied the infection of chimpanzees with HIV-1 and found that those receiving >1 $TCID_{50}$ by intravenous injection were persistently infected for up to 18 months. Chimpanzees inoculated with low doses (0.1 $TCID_{50}$) did not become infected, suggesting that immune systems can contain small inocula of virus.

A large inoculum of HIV-infected blood such as a unit of transfused blood carries a higher likelihood of virus transmission. Donegan et al. (105) examined recipients of infected blood units with no other risk factors for HIV infection and found 89.5% were seropositive. Ho et al. (22) estimates that 250 mL of HIV-contaminated blood contains 10^4–10^6 $TCID_{50}$ of HIV. In contrast, a much lower risk is associated with occupational exposures (0.3%) in which the amount of blood involved is unknown, but calculated by Ho to contain 0.06–7 $TCID_{50}$ of HIV.

A risk factor for occupational HIV infection identified by a CDC case control study (74) was injury with a large-gauge, hollow-bore needle, which may be directly associated with the amount of blood exposure. This is consistent with laboratory studies that have indicated that less blood is transferred by suture needles (solid bore) than by phlebotomy needles (hollow-bore) of similar diameter (106, 107).

The concentration of virus in blood or body fluid is dependent on the stage of the patient's illness and the antiviral treatment of the patient (21, 22). In the CDC case control study of occupationally acquired HIV infections transmitted by percutaneous injury, a factor associated with increased risk of infection was exposure to a source patient in the terminal stage of illness (74), and may have a direct association with the amount or dose of virus present at the time of exposure. Saag et al. (21) evaluated the plasma viremia levels in patients infected with HIV and found that (*1*) none of the asymptomatic adults, (*2*) 12% of adults with AIDS-related complex, and (*3*) 93% of AIDS patients had cell-free infectious virus in their plasma. Titers of the virus ranged from 10 to 10^8 TCID/mL of plasma, with a mean of $10^{2.8}$ TCID/mL in patients with AIDS. Patients with acute HIV infection had viral titers of 10–10^3 TCID/mL.

Saag et al. (21) also found that therapy with zidovudine (AZT) led to a significant decline in titer. Ho et al. (22) found a 25-fold lower titer mean in AIDS patients treated with AZT versus untreated AIDS patients. Reverse transcriptase inhibitors, such as AZT, and protease inhibitors protect uninfected cells from becoming infected and, therefore, reduce the viral burden in patients' blood (108).

Research or production laboratory workers, by the nature of the work performed, are placed at greater risk because of the high viral concentrations in culture (>10^8 TCID/mL). Published recommended barrier protection and precautions developed by NIH and CDC reduce worker exposure to high risk operations (6, 109, 110).

3.2.2 Specimen Age The length of time the blood has been removed from the source prior to exposure may also influence the number of infectious viruses present in the inoculum. Although most occupational infections have occurrred after exposure to "fresh" blood, HIV has demonstrated stability in the environment in both liquid and dry states (34), and may survive for hours to days at room temperature.

3.2.3 Other Other factors contributing to the overall risk of HIV transmission may include the virulence of the viral strain (111), post exposure first aid or prophylactic practices, or inflammation around the exposure site (numbers of CD4[plus] cells available) (77). Other healthcare-worker-

related factors contributing to risk are skin integrity and immunological status (66). Pinto et al. (112) demonstrated that parenteral exposure to HIV can induce cell-mediated immune response in the absence of seroconversion. It is possible that this immune response is protective against a low HIV infection, and may contribute to the low infectivity rates of healthcare workers.

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4 Hepatitis Viruses
At the time of writing, at least six viruses are known to cause hepatitis: hepatitis A, B, C, D, E, and G. Epidemiologically, the viruses can be divided into two groups according to mode of transmission. The hepatitis A and E viruses are transmitted primarily by the fecal–oral route. The hepatitis B, C, D, and G viruses are transmitted by direct contact with blood or body fluids. Hepatitis B and C viruses are frequently responsible for occupational infections.
4.1 Hepatitis B Virus (HBV)
Hepatitis B virus is transmitted parenterally, sexually, and perinatally, and is the major cause, worldwide, of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma. High risk groups in industrialized countries include intravenous drug users, homosexual men, and those with multiple sexual partners (113). Others at substantial risk of infection include hemodialysis patients, institutionalized patients, and healthcare workers with occupational exposure to blood (114).

Healthcare personnel have been known to be at greater risk for HBV infection than the general population (115, 116). The incidence of clinical cases of hepatitis B in healthcare workers before the availability of the hepatitis B vaccine (*i.e.*, before 1982) was reported to be between 50 and 120 per 100,000 (117, 118), much higher than that of the general population of <10 cases per 100,000 (114). Level of risk was related to several factors, including the frequency of exposure to blood, body fluids, or blood-contaminated sharps; the duration of employment in a high risk occupation where blood exposure was common; and the underlying prevalence of HBV infection in the patient population. High prevalence of infection was found in occupations associated with the emergency department, laboratory, blood bank, intravenous team, and the surgical house officers (119).

Since 1982, changes in infection control practices, including the recommendation in 1987 of "universal precautions" (6), and the availability of the hepatitis B vaccine to at-risk workers have undoubtedly been responsible for the decline in the numbers of occupational hepatitis B infections (120). The proportion of reported hepatitis B cases associated with healthcare workers has declined from 4% in 1982 to 1% in 1988. The annual number of new HBV infections in healthcare workers has steadily declined from 12,000 in 1985 to 1000 in 1994 (121). Several reports from university hospitals confirm the decline after initiation of the hepatitis B immunization programs. Lanphear et al. (122) reported a decline in clinical hepatitis B in healthcare workers from 82 cases per 100,000 in 1980–1984 to no cases between 1985 and 1989. At Duke University, the number of cases of clinical hepatitis B in hospital employees has declined from 2 cases per 1000 in 1979 to none since 1992, with a vaccine acceptance rate of 90% (122a).
4.2 Hepatitis C Virus (HCV)
Choo et al. (123) discovered the hepatitis C virus (HCV) genome in 1989 and developed a serological test for the agent. Since then, HCV has been found to be the primary agent of parenterally transmitted non-A, non-B (NANB) hepatitis and a major cause of acute and chronic hepatitis throughout the world (124). High rates of HCV infection occur in intravenous (iv) drug users, where it has been estimated that two-thirds of addicts are anti-HCV seropositive within 2 years of regular use of IV drugs, increasing to close to 100% seropositivity after 8 years (125). Other groups at high or moderate risk include patients with repeated direct exposures to blood such as hemodialysis patients (126) and hemophiliacs (127). Lower rates are found in those with inapparent parenteral or mucosal exposures such as sexual contacts of infected persons (128) or transmissions

from mother to infant (129). Blood transfusions have transmitted the virus. Before testing of the virus was available in 1989, the risk of HCV infection per unit was 0.45%; after antibody testing became available, 0.06% (130).

Although HCV transmission occurs in the healthcare setting, the seroprevalence rate in workers is only slightly higher than the corresponding general population. In general, most studies document an HCV seroprevalence of between 1 and 2.8% for healthcare workers compared with the rate of 0.3–1.5% in blood donors (the community rate) (131).

Prospective studies that record seroconversions after documented percutaneous exposures indicate the risk of HCV infection after a single injury to a healthcare worker can range from 0.75% (132) to 10% when PCR methodologies are used to determine HCV-RNA (133). The wide range of risk reflects the differences in study design, diagnostic tests used, number of cases followed, source patient status, and community prevalence. In general, after pooling data from 9 published prospective studies, a risk of 2.5% after a percutaneous injury is a reasonably accurate estimate (132).

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5 Relative Risks for Occupational Infection
The anxiety surrounding HIV in the laboratory setting has been partially due to the historical problem of occupational hepatitis B infection and its designation as a model for transmission of a bloodborne pathogen. In the early 1980s, the CDC estimated that 12,000 healthcare workers became occupationally infected with hepatitis B each year, resulting in over 250 deaths (134). In contrast, the total number of occupationally acquired HIV infections in 17 years is estimated to be 187 (54 documented, 133 possible), an average of approximately 10 per year.

The risk of hepatitis B infection following a single parenteral exposure to hepatitis B surface antigen–positive blood (6–30%) (135) is much higher than the risk of HIV infection from a similar exposure to HIV–infected blood (0.3%). The risk of hepatitis C infection from a single percutaneous exposure to antihepatitis C–positive blood is approximately 2.5% (131). The differences in transmission rates correlate directly with average titers of the viruses found in infected sources. Viral titers of hepatitis B during the acute stage of disease can reach 10^2–10^8 viral particles per milliliter of blood (136, 137), hepatitis C titers generally reach 10–10^6 viral particles per milliliter (137), and HIV titers average around 10–10^3 viral particles per milliliter (22).

Although hepatitis B transmission rates are higher than other bloodborne pathogens in the occupational setting, it is generally a self-limiting disease in the general population (only 5% develop chronicity) and is entirely preventable with vaccination for workers at risk. The chronic nature of hepatitis C and HIV infection increases the reservoir of infected sources in the population and the potential for exposures.

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6 Other Bloodborne Pathogens
6.1 Retroviruses

Since 1980, five types of human retroviruses have been isolated: HTLV-I, HTLV-II, HIV-1 (formerly HTLV-III), HIV-2 (formerly HTLV-IV), and HTLV-V. On the basis of morphological features and molecular hybridization studies, HTLV-I, II, and V are classified as oncornaviruses and are associated primarily with malignancies such as leukemia and lymphoma. HIV-1 and HIV-2 have likewise been classified together as lentiviruses (16) and cause cell lysis and death.

6.1.1 Human T-Lymphotropic Virus Types I and II (HTLV-I, HTLV-II) The HTLV-I and -II viruses are classified as oncornaviruses and are associated with malignancies such as leukemia and lymphoma. The HTLV-I was the first human retrovirus to be isolated (14), and is a cause of adult T-cell leukemia–lymphoma, and tropical spastic paraparesis (138). The seroprevalence of the virus is 1.4 per 10,000 in screened blood donations in the United States (139). HTLV-I is transmitted as other bloodborne pathogens, namely, sexual contact, perinatally, and through contaminated blood. One occupational transmission has been reported in a healthcare worker from Japan who was caring for a patient with adult T-cell leukemia–lymphoma (140).

In 1982, a related virus, HTLV-II, was isolated from a patient with a T-cell variant of hairy cell leukemia (141). The epidemiology of HTLV-II is not as well defined as HTLV-I because of the lack of a specific screening test. However, when specific DNA amplification tests were performed in one study, a risk factor of IV drug use was associated with HTLV-II seropositivity (142).

6.1.2 Human Immunodeficiency Virus, Type 2 (HIV-2) In 1986, a second human retrovirus capable of causing AIDS was isolated from patients of western African origin (143). Originally named human T-lymphotropic virus type IV (HTLV-IV) and later renamed HIV-2, the virus is endemic to western Africa, where it is the dominant HIV. Because of the high incidence of HIV-2 in this region, but low rate of AIDS, there is speculation that the ability of this virus to cause disease is less efficient than HIV-1 (144).

In June 1992, the U.S. Food and Drug Administration recommended screening all blood and blood products with the combined HIV-1/HIV-2 enzyme immunoassay (145). Only a few cases of HIV-2 have been detected among the blood donations in U.S. blood centers, and most of them have been from donors with western African association (146).

HIV-2 seems to be transmitted in the same way as HIV-1. As of 1988, no occupational infections have been documented, although there is documentation of parenteral transmission through IV drugs and blood transfusions (147).

6.1.3 Human T-Lymphotropic Virus, Type V (HTLV-V) The HTLV-V is the designation given to an apparently new retrovirus isolated from a cluster of patients in southern Italy with a clinical syndrome resembling mycosis fungoides. This virus is significantly cross-reactive with and genetically related to HTLV-I (16). As with HIV-2 and HTLV-II, there is a lack of epidemiological data regarding HTLV-V.

6.2 Other Pathogens

Concern over laboratory-acquired infections has focused on HIV and the hepatitis viruses. Several other infectious agents may not be included under the category of classic “bloodborne pathogens,” but may warrant mention because of the potential for occupational transmission because: (*1*) the agents may be found in high titers during the septic phases of their disease processes, (*2*) rates of community infections may be increasing and thus provide a larger reservoir for exposure, or (*3*) occupational infections may not be recognized or diagnosed because of the unusual route of exposure.

No published information is available regarding the risk of occupational transmission of any of these agents; however, documented cases of occupational parenteral transmission or transmission through blood transfusions has been recorded in the literature.

Many of the agents are rarely found in the United States and may not pose a significant risk at this

time. For example, Chagas disease is endemic in Latin America where blood transfusions frequently transmit the trypanosomes. However, Kerndt et al. (148) discovered a 2.4% seropositivity rate in Los Angeles after testing over 1000 blood donations.

Treponema pallidum, the causative agent of *syphilis*, is found in highest numbers during the secondary, hematogenous stage, but is also found intermittently in blood if syphilis is left untreated. During 1990, the rate for primary and secondary syphilis in the United States (20.3 per 100,000) was the highest since the 1940s (149). Outbreaks have been linked epidemiologically to increased crack-cocaine use and HIV infection. The increasing numbers of patients with syphilis and HIV increases the possibilities for occupational exposures and infection. Nosocomial transmission of syphilis has occurred by needlesticks, blood transfusions, and tattooing (150, 151).

Few agents have been implicated in documented occupational infections with clinical exposures, but the amount of infectious agents present during septic phases of infection indicate the real potential for percutaneous transmission. For example, *Babesia microti* is present in 30–85% of peripheral red blood cells during the parasitemia stage of infection (152), and has been transmitted through blood transfusions (153, 154). In acute *Brucella melitensis* infections, 70–90% of blood cultures will grow the organism (155, 156). Human parvovirus B19 can demonstrate a high viral titer (10^{10} virions/mL) during a brief viremic stage (157), and has been transmitted through blood transfusions. In fact, Barbara and Contreras (157) estimated that up to 90% of recipients of factor VIII are likely to be seropositive for parvovirus B19, the causative agent of erythema infectiosum, also known as "fifth disease."

Amplification of some bloodborne agents in the laboratory environment has resulted in laboratory-acquired infections due to contact with higher doses of agent than is found in clinical situations. Examples include Arboviruses (158) or *Leptospira sp.* (151). In many of the reported laboratory-acquired cases, no specific incident for exposure could be recalled. Rather, the worker simply "worked with the agent" (151, 158), implying either aerosolization of high titers of organisms or inadvertant inoculation of mucous membranes or nonintact skin by contaminated hands. Most of the agents caused an occupational infection prior to the publication of the standard laboratory containment guidelines (159) designed to protect laboratory workers from aerosols, splashes, and other hazardous exposures.

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7 Strategies for Infection Prevention
Within one year of the first recognized cases of the newly defined disease, AIDS, the CDC issued guidelines (160) for clinical and laboratory staff regarding appropriate precautions for handling specimens collected from AIDS patients. Later, the CDC reemphasized precautions that had been recommended previously for handling specimens from patients known to be infected with hepatitis B, specifically, minimizing the risk for transmission by the percutaneous, mucous membrane, and cutaneous routes of infection. After anecdotal laboratory-associated infections with HIV reports of the CDC issued its first agent summary statement for work with HTLV-III/LAV in 1986 (100). The statement included a summary of laboratory-associated infections with HTLV-III (HIV), the hazards that might be encountered in the laboratory, and advice on the safety precautions that should be taken by laboratories. Biosafety level 2 precautions were recommended for work with clinical specimens, body fluids, or tissues from humans or laboratory animals *known or suspected to contain* HTLV-III/LAV (HIV). Biosafety level 3 additional practices and containment equipment were recommended for activities involved with culturing research laboratory-scale amounts of the virus. A biosafety level 3 facility and biosafety level 3 practices and procedures were recommended for all

work involving industrial-scale, large-volume concentrations of the virus (see Table 20.3).

Table 20.3. CDC/NIH Recommended Precautions for Laboratory Work with HIV-1[a]

Facility	Practices and Procedures	Activities Involving
BL2	BL2	Clinical specimens
		Body fluids
		Human/animal tissues infected with HIV
BL3	BL3	Growing HIV at research lab scale
		Growing HIV-producing cell lines
		Working with concentrated HIV preparations
		Droplet/aerosol production

[a] Refer to text for references (BL = biosafety level).

Reports issued by CDC (91) in May 1987 documented that laboratory workers and other clinical staff were occupationally infected with HIV via nonintact skin and mucous membrane exposures. Because the HIV serostatus of the patient sources were unknown at the time of exposure and the exposures were nonparenteral, the CDC issued the "universal blood and body fluid precautions" recommendations in August 1987 (6). The major premise involved the *careful* handling of all blood and body fluids as if *all* were contaminated with HIV, HBV, or other bloodborne pathogens. This "universal precautions" concept formed the basis for all subsequent recommendations from CDC (109, 134) and other professional organizations such as the National Committee for Clinical Laboratory Standards (NCCLS) (161).

The counterpart of universal precautions in a laboratory situation involves the *consistent* use of biosafety level 2 facilities and practices as outlined in the CDC/NIH manual, *Biosafety in Microbiological and Biomedical Laboratories* (110). The biosafety level 2 precautions are most appropriate for clinical settings or when exposure to human blood, primary human tissue, or cell cultures is anticipated. Standard microbiological practices form the basis for biosafety level 2 with additional protection available from personal protective equipment (PPE) and biological safety cabinets (BSCs) when appropriate.

In 1988, two reports of research laboratory workers with documented occupational HIV infection prompted an investigation by an expert team to review possible sources of exposure and any need to revise current practices to reduce hazards in the research laboratory (99). Subsequently, an agent summary update was issued and included in the 1988 edition of *Biosafety in Microbiological and Biomedical Laboratories* (162). The expert team did not advise alteration of the CDC/NIH biosafety recommendations for laboratories, but stressed the need for reinforcement of safety practices through proficiency and administrative discipline.

In addition to the advisory nature of the CDC/NIH guidelines, the federal Occupational Safety and Health Administration (OSHA) issued a final standard to regulate occupational exposure to bloodborne pathogens (163). The standard builds on the implementation of "Universal Precautions" specifying the need for control methods, training, compliance, and recordkeeping.

OSHA also recognized that employees in HIV/HBV research laboratories and production facilities may be placed at a higher risk of infection following an exposure because of the concentrated

preparations of viruses. Requirements for practices and special procedures, facility design, and additional training for these workplace situations are included in the OSHA standard and are consistent with the CDC/NIH laboratory biosafety guidelines for biosafety levels 2 and 3.

7.1 Specific Precautions

OSHA has issued the bloodborne pathogen standard as a "performance" standard. In other words, the employer has a mandate to develop an exposure control plan to provide a safe work environment, but is allowed some flexibility in order to accomplish this goal. OSHA embraces the basic philosophy of the CDC "universal precautions," and marries it with combinations of engineering controls, work practices, and personal protective equipment in order to accomplish the intent of the standard.

Recognizing the risks inherent in needlestick and sharps exposures, OSHA recently (at time of writing) introduced the Healthcare Worker Needlestick Injury Prevention Act of 1999 (164). The bill would amend the federal Bloodborne Pathogens Standard to require that employers utilize needleless systems and devices with engineered sharps protections to prevent occupational exposure to bloodborne pathogens. It also enhances needlestick reporting requirements and establishes a national clearinghouse to collect data on safety devices. Four states have already adopted revised bloodborne pathogens regulations requiring the use of safety devices as of August 1999: California, Maryland, Texas, and Tennessee.

Exposure control plans for laboratories must adhere to the rules of the OSHA standard, but can also benefit from safety recommendations from other professional organizations such as CDC, NIH, or NCCLS (National Commitee for Clinical Laboratory Standards). Specific rules and recommendations that might augment a laboratory safety plan are worth noting.

7.1.1 Sharps Precautions Since injuries from contaminated sharps represent the highest risk for HIV transmission, clinical and research laboratory safety plans should restrict the use of needles and other sharp instruments in the laboratory for use only when there is no alternative, such as performing phlebotomy. For laboratory procedures, other means should be considered to achieve the job, such as the use of blunt cannulas or small-bore tubing. If needles must be used, investigate the use of "self-sheathing" needles or "needleless" systems that have recently been designed to prevent needlesticks.

Used needles should never be bent, broken, recapped, removed from disposable syringes, or otherwise manipulated by hand before disposal; rather, they should be carefully placed in conveniently located puncture-resistant containers (110). Removal of needles from nondisposable vacutainer sleeves or syringes should be accomplished with a mechanical device such as forceps or hemostats, or by using notched slots designed into needleboxes for safe removal of the needle. The OSHA standard allows a "one-handed" recapping technique only if there is no alternative feasible. All disposable sharps encountered in the laboratory, including pipettes, microtome blades, micropipette tips, capillary tubes, and slides, should also be carefully placed in conveniently located puncture-resistant containers for disposal. Nondisposable sharps should be placed in a hard-walled container for transport to a processing area.

Plasticware should be substituted for glassware whenever possible. Broken glassware should never be handled directly by hand, but must be removed by mechanical means such as a brush and dustpan, tongs, or forceps. Cotton swabs can be used to retrieve small slivers of glass.

7.1.2 Engineering Controls Recognizing that human behavior is inherently less reliable than mechanical controls, OSHA advocates the use of available technology and devices to isolate or remove hazards from the worker. The use of "self-sheathing" needles is an example of an engineering control to help isolate the worker from the hazard of needlestick exposure.

Another engineering control in the laboratory is the use of a properly maintained biological safety cabinet (BSC) to enclose work with a high potential for creating aerosols or droplets, namely, blending, sonication, necropsy of infected animals, intranasal inoculation of animals, or opening lyophilized vials under pressure. *All* work with infectious material in an HIV research laboratory

should be performed in a BSC or other physical containment device. For example, high energy activities such as centrifugation that are performed outside a BSC should be designed for aerosol containment. Sealed safety cups or rotors should be used for centrifugation, and changed out in a BSC. Before centrifugation, tubes should be examined for cracks, and any glass fragments in the centrifuge cups should be carefully removed with forceps or hemostats. Microwell plate lids can be sealed with tape or replaced with adhesive-backed Mylar film prior to centrifugation.

Plastic shielding can be used to reduce the exposure to splatter or droplets from fluorescent activated cell sorters or other automated laboratory equipment that might generate droplets of infectious material. Likewise, the plexiglass radiation shield used in reverse transcriptase assays offers protection from splatter. However, if used in a BSC, the sloped top may divert airflow in the cabinet, and must be removed to provide optimal protection by the BSC.

High speed blenders and grinders are available that contain aerosols of infectious material, and need to be opened in a BSC after processing. Enclosed electrical incinerators are preferable to open Bunsen burner flames for decontaminating bacteriological loops to prevent splatter, and may be used within or outside a BSC.

7.1.3 Work Practice Controls The manner in which a task is performed can minimize the likelihood of exposures in the laboratory. For example, careful disposal of used needles without recapping or otherwise manipulating by hand can reduce the likelihood of needlesticks.

Standard microbiological practices have been recommended by CDC and NIH guidelines for all laboratory containment levels (110). Most of the practices are designed to prevent indirect transmission of infectious material from environmental surfaces to the hands, and from hands to the mouth or mucous membranes. Such practices include prohibition of mouth pipetting, eating, drinking, smoking, applying cosmetics, or handling contact lenses in the laboratory, and attention to environmental decontamination.

One of the best work practices for any laboratory setting is that of frequent and adequate handwashing when hands are visibly contaminated, after completion of work, before leaving the lab, after removing gloves, and before eating, drinking, smoking, or changing contact lenses. Any standard handwashing product is adequate, but products should be avoided that disrupt skin integrity. When knee- or foot-pedal-controlled faucets are not available, faucets should be turned off by using paper towels used to dry hands to prevent recontamination of hands. Proper attention to handwashing will prevent inadvertant transfer of infectious material from hands to mucous membranes.

In clinical settings, skin lesions may be covered by occlusive dressings and, if lesions are on the hands, gloves worn over the dressings to prevent contamination of nonintact skin. However, workers with skin lesions or dermatitis on hands or wrists should not perform procedures with concentrated HIV material even if wearing gloves. Other work practices can reduce the amount of splatter from laboratory procedures. Covering pressurized vials with plastic-backed or alcohol-soaked gauze when removing needles or when removing tops of pressurized vacutainer tubes will minimize the exposure to splatter. To prevent popping stoppers on evacuated tubes or vials, blood should never be forced into the tube by exerting pressure on the syringe plunger; rather, tubes and vials should be filled by internal vacuum only. Extreme caution should be used when handling pressurized systems such as continous-flow centrifuges, apheresis, or dialysis equipment. Use of imperviously backed absorbent material (“lab diapers”) can reduce the amount of splatter on laboratory work surfaces when liquids accidentally leak or fall during lab procedures and can aid in laboratory cleanup. Remember to keep the air-intake and exhaust grilles in BSCs clear of any surface covers or equipment.

Safe transport of specimens or infectious material within the laboratory or to other areas can minimize the potential for accidental spills or injuries. Specimens should be contained in a closed, leakproof primary container, and placed in a secondary container (*i.e.*, a plastic bag) to contain leaks during transport. OSHA regulations do not mandate labeling or color-coding specimens if the

specimens are handled only within the facility, a policy implementing "universal precautions" is in effect, and the containers are recognizable as human specimens. Bulk samples may be safely transported in a rack within a sealable plastic container such as a modified "tackle box." The box may need to be labeled with a biohazard symbol or color-coded if the contents are not clearly visible as specimens. Luer caps should be used to transport syringes (needles removed with forceps or hemostats and properly disposed) or needles carefully recapped using a one-handed technique. Capillary tubes should be transported in a solid-walled secondary container such as a screw-top test tube. Transport of cultures or hemocytometers from the BSC within the laboratory may be facilitated by placing them on a tray to limit the number of trips and opportunities for spillage.

Designation of "clean" versus "dirty" areas of the laboratory or within BSCs can help to prevent inadvertent contamination. Work should be planned to move from clean areas to dirty areas. Routine cleaning of work surfaces must be done after procedures are completed and at the end of each workshift, with additional decontamination as needed for spills. Routine cleaning can be accomplished using a variety of disinfectants, including iodophors registered as hard-surface disinfectants, phenolics, and 70% ethanol [with consideration given to the need for longer contact time when decontaminating dried viral cultures (165)]. Diluted bleach has been most widely used for routine disinfection [10% bleach (0.5% sodium hypochlorite) for porous surfaces and 1% bleach (0.05% sodium hypochlorite) for cleaned, hard, and smooth surfaces]. Aldehydes are not recommended for surfaces because of their potential toxicity.

Prompt decontamination is important following spills of infectious materials, since HIV is able to survive for several hours in the environment (see Table 20.1). Appropriate spill cleanup in a clinical setting should involve the following steps:

1. Absorb the spill with towels or "lab diapers" to remove the extraneous organic material.
2. Clean with soap and water.
3. Decontaminate with an appropriate disinfectant [CDC recommends an EPA-registered "hospital disinfectant" that is also "tuberculocidal" or, a 1–10% bleach solution is sufficient (6)].

Large spills of cultured or concentrated agents may be safely handled with an extra step:

1. Flood the spill with an appropriate disinfectant *or* absorb the spill with granular material impregnated with disinfectant.
2. Carefully soak up the liquid material with absorbent material (paper towels), or scrape up the granular absorbent material and dispose of according to the waste-disposal policy.
3. Clean the area with soap and water.
4. Decontaminate with fresh disinfectant.

Laboratory equipment (analyzers, centrifuges, pipettors) should be checked routinely for contamination and appropriately decontaminated. Any equipment sent for repair must also be decontaminated before leaving the laboratory, or labeled as to the biohazard involved.

Because the intent of the OSHA Bloodborne Pathogen Standard is worker protection, the rules for appropriate waste disposal emphasize adequate packaging. Sharps disposal containers must be puncture- and leakproof as well as easily accessible. Other "infectious" or "medical" waste must be placed in leakproof containers or bags that are color-coded red or orange, or labeled with the word "biohazard" or the universal biohazard symbol. All disposal containers should be replaced before they are full.

Blood or body fluids may be disposed of by carefully pouring down the sanitary sewer if local health codes permit, but not poured into a sink where handwashing is performed. Liquid and solid culture materials, however, *must* be decontaminated before disposal, most commonly by steam sterilization

(autoclaving). Tissues, body parts, and infected animal carcasses are generally incinerated. *All* laboratory waste from HIV research-scale laboratories or production facilities and animal rooms must be decontaminated before disposal (biosafety level 3 practices). Additional "medical" or "infectious" waste definitions and requirements may exist locally and must be consulted for proper disposal policies.

7.1.4 Personal Protective Equipment (PPE) Another strategy to minimize worker exposure to infectious material is the use of PPEs that are appropriate for the laboratory procedure and the type and extent of exposure anticipated. Examples include a variety of gloves, gowns, aprons, and face, shoe, and head protection. Personal protective equipment may be used in combination with engineering controls and/or work practices for maximum worker protection.

Gloves are required by OSHA when hand contact with blood, other potentially infectious materials, mucous membranes, or nonintact skin is reasonably anticipated. The federal regulations also require gloves when handling or touching contaminated items or surfaces, and for performing vascular access procedures. Gloves are appropriate in the laboratory when handling clinical specimens, infected animals, or soiled equipment, when performing all laboratory procedures in research laboratories, cleaning spills, and handling waste.

For routine procedures, vinyl or latex gloves are effective when appropriately used for prevention of skin exposure to infectious materials. Gloves are not intended to prevent puncture wounds from needles or sharps. However, evidence of a "wiping" function exists that may reduce the amount of blood or infectious material exposure from the outside of the needle as it penetrates a glove or combination of gloves. Johnson et al. (166) found that two or three layers of latex gloves appeared to reduce the frequency of HIV-1 transfer by surgical needles to cell cultures. They also found that Kevlar gloves (untreated), Kevlar gloves (treated with the virucidal compound, nonoxynol-9), and nonoxynol-9-treated cotton gloves used as intermediate layers between two layers of latex gloves significantly reduced the amount of HIV-1 transfer when compared with a single latex glove barrier. Gerberding et al. (167) reported that when surgeons wear double gloves, the rate of puncture of the inner glove is 3 times less than the rate of puncture of a single glove.

Other gloves are available that provide puncture "resistance" such as stainless-steel mesh (chain mail) gloves to protect against injury from large sharp edges such as knife blades. Nitrile gloves (synthetic rubber) have some degree of puncture resistance that may eliminate problems with rings or fingernails, yet retain the necessary dexterity required for performing laboratory procedures. A thin leather glove has been developed that can be worn under latex gloves for an an additional barrier against needlesticks or animal bites. Even heavyweight utility gloves (dishwashing gloves) provide extra protection and should be worn when the procedure permits, such as cleaning contaminated equipment or spills.

Undetected physical holes and leaks require that gloves be frequently inspected and changed. The U.S. Food and Drug Administration (FDA) has issued acceptable quality limits (AQLs) for defects at 2.5% defective for surgeons' gloves and 4.0% for latex exam gloves (168), although the AQL varies widely among manufacturers. The reported percentage defective due to holes for nonsterile latex gloves ranges from 0 to 32%; for nonsterile vinyl gloves, from 0 to 42% (161). Clearly, for high risk situations such as gross contamination of gloves with blood, bloody body fluid, or high concentrations of HIV-1, the use of double gloves will lower the risk of hand contamination from seepage through undetected glove defects. Although they are more puncture-resistant, nitrile gloves are designed to tear apart when any pressure is applied to a hole in the glove, so that any violation of the glove will be detected.

Gloves must never be washed or disinfected for reuse. Detergents may cause enhanced penetration of liquids through undetected holes causing a "wicking" effect (134, 161). Disinfectants, such as 70% ethanol, can also enhance the penetration of the glove barrier and facilitate deterioration (161, 169).

Gloves must be changed when visibly contaminated, torn, or defective, or when tasks are completed. Since hands may be inadvertently contaminated from laboratory surfaces, gloves should be removed before handling telephones, doorknobs, or “clean” equipment. Alternatively, “dirty” equipment may be designated and marked to be handled only with gloved hands. Laboratory workers should practice the aseptic technique for glove removal, specifically, the contaminated side remains on the inside as gloves are removed to protect the worker from skin contamination. Hands should always be washed after glove removal.

When soiling of clothing is anticipated, laboratory coats, gowns, or aprons are recommended. However, when a potential for splashing or spraying exists, solid-front, fluid-resistant gowns are appropriate. If the anticipated exposure involves soaking, solid-front fluidproof gowns are required, as well as hoods/caps, facial protection, and shoe covers. Biosafety level 3 practices advise a solid-front or wraparound, long-sleeved gown or coveralls for adequate protection in research laboratories or production facilities.

Gowns with tightly fitting wrists or elasticized sleeves should be worn for work in BSCs. Alternatively, water-resistant “gauntlets” that provide a barrier between the glove and the laboratory coat are available to reduce skin exposure of the wrist and arm.

Laboratory coats or gowns should not be worn outside the laboratory. In HIV-1 research laboratories or production facilities, the gowns or other protective clothing must be decontaminated before laundering or disposal (BSL-3 practices).

When splashing of blood or infectious material into the mucous membranes of the face is anticipated, a mask and goggles or faceshield must be used. Most laboratory procedures involving this degree of exposure should be conducted within containment equipment such as a BSC. Face protection might be needed for activities conducted outside a BSC, such as performing an arterial puncture, removing cryogenic samples from liquid nitrogen, or in some animal care areas. Masks and eye goggles or faceshields also serve a passive function as a means of preventing accidental contact of contaminated gloved hands with the eyes, nose, and mouth during the course of work activities.

Whatever the PPE needs of any particular laboratory, OSHA requires that the employer provide an adequate supply of PPEs in the appropriate sizes. Hypoallergenic gloves must be available for employees who develop allergies to glove material or the powder inside gloves. Any defective PPE must be replaced, and reusable protective clothing must be laundered and maintained by the institution. Finally, all laboratory workers must be instructed in the proper use of PPEs and their location.

7.2 Employee Training and Monitoring

One of the most important components of an exposure control plan for the laboratory is a formal training program. “On-the-job training” is not acceptable as adequate safety training in the laboratory. The recommendations from CDC (109) and NCCLS (161) that emphasize education of laboratory workers have been incorporated into the OSHA bloodborne pathogen standard (163).

Interactive training sessions must be conducted on initial hire and with annual updates by a person knowledgeable about the standard. Employees must be educated regarding their risks and the institution's plan to control these risks.

Recognizing the increased risk of working with concentrated viral preparations, OSHA requires that employees in HIV research laboratories and production facilities receive *additional* initial training. Employees in these situations must demonstrate proficiency in standard microbiological practices as well as practices and techniques specific to the facility *prior* to work with HIV. This might include prior experience in handling human pathogens or tissue cultures, or participation in a training program with a progression of work activities to develop proficiency before pathogens are handled.

Employers must ensure compliance with the OSHA standard. The CDC (109) and NCCLS (161) recommend that workplace practices be monitored at regular intervals by a biosafety expert. The NCCLS suggests that audits be conducted that evaluate the existence and effectiveness of training programs and the job descriptions of the safety trainers. The audit should also examine the adequacy of the laboratory facilities and equipment, the standard operating practices, and the written safety protocols. Corrective measures should be implemented if needed. If breaches in protocol are detected, employees should be reeducated and, if necessary, disciplinary action taken.

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8 Postexposure Management
The implementation of a bloodborne pathogen exposure control program that includes Universal Precautions and the recommendations from CDC and NIH may reduce the incidence of occupational exposure to HIV and other bloodborne pathogens; however, use of prevention strategies will not entirely eliminate the risk of accidental exposures and subsequent occupational infection. OSHA estimates that full compliance with the bloodborne pathogen standard would reduce the risk of mucous membrane and skin exposure by 90%, and the risk of parenteral exposure by 50% (170). Therefore, a postexposure evaluation program is a necessary and mandated component of a workplace safety program.

Work settings in which workers handle blood, other potentially infectious materials, or concentrated HIV viral material must adhere to the OSHA postexposure protocol that requires confidential medical evaluation, follow-up, and documentation of an exposure incident. OSHA defines an "exposure incident" as a "specific eye, mouth, other mucous membrane, non-intact skin, or parenteral contact with blood or other potentially infectious materials that results from the performance of an employee's duties" (163). The bloodborne pathogen standard requires follow-up according to the U.S. Public Health Service recommendations, specifically, CDC guidelines.

The postexposure management of hepatitis B exposures has been well defined on the basis of the vaccination status of the exposed employees (4, 171). The management of such exposures involves serological testing of the vaccinated employee for a protective antibody level against HBV. If antibody levels are negative or not detectable, a booster dose of HBV vaccine is given. For nonvaccinated employees, the HBV vaccine is offered in combination with hepatitis B immune globulin (HBIG).

HCV postexposure management has been defined (172) and involves serological testing of the employee at intervals up to 6 months postexposure for antibody to HCV as well as liver enzyme testing. The CDC does not recommend immune globulin for such exposures.

Analysis of data in the CDC case control study of occupationally acquired HIV infection suggested that use of AZT postexposure might be protective for healthcare workers (74). The risk for HIV infection in this study was reduced approximately 79% in workers who were given AZT prophylactically following exposure. Because of these results, the CDC recommended the use of antiviral agents for postexposure treatment after high risk exposure to HIV-infected patients (9). These guidelines outline a number of considerations in determining whether a healthcare worker should receive postexposure prophylaxis and in the choosing the type of prophylaxis regimen.

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Tuberculosis and Other Mycobacteria
Donald E. Gardner, Ph.D., Fellow ATS

1 Introduction

The genus *Mycobacterium* is one of the most widely distributed bacteria genera in nature and includes those organisms that cause two of the world's most prevalent infectious diseases in humans, *M. tuberculosis*, the agent of tuberculosis and *M. leprae*, the agent of leprosy. A large number of other species in this genera are widespread and occur as contaminants in soil, water, or organic debris. These organisms may be ingested or inhaled in dust particles and produce syndromes that are indistinguishable from classic tuberculosis. The term tuberculosis (TB) is commonly applied to all cases of mycobacterial infections except leprosy. Many of these infections are now being recognized more frequently in immunosuppressed patients who have organ transplants, individuals being treated for leukemia or cancer, and patients suffering from AIDS. In most cases of TB in humans, the lungs are the major organ affected but other tissues and organs such as bone, skin, and the digestive tract may also be infected. Although this chapter focuses primarily on tuberculosis, a discussion of a few of these other opportunistic organisms in this genus that are associated with human disease are also discussed.

The bibliography provided will guide the readers to works which they can consult for more detailed information about these organisms. These references contain discussions on taxonomy, growth requirements, as well as the morphological characteristics, physiology, pathogenicity, and the metabolic activity of these organisms (1–6).

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2 Historic Perspective

Throughout the ages, tuberculosis has been a scourge of humankind. Human fossils excavated from Neolithic burial grounds dating about 6,000 years ago show evidence of TB of the spine (7). Robert Koch is credited with discovering the tuberculosis bacillus in 1882 and reporting that it was the causative agent of TB in both humans and cattle. Tuberculosis gets its name from the small nodules (tubercles) commonly found in infected individuals; however, throughout history it has been known

by many other names, including scrofula, phthisis, and consumption.

The Industrial Revolution created ideal conditions for the spread of this organism. Malnutrition, overcrowding, poorly ventilated factories and homes, unsanitary conditions, poverty, and certain occupational settings provided the means for this organism to spread. Tuberculosis was the leading cause of death from infectious disease in the United States and Western Europe until the first decade of this century, and it remained the second leading cause of death (the first was malaria) from that time until the advent of antimicrobial drugs in the 1950s, when infection rates began to decline steadily (8). This trend was reversed between 1985 and 1992 when the frequency of TB started to increase at an alarming rate. At that time, many hospitals lacked the appropriate ventilation systems, ultraviolet lights, isolation areas, and clinical expertise needed to treat active tuberculosis and to prevent this organism from spreading.

Among persons infected with the tubercle bacillus, as detected by a positive tuberculin test (see later), only a small proportion develop overt disease. Thus humans seem to have a considerable natural resistance to TB. It is important to understand the difference between infection and disease (this series, Chapter 19). Infection implies that a microbe has taken up residence in a host and may be capable of multiplying within the host—perhaps with no outward signs of disease. Thus, it is possible to be infected but not have the disease symptoms commonly associated with the agent, although disease may develop at a later time. This is often the situation with exposure to the TB organism. The transition from infection to mild or severe disease depends strongly on various factors besides the presence of the bacilli.

Even with this natural resistance to TB, today worldwide, this organism kills more people than any other infectious disease and infects more than 1 billion people; of these, an estimated 20 million actually develop the disease. Each year, the number of new infections continues to increase. For example, in 1990, the number of new TB infections was 7.5 million with 2.5 million deaths, and by 1995 new infections increased to 8.9 million and the death rate had increased to 3 million. By the year 2000, 10.2 million new cases are expected with 3.5 million deaths. (9–12).

In the United States, about 30,000 active cases are reported yearly, but the number of Americans infected could be as high as 15 million. From 1985 to 1991, the estimated number of new cases increased nearly 20%. Tuberculosis is even more threatening elsewhere in the world. During this same period, TB increased 30% in Europe, and it rose nearly 300% in parts of Africa (12).

TB is reemerging for a number of reasons. First, the prevalence of drug-resistant strains has risen dramatically. Initially, only about 1–2% of the strains of *M. tuberculosis* had significant drug resistance (8, 13). In the 1960s and 1970s, the number of new resistant strains increased by about 3–5% in the United States. Today, about 33% of the tuberculosis strains isolated are resistant to at least one drug, and about 19% are resistant to two or more antimicrobial agents (13). This makes the disease more lethal and treatment longer and more difficult. When multiresistant TB strains are identified, the case fatality rates may exceed 80% in certain compromised individuals.

Secondly, a weakening of the host's immune system through inherited diseases, aging, immunosuppressive medications, and human immunodeficiency virus (HIV) infections has resulted in a massive increase in the incidence of tuberculosis in individuals who might have otherwise been able to defend themselves against this illness. The HIV epidemic is perhaps the most significant factor responsible for this dramatic upsurge in tuberculosis. TB is often the first sign that a person harbors HIV (14). The TB incidence rate among people infected with HIV is nearly 500 times the rate for the general population. An alarming aspect of these coepidemics is that the impaired defenses caused by HIV infection facilitate the transmission of drug-resistant strains of tuberculosis (8, 13, 15). In the United States, 50% of the autopsied AIDS patients have mycobacterial infections (8, 13).

Another reason for this increase is attributed to inadequate health care provided for the poor,

homeless, and drug addicts. Many of these people have little access to health care, some refuse care when it is offered, and many quit treatment before the disease could be arrested. The latter event facilitates drug-resistant strains. Some of the most recalcitrant dropouts are individuals who are drug-addicted, alcoholic, or mentally ill. Many have no permanent homes and cannot be traced by public health officials. A final reason that more cases are appearing today is the increase in number of elderly people in our society. TB is common among the elderly. Of the total cases reported in the United States in 1995, about 25% involved individuals over 65. It is possible that many of them could have been infected years previously, when TB was more common, but their disease broke out only as a consequence of the immunosuppression associated with natural aging. In addition, these individuals often spend later life in health-care facilities where people are more likely to be in close contact with other elderly individuals, thus increasing the risk of contracting the disease. For example, nursing home residents are 10 times more likely to contract TB than the general population.

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3 The Organisms
Human TB is caused by *Mycobacterium tuberculosis* var. hominis. The genus *Mycobacterium* is the only genus in the family *Mycobacteriaceae* and is represented by various pathogenic species, which characteristically produce chronic granulomatous lesions. Although the genus *Mycobacterium* includes other obligate parasites, saprophytes, and opportunistic pathogens that live freely in soil and water, the major ecological niche for *M. tuberculosis* is the tissue of humans and other warm-blooded animals. The following section contains a description of some of the important species of *Mycobacterium*. The reader can consult various text and review articles for additional information about these organisms (5, 16–20).

These bacilli are straight or slightly curved, rod-shaped organisms. They vary from about 0.2–0.6 mm wide, and from 1–10 mm long, occasionally occurring as filaments but rarely branching. On the surface of a liquid media, their growth appears mold-like. The name “myco” suggests fungus-like and was derived because they occasionally exhibit filamentous or mycelium-like growth. These organisms are aerobic, nonmotile, and nonspore forming. Although mycobacteria have previously been described as unencapsulated organisms, recent electron microscopic data have provided evidence that pathogenic *Mycobacterium* has a capsule that aids in protecting the cells from the activities of the host's alveolar macrophages (21). These bacilli are very resistant to drying, thus increasing their ability to remain viable during prolonged stays outside the body. This resistance to drying is due to the large amounts of complex long-chain lipids (C_{78}–C_{90}) in their cell walls (40% of total cell dry weight). This high lipid content is also responsible for the fact that mycobacterial cells are difficult to stain by conventional methods, and once stained, they resist decolorization by either 95% ethanol or 3% hydrochloric acid. All mycobacteria have this characteristic and are often referred to as “acid-fast.” Acid fastness is the most important characteristic of a mycobacterium because it can be used to differentiate these types of bacteria from other organisms. *Mycobacterium* species are euphemistically also referred to as “red snappers” because they appear red when stained and appear to break sharply when they reproduce. Another important component of the cell wall of these organisms is trehalose dimycolate, an indicator of the virulence of the organism. When this is present, the virulent strains tend to grow in a characteristic “serpentine” cord-like pattern in an artificial medium, where avirulent strains do not (22).

Because the great majority of *Mycobacterium* can be cultured on artificial media, these organisms are not considered obligate parasites. The major exception is *M. leprae* which has not been cultured on artificial media but grows only in certain animal or tissue cultures of macrophages. Growth rates

for these organisms in culture range from slow to very slow. The transport of nutrients into the cell through the lipid layer in the cell wall is very slow, which is a factor in the slow growth rate of these organisms. It sometimes takes weeks for a visible colony to form. Waxes that make up the cell wall of these organisms also play a major role in their pathogencity and aids them in resisting digestion by phagocytes. In fact, this organism can actually multiply inside phagocytes.

Except for *M. leprae*, the *Mycobacterium* are classified into two broad categories—typical (e.g., *M. tuberculosis*, *M. bovis*, and *M. africanum*) and atypical which includes virually all the other species. All of these various members of *Mycobacterium* are closely related on the basis of DNA homology (23). The different organisms can be separated and identified by their growth rate, pigmentation in the light or dark, catalase and niacin production, nitrate and tellurite reduction, and Tween 80 hydrolysis. They have also been called MOTT (Mycobacteria other than tuberculosis). These atypical mycobacteria cause diseases that mimic TB and are clinically, roentgenographically, and pathologically identical to the disease produced by *M. tuberculosis*, except for one major difference. These infections are usually not communicable. In most cases, the causative agent can be differentiated from tuberculosis only by culturing the organism (24).

Mycobacterium africanum causes TB in tropical Africa; *M. bovis* causes TB in cattle, and it is highly virulent in humans and other primates, certain carnivores (e.g., dogs, cats, and swine), parrots, and some birds of prey. The organism is a bit shorter and plumper than *M. tuberculosis*, but the difference is slight. The disease produced in humans is virtually indistinguishable from that caused by *M. tuberculosis* var. hominis and is treated similarly (25). However, there are some differences between these two organisms. For example, *M. bovis* is highly pathogenic in rabbits, whereas *M. tuberculosis* is much less so. In culture, *M. bovis* tends to grow more slowly and cannot tolerate as high a concentration of glycerol. Serological tests and skin tests, however, cannot be used to differentiate between the two organisms.

Drinking unpasteurized milk and other dairy products from tuberculous cows has been responsible for much human TB. The ingested organisms presumably penetrate the mucosa of the oropharynx and intestines and give rise to early lesions in the cervical or mesenteric lymph nodes. Subsequent dissemination from these sites infects principally bones and joints. Such infection of vertebrae was largely responsible for the hunchbacks in previous generations. When inhaled (e.g., dairy farmers), the organism can also cause human pulmonary tuberculosis. TB due to *M. bovis* has now become very rare in many countries as a result of widespread pasteurization of milk and the elimination of tuberculosis in cattle.

In poultry and swine *M. avium* is an important cause of disease and can also infect humans. It was first recognized in the 1800s as the causative agent of a disease in chickens, but was not recognized as a cause of human disease until 1943. These organisms, which are collectively known as *M. avian* complex (MAC) are ubiquitous in nature and have been isolated from water, soil, plants, house dust, and a myriad of other environmental sources. These organisms usually have low pathogenicity and frequently colonize in individuals without causing disease. Human cases of MAC infection, unrelated to AIDS, occur more frequently in farming populations than in urban patients. The risk of contracting *M. avium* disease is very high among HIV + individuals. Lung infections caused by MAC most often occur in individuals (primarily men) who are smokers, whose lungs have been damaged by an old tuberculosis infection, bronchitis, or emphysema, or who have AIDS (14). There seems to be a clear difference in the disease pattern for the different types of mycobacterial infection in AIDS patients. Exposure to the usual human strain of TB seems to be related to an early onset of the disease in HIV + individuals, whereas the *M. avium* strain emerges only in the later stages of the disease (26). There has been speculation that there are different levels of immunity against the two organisms (i.e., an immunocompetent host, in general, can better control the growth of *M. avium* than *M. tuberculosis*) (25).

Some mycobacteria grow in swimming pools and even in aquariums. Aquarium workers and fishermen are at risk of being exposed to *M. marianum*, an organism that is associated with fish

(swimmer's granuloma). The site of this infection is primarily soft tissue, usually of the extremity.

Leprosy (Hansen's disease) is a chronic infectious disease caused by *M. leprae*, which has a unique tropism for two tissues—peripheral nerves and skin. The World Health Organization estimates that the global prevalence of leprosy is 10–12 million and the majority of cases occur in Asia and Africa. *M. leprae* is virtually indistinguishable in morphology and staining properties from *M. tuberculosis* and has many clinical features in common with TB. Because *M. leprae* has never been cultured successfully *in vitro*, it appears to be an obligate intracellular pathogen that requires the environment of the host macrophage for survival and propagation. This bacillus resists intracellular degradation by macrophages, perhaps by escaping from the phagosome into the cytoplasm, where it can accumulate to high levels (10^{10} bacilli/g of tissue) in lepromatous leprosy.

In voles, guinea pigs, rabbits, and calves, *M. microti* are associated with TB lesions. Other species such as *muris* and *piscium* are tubercle bacilli that cause a similar type of disease, but the primary hosts are fish, frogs, and turtles. *Mycobacterium cheloni* is frequently found in the soil and water, and in 1980 a microbiologist recognized this bacillus as a cause of lung disease, wound infections, and skin abscesses in humans (4, 22). In 1991, *M. haemophilum* surfaced as a pathogen when cases occurred in immunocompromised individuals in New York hospitals (4, 22).

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4 Sources
In the United States, humans are the most common reservoir and source of human TB. Individuals with active pulmonary TB are potential sources of danger to all those with whom they come in contact. Numerous studies of TB epidemics in closed populations (e.g., on naval vessels, in nursing homes) have documented the highly contagious nature of this organism. Because the infection is acquired by inhalation in most cases, it is natural that the lung should be the most common target organ for the disease. (Chapter 19, this volume). These organisms are spread by droplet aerosols released when a person with active TB coughs, sneezes, talks, or even sings. An individual with a moderately advanced case of TB may expel from 2–4 billion bacteria in a single 24-h period. The small droplets (1–10 mm) may stay afloat in room air for several hours, increasing the risk of infection (27). Because of the high lipid content of their cell walls, mycobacteria can retain their pathogenic properties in dried sputum for months or even years. When inhaled, these organisms can reach the smallest terminal airway passages without being trapped and removed by the host's upper airway clearance mechanisms (Chapter 19, this volume). Prime settings for transmitting this disease are hospitals and other health-care facilities that place health-care workers in close proximity to patients with this disease. The recent outbreaks of multidrug-resistant organisms have refocused attention on the detection, transmission, and prevention of TB in these health-care settings. Airborne transmission of these organisms is a major concern in other institutions such as jails, homeless shelters, AIDS hospices, and drug treatment facilities.

Fomites do not play a major role as a source of these organisms. However, within a clinical laboratory environment or autopsy rooms, workers may come into contact with them.

A clinical difference between *M. tuberculosis* and the nontuberculosis (atypical) mycobacteria is the lack of transmission of the latter from patient to patient (24). Rather, these organisms exist saprophytically in the soil or water or in association with some infected-animal reservoir. In developing countries, where bovine TB has not been eliminated, cattle are the reservoirs for the bovine strains, and transmission to humans commonly occurs by ingestion of unpasteurized milk or dairy products. Sometimes these organisms may be transported through the air to infect farmers and

animal handlers.

Individuals who work with marine life or in an aquatic environment may be exposed to *M. marianum* infections. Those at risk include fishermen, marine biologists, pet store employees, and zoo personnel. The organism gains entry into the host through breaks in the skin or through bites by marine organisms, and *M. marianum* may cause nonhealing skin ulcers, arthritis, lymphadenitis, or tenosynovitis.

With *M. leprae*, the primary source of infection is the infected individual, and the route of transmission is through the air. A patient with untreated leprosy may discharge up to 8×10^8 bacilli in a single nose blow. Leprosy may also be transmitted via penetrating wounds and insect bites. However, shedding from the nose is more important in the transmission of this disease, than shedding from skin lesions (28). Even with this high number of organisms released into the air, leprosy is not very contagious and human-to-human transmissions usually requires prolonged contact. Natural infections that can be transmitted to humans have also been documented in certain animals such as monkeys and armadillos.

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5 Health Issues
TB is a particularly good illustration of an infectious disease process that involves an ecological lifelong balance between a host and a microbe. TB in humans is predominately an airborne infection of the lungs that is almost always initiated by inhalation. Once the organisms have been inhaled and deposited in the lung, these organisms can be found in the lung's phagocytic cells (alveolar macrophages) that tend to protect them from antibodies and other host immune defenses. Individual susceptibility to TB and the severity of the disease are based on the virulence of the organism, the duration of exposure, concomitant exposure to other toxicants, medication for treatment of other diseases, and the nutritional status of the host. Once the organism has survived the transport through the environment and has infected a susceptible host, the TB infectious process can be divided into two stages that are commonly referred to as primary and secondary infections. During the primary phase, after an incubation period of 4–8 weeks, the infected individual is usually asymptomatic but may produce nonspecific symptoms such as fatigue, weakness, anorexia, and low-grade fever. However, in most cases the host may not even be aware that such a pathogen has invaded the body. Initially, the infecting organisms do not elicit a marked inflammatory reaction because they do not immediately produce any toxins or tissue-destructive enzymes. In most healthy people, the primary infection often subsides spontaneously as a result of the activities of the immune system, especially if the infecting dose is low. Even so, a scar remains on the lungs as evidence of a previous infection. At this stage, approximately 5–10% of the individuals infected with this organism show symptoms and develop active TB within the first year; the remaining infected individuals continue to be at risk with a latent infection. Initially, the macrophages that have become laden with numerous intracellular bacilli may be unable to destroy the invading cells. However, after a few weeks a cell-mediated immunity develops. Sensitized lymphocytes attract and activate these macrophages, which greatly enhances the phagocyte's bactericidal capability. As the initial lesion heals, tiny granulomas or tubercles are formed that can harbor the bacilli indefinitely. In the majority of cases, the infection is arrested, and the bacilli remain in a dormant state walled up in these primary lesions (tubercles).

The pathogenesis of this infection cannot be separated from the host's immune response. During the infectious stage, much of the tissue damage is caused by the host's own immune response, rather than by bacterial toxins. Activated macrophages may release various enzymes and cytokines that may ultimately cause damaging inflammation at the site of the infection. TB is a good example of

such a host-mediated pathogenesis where the tissue damage is actually caused by toxic factors released from the lymphocytes and macrophages that infiltrate the site of the infection. Often the host response is so intense that the tissue is substantially destroyed, allowing the invading bacteria to proliferate further (6). In most of these infections, the host's cell-mediated immunity generally continues to control the infection. However, within the “healed” lesions, there may still be viable organisms that remain dormant for years, even decades, without producing any further symptoms of the disease.

Most individuals recover from primary TB, but in a small percentage of cases, the primary infection may progress, and further lung destruction can occur. In general, about 10% of the people with latent infections develop active TB sometime in their lives. The risk of reactivating a primary infection is greatest during the first two years after the initial infection. An individual with HIV has a 10–15% risk per year of progression of the infection. This reactivation of the disease is referred to as secondary TB. During this reactivation process, symptoms may include a cough that produces mucopurulent sputum, occasional hemoptysis, and chest pain. During reactivation, the individual pulmonary lesions may merge and enlarge; the resulting necrotic tissue (interior of the tubercle) will become cheese-like (caseous). If the body's defenses arrest the disease at this time, this caseous lesion slowly heals, undergoes fibrosis, or becomes calcified with cavities containing the living bacilli. These cavities show up on X-rays and are referred to as Ghon complexes. Later, this lesion may become more liquid, a process called liquefaction, and will commence to discharge the isolated viable organisms. Within these liquidified cavities, the bacilli can replicate to very high numbers (as many as 10^9 bacilli in a single lesion). At this stage, the organisms are highly infective and can be expected to serve as a source for the continual spread of the disease.

The organism can exist in these lesions for long periods or can disseminate to almost any organ of the body, including the central nervous system, the genital tract, bone, kidney, or lymph nodes. When the organisms spread to other parts of the body, this condition is known as miliary tuberculosis. The name is derived from the numerous millet seed-like tubercles formed in the infected target tissue. The tubercle bacilli can spread to other organs in three ways: (1) the organism may continue to gradually destroy the infected tissue at the primary site of infection and then proceed to invade other tissues from this initial site; (2) the organism can spread from the initial site of infection along the lymphatic vessels to the lymph nodes that drain the infected area; or (3) the tuberculous lesion may perforate the walls of a blood vessel, releasing millions of bacilli into the blood stream.

Pulmonary disease due to *M. avian* complex (MAC) typically occurs in white males, 45–65 years old with some preexisting lung disease such as chronic bronchitis, emphysema, a previous TB lesions, bronchiectasis, or pneumoconiosis. Patients with AIDS may have either a focal or disseminated MAC infection. MAC is commonly isolated from sputum or stool cultures from patients with HIV infection. It is thought that MAC is acquired and colonizes in either the gastrointestinal or respiratory tract before dissemination in HIV-infected patients. MAC infectious may also involve the peripheral lymph nodes. Bacteremia occurs in almost all such patients, and the organism can be found in the circulating monocytes (29).

Leprosy is a chronic granulomatous disease. The principal manifestations of the disease includes anesthetic skin lesions and peripheral neuropathy with peripheral nerve thickening. The medical complications of leprosy arise from nerve damage, immune reactions, and infiltration of the organisms to other sites (28).

6 Who is at Risk?

A number of factors increases the risk of infection and can substantially increase the likelihood of reactivation. These include certain diseases such as diabetes mellitus, Hodgkin's disease, silicosis, AIDS, chronic renal failure, and other conditions, such as body weight 10% below the ideal, children under 5 years old, and treatment with corticosteroids or other immunosuppressive drugs.

Cases of TB are not evenly distributed throughout all segments of the U.S. population. Certain ethnic subpopulations have a higher risk of TB, either because they have a higher likelihood of exposure and infection or because they are more likely to progress to an active disease state (19). For example, African-Americans, Eskimos, Native Americans, Asians, and Hispanics account for about two-thirds of the new cases. This organism affects twice as many men as women and is four times more likely to infect non-Whites as Whites. The literature also indicates that certain other individuals may have a greater risk of developing TB, including those in correctional institutions, alcoholics, intravenous drug users, the homeless, and the elderly.

At particular high risk are those whose immune systems are suppressed, such as cancer patients receiving chemotherapy, organ transplant recipients, and individuals with AIDS. Generally at risk are people living in crowded, poorly ventilated, and unsanitary conditions. The risk of infection with TB is proportional to the duration of exposure to an infected individual and the concentration of the airborne infectious droplets. Individuals infected with tuberculosis have a 100-fold greater risk of developing active TB if they are also HIV+. *Mycobacterium* infections that occur in HIV infected people may represent either a reactivation of a latent infection or a new infection. Progression from tuberculous infection to clinical disease occurs in only about 5% of non-HIV infected individuals, but this increases to about 30% in HIV infected persons. Today, a major risk factor is the increasing incidence of the disease and also the increased prevalence of cases that display multiple drug resistance. Such cases are difficult to treat and further the possibilities for widespread transmission of the disease. Delays in diagnosing and treating TB contribute to increased morbidity and mortality and the nosocomial spread of TB.

Transmission of this disease in the workplace is not well understood, and a cause–effect analysis is often not possible. The infectious dose required to cause an infection may be influenced significantly by environmental contaminants in the workplace. At high risk are individuals with certain occupations where the atmosphere may be contaminated with substances that may adversely effect the functioning of the host's normal defense mechanisms. This includes occupational environments encountered by miners, tunnel diggers, quarry workers, steel and iron foundries workers, ceramic workers, stone cutters, workers manufacturing abrasive soaps, glassmakers, and those involved in sandblasting operations. For example, the association between silicosis (silicotuberculosis) and pulmonary tuberculosis is well-accepted. Silicosis, one of the oldest known occupational lung diseases, develops in people who inhale silica dust for many years. People with silicosis are three times more likely to develop TB than people without silicosis. Mycobacterial infection must always be suspected when a silicotic patient experiences worsening respiratory symptoms and chest radiographs. In some incidences, (foundry workers) an increased incidence of pulmonary tuberculosis may occur, even in individuals who did not show radiographic evidence of silicosis but had been employed in the industry for more than 25 years.

Tuberculosis remains a significant hazard to hospital personnel despite the widespread use of certain screening tests for the early identification of cases and knowledge of the way the disease is spread. Medical students and physicians have two to three times the prevalence of infection with tuberculosis as nonmedical, age-matched controls (16). The AIDS epidemic has increased the likelihood that health-care workers will come in contact with an individual with active pulmonary tuberculosis. This is often unrecognized by medical personnel at the time of admission, when transmission is most likely to occur.

Direct contact with infectious material is possible at all stages in a diagnostic laboratory, and these infectious organisms are known to be transmitted during autopsies (30, 31). Certain medical

procedures routinely performed on patients may carry additional risk of TB transmission due to the generation of large amounts of infectious respiratory droplets. Procedures needed for sputum induction, such as aerosolized pentamidine treatment that induces coughing in the patients, bronchoscopy, and endotracheal intubation and suctioning, should be carried out in well-ventilated, negative-pressures rooms, and health-care workers should wear particulate respirators while in these areas.

The fetus may also be at risk of acquiring TB from its mother before or during birth by breathing or swallowing infected amniotic fluid.

6.1 Sampling Analysis and Detection

A key to the diagnosis of TB is a high index of suspicion of the disease and the prompt use of appropriate sampling and diagnostic procedures for identifying the causative agent. Sampling, isolation, staining procedures, cultural media, and procedures for identifying the *Mycobacterium* (e.g., growth characteristics, biochemical tests) have been outlined and recently reviewed (2, 3). The initial step in laboratory diagnosis is a microscopic examination of smears taken from collected sputum or other specimens. Although different types of specimens may be submitted for mycobacterial examination, the vast majority submitted will be specimens from the respiratory tract. They may include sputum (both expectorated and induced), bronchoalveolar lavage fluid, or bronchial washings from patients unable to produce sputum. Other samples commonly tested include blood, urine, and gastric aspirates. Blood and stool specimens may be submitted from patients with AIDS. Miliary TB usually requires transbronchial liver or marrow biopsy samples for diagnosis. Samples should be stained for the acid-fast bacilli. However, a positive confirmation of TB requires isolating the suspected organism in culture, which may take from 3–6 weeks.

Because the bacteria grow more rapidly in broth culture, many clinical laboratories grow the specimens in a medium containing radiolabeled palmitic acid as a substrate; the release of CO_2 indicates the presence of mycobacteria. However, this procedure may still take from 7–14 days. Although many different media are available for culturing the organism, the most commonly used medium in the United States is Middlebrook–Cohn 7H11. This has the advantage of transparency, and permits earlier recognition of the colonies. But it has the disadvantage of requiring 5% CO_2 in the incubator. The availability of biphasic isolation media, the refinement of high-performance liquid chromatography for identifying mycobacteria, the widespread use of nonisotopic probes for culture identification, and the application of nucleic acid amplification techniques for direct detection of *M. tuberculosis* in clinical specimens are important new developments in sampling and detecting these organisms. In addition, progress in understanding the molecular genetics of drug resistance in mycobacteria has been substantial, and sensitive growth indicator systems for more rapid susceptibility testing are being developed (3).

6.2 Prevention and Treatment

Growing support for the germ theory of disease in the late 1800s and the early 1900s led to a dramatic reduction in the frequency of infectious disease epidemics. It was reasoned that if microorganisms cause disease, then it is possible to control disease by controlling the microorganism. Today it is generally agreed that there is little possibility of stopping the transmission of TB. Thus it seems clear that the complete eradication of TB is not immediately possible. Therefore, controlling the transmission of these organisms is essential.

The occupational risk of TB continues to be a subject of considerable debate in the United States (32). The Occupational Safety and Health Administration (OSHA) has issued an enforcement policy dealing with occupational exposure to TB (33). This OSHA document specifies administrative actions, engineering controls, and personal protective equipment for workers in health-care facilities, correctional institutes, homeless shelters, long-term health-care centers, and drug treatment facilities. Early identification of potentially infected patients and worker training are aspects that are emphasized (31, 32).

Although the Centers for Disease Control and Prevention (CDC) officially have no regulatory

responsibilities, they have provided guidelines and recommendations for health-care workers to prevent and control nosocomial infectious. These guidelines include providing consultation on methods for disease diagnosis, antimicrobial susceptibility testing, defining risk factors for transmission, conducting surveillance of health-care workers, exposure incidence, and the development of strategies for prophylaxis (19, 33, 34). Institutional outbreaks of TB have been associated with the failure to isolate infectious patients, delays in initiating therapy, inadequate treatment, and placing of TB patients in rooms with ventilation that directs contaminated airflow into other rooms or hallways.

The most effective intervention to halt the transmission of TB is early identification of infectious cases and antituberculosis therapy. Three hierarchical elements compose the core of these recommendations (34). The first recommendation is isolation of potentially infectious cases. Early detection of TB is difficult because the disease has a slow chronic course and individuals may be infective for months before seeking treatment. The undiagnosed case of TB has long been considered the greatest potential disseminator of disease. Placing patients into respiratory isolation has been effective in reducing the rate of employee infections. Respiratory isolation of patients in appropriate ventilated rooms is necessary for inpatient facilities. Patients should be instructed to cover their mouths and noses when coughing or sneezing, which will reduce respiratory droplet generation.

The second recommendation is the use of appropriate environmental controls. The three types commonly used are discussed here; they include the use of (1) appropriate ventilation, especially in isolation rooms; (2) high-efficiency filtration; and (3) germicidal irradiation.

Droplet nuclei generated by coughing of an individual with pulmonary TB may remain suspended in room air for long periods of time. The concentration of droplets may be reduced or eliminated by appropriate ventilation. Air contaminants can be removed from the room by either direct exhaust to the outside or by recirculating the air through the general ventilation system. Care must be taken when the air is recirculated into other rooms; otherwise additional individuals may be exposed to the organism. Vents that exhaust to the outside should be located away from intake vents and pedestrian traffic. Currently, ventilation rates of six air exchanges or greater per hour are recommended in TB isolation rooms in existing facilities and ≥than 12 air changes per hour are recommended in new or renovated facilities. Isolation rooms need to be maintained under negative air pressure, which requires that the rate of air exhaust exceed the rate of air intake.

The use of high-efficiency particle air filters (HEPA) in ventilation systems can be effective in removing particles ≥0.3 mm in diameter with 99.7% efficiency. The use of HEPA filtration may be useful in the recirculation of air in waiting rooms or emergency rooms where an increased risk of TB exists.

Ultraviolet (UV) germicidal irradiation is an effective means of air disinfection for droplet infections such as TB. UV lamps have been recommended as a supplement to a well-designed ventilation system in high-risk settings. Such lamps are usually installed on ceilings; however, adequate air mixing within the room is important to ensure its effectiveness. They may also be installed in ventilation ducts.

The third recommendation is the use of personal respiratory protective equipment. Standard surgical masks do not provide adequate protection against infectious droplet nuclei produced by persons with pulmonary TB. However, the use of protective devices, such as high efficiency particulate respirators that filter particles ≥1 mm in size with ≥95% efficiency, has been recommended for individuals, who working in rooms in which patients with known or suspected TB are isolated, during cough-inducing procedures, and in other settings where the risk for TB exposure is greatest (34). There is much controversy surrounding the recommendations for the use of mask and respirators. It has been argued that a safer working environment awaits new means of diagnosis, not a better respirator.

In 1986, the EPA published guidelines for infectious waste management. The Agency suggested that

all generators of such infectious waste develop proper management for its disposal. Most states have developed specific regulations for handling infectious waste, but these vary considerably in scope and complexity (35). In general, these guidelines direct each institute to have a written plan for properly managing infectious waste, including properly training all personnel who are involved in generating, collecting, transporting, and/or storing infectious waste.

A good discussion of prophylactics and treatment methods available can be found in Merck (24). In the nineteenth century, some of the treatments for the disease included drinking elephant's blood, spending time by the sea, or touching the hand of a reigning monarch. During the late 1880s, the medical community came to believe that fresh air and relaxation were beneficial. Consequently, the use of sanitariums, where patients were assured of clean fresh air, rest, and care, became the preferred treatment. In 1944, with the discovery of the drug streptomycin by Dr. Selman Waksman, the medical community began to actually control the disease.

Because the risk of *M. tuberculosis* carriers developing an active disease depends on the individual's standard of living, working environment, and general health, individuals who have TB must take special care not to spread the disease. Sputum should be safely disposed of. In the future, the ability of infected individuals to survive such an infection will depend on the availability of adequate medical care and whether drug research can outpace the evolution of new drug-resistant strains of this bacillus. The risk of infections can be reduced by improving social conditions, such as overcrowding, education of the public in the mode of spread, and appropriate methods for control.

Presently a combination of antibiotics is used to treat TB. The most common combination is isoniazid, rifampin, and pyrazinamide. If drug resistance occurs, these medications can be supplemented with other antimycobacterial agents (e.g., ethanbutol and streptomycin) (3, 15, 36, 37). For individuals with strains that are sensitive to the usual antituberculosis drugs, correct treatment yields an excellent prognosis. However, in people with strains that resist two or more of the major drugs, the death rate may approach 80%. Prolonged treatment is necessary because the bacillus grows slowly, and these antibiotics are effective only against growing cells.

Diagnostic tests include chest X rays, tuberculin skin tests, sputum smears, and cultures to identify the organism. Chest X rays may show nodules, patchy infiltrates, cavity formation, scar tissue, and calcium deposits. However, it may not be possible to distinguish active from inactive TB. As stated earlier, the diagnosis of TB disease requires isolating the organism from sputum or other suspected materials.

TB is easy to detect by a skin test with tuberculin, which is a purified protein derivative (PPD) of the tubercle bacilli. Infected persons develop a cellular immune reaction against *M. tuberculosis*, demonstrated by a positive tuberculin skin test within 2 to 8 weeks after the initial exposure. Conversion of the tuberculin skin test from negative to positive reveals only whether a person has had previous exposure to the organism, either from immunization or from coming in contact with the TB organism. It has been estimated that 5% of the U.S. population is tuberculin positive; however, the rate varies considerably according to age, ethnic group, and location. Hospital personnel should be skin tested for tuberculosis when they are first employed and after known exposures. In some cases, skin testing should be repeated annually. For health-care workers who “convert,” their skin test should be evaluated by physical examination and a chest X ray to rule out the possibility of a progressive primary infection. If active pulmonary infection is identified, combination therapy with isoniazid and other antituberculous drugs can be effective in controlling active infection and decreasing the likelihood of additional respiratory transmission. Smoking must be stopped and nutrition improved.

A second method of prevention is to initiate a vaccination program to protect uninfected populations. The vaccine available is called BCG (bacillus of Calmette and Guerin). Worldwide, the BCG vaccine is one of the most common vaccines used today (3). It is a live strain of the tuberculin bacilli which has been rendered avirulent. It has been recommended that all individuals at high risk,

including health personnel, be vaccinated.

Elimination of bovine tuberculosis among cattle can be accomplished by identifying the animals at risk by routine tuberculin testing. The proper pasteurization of milk and milk products can be effective in preventing the spread of this disease to humans.

Controlling dust and other airborne contaminants is essential in industrial plants and mines. When such airborne substances cannot be controlled, such as in the sandblasting industry, workers should wear hoods or masks that filter out the particles.

Tuberculosis and Other Mycobacteria

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Petroleum, Coal Tar, and Related Products
Richard W. Niemeier, Ph.D.

Introduction
In 1619, Dudley discovered that when certain (bituminous) coals wre heated in the absence of oxygen, referred to as “charking,” “coak” was produced, which could be substituted for wood charcoal. By 1800, commercial products included coke-oven gases (“illuminating gas”), a low-boiling distillate known as coal naphthas (light oil of tar, also known as light liquid naphtha or benzine), and a “buttery-solid” condensation product containing carbon, “naphthaline,” paranaphthaline or anthracene, paraffin, chrysene, pyrene, phenanthrene, fluorene, and biphenyl, called coal tar. Further fractional distillation of coal tar yields coal tar creosote “oil” (containing phenols, cresols, and xylenols, in contrast to pharmaceutical creosote, which contains guiacol, cresol, phenol, and xylenol from beechwood tar), coal tar pitch, and naphthalene (1). Because coal tar, coal tar pitch, and coal tar pitch volatiles (CTPV) may occur together, they are combined in this review.

The chemical composition of coal tar, coal tar pitch, and related materials is complex and variable. The estimated number of compounds present in these complex mixtures is in the thousands. Because of variation in source materials and manufacturing processes, including different temperatures and times of carbonization, no two coal tars or pitches are chemically identical, and their toxicity may differ with their origin (2). In general, however, approximately 80% of the total carbon present in coal tars exists in aromatic form (3).

Benzo[a]pyrene (B[a]P) is probably the most potent, widespread occupational carcinogen in coal tar, coal tar pitch and its volatiles, coke oven emissions, and creosote, all of which have corresponding work exposure standards (4); however, there is no occupational workplace standard for B(a)P. It may account for more than 75% of the carcinogenic activity of coal tar pitch fume condensate (5). Individuals who work in tarring facilities, roofing operations, power plants, and asphalt and coke manufacturing facilities may be exposed to benzo[a]pyrene and related PAHs. These mixtures may differ qualitatively and quantitatively.

Coal tar is completely or nearly completely soluble in benzene and nitrobenzene and it is partially soluble in acetone, carbon disulfide, chloroform, diethyl ether, ethanol, methanol, petroleum ether, hexane, and sodium hydroxide solution, and slightly soluble in water. It has a characteristic naphthalene-like odor. Coal tar is heavier than water and on ignition it burns with a reddish, luminous, and very sooty flame. Coal tar fumes are highly flammable and are easily ignited by heat, sparks, or flames. Vapors are heavier than air. They may travel to a source of ignition and flash back and may form explosive mixtures with air. Vapors will spread along ground and collect in low or confined areas (sewers, basements, tanks). Vapor explosion is a potential hazard indoors, outdoors, or in sewers. Some may polymerize explosively when heated or involved in a fire. Runoff to a sewer may create a fire or explosion hazard. Containers may explode when heated. Coal tar may be transported hot (3).

The greatest complexity occurs when toxicity is based on the effects of a class of compounds or of a material of a certain physical description. Some polynuclear aromatic hydrocarbons (PNA) and polycyclic aromatic hydrocarbons (PAHs) are carcinogens of varying potency, and they usually exist in mixtures with other PNAs/PAHs and with compounds (activators, promoters, inhibitors) that modify their activity. Analysis of each individual compound is very difficult and when done does not yield a clear answer. Given the complexity of the mixture of biologically active agents and their interactions, a calculated equivalent dose would have little accuracy. In these instances, it is common to measure some quantity related to the active agents and to base the occupational exposure limit on that index. An occupational exposure limit for PNAs has been based on the total weight of benzene- or hexane-soluble airborne material (6). This limit may be appropriate for coal tar pitch volatiles for which it was developed, but it may not work for other PNA/PAH containing materials. Crude oil, asphalt fumes, and cracked petroleum stocks may contain PNA/PAH. The coal dust particles mixed in with coal tar pitch volatiles are not soluble in benzene, but almost all of the petroleum-derived

materials admixed with PNAs/PAHs are soluble in benzene. For example, a heavy aromatic naphtha may or may not contain PNAs/PAHs depending on the manufacturing process but is completely soluble in benzene. Thus a measurement of the benzene-soluble fraction of a heavy aromatic naphtha aerosol will reveal nothing about the PNA/PAH content. Alternate indices include the single carcinogen B(a)P, the sum of a subset of six carcinogenic PNAs (benz[a]anthracene, benzo[b] fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthen, benzo[a]pyrene, and benzo[e]pyrene) or 14 or more individual PNAs (7, 8). The NIOSH Manual of Analytical Methods (6) contains numerous methods for coal tar pitch volatiles (#5042), coal tar naphtha (#1550), benzene, cresols, PNAs, and PAHs (6).

Some of the highest measured levels of coal tar pitch volatiles (CTPV) have occurred in the aluminum reduction industry, especially in the Soderberg process potrooms where concentrations as high as 63 mg/m^3 have been reported (9). That same review mentioned that the highest level reported in a roofing operation using coal tar pitch was 2.38 mg/m^3. The NIOSH (10) review of coke oven plant workers exposed to CTPV stated that one category of worker, the lidman, had the highest exposure, a range up to 18 mg/m^3, and an average exposure of 3.2 mg/m^3. The NIOSH Immediately Dangerous to Life and Health (IDLH) value has been revised for CTPV from 700 mg/m^3 to 80 mg/m^3 based on toxicity data in animals (11–14).

The problem of differentiating the several classes of compounds in a mixed atmosphere such as coal tar pitch volatiles adds complexity to sampling method selection, and it is sometimes necessary to make, and clearly state alongside the results, certain simplifying assumptions. It is commonly assumed when measuring the more toxic soluble form of an element, that the "safe" assumption may be made that all the element present was soluble (8).

In a study of bioremediation effectiveness, the ability of indigenous soil microorganisms to remove these contaminants from aqueous solutions was determined by GC analysis of organic extracts of biotreated groundwater. Changes in potential environmental and human health hazards associated with the biodegradation of this material were determined at intervals by "Microtox" assays and fish toxicity and teratogenicity tests. After 14 days of incubation at 30°C, indigenous microorganisms effectively removed 100, 99, 94, 88, and 87% of measured phenolic and lower molecular weight polycyclic aromatic hydrocarbons and S-heterocyclic, N-heterocyclic, and O-heterocyclic constituents of creosote, respectively. However, only 53% of the higher molecular weight polycyclic aromatic hydrocarbons were degraded. Despite the removal of a majority of the organic contaminants through biotreatment, only a slight decrease in the toxicity and teratogenicity, of biotreated goundwater was observed (3).

Table 22.1. Typical Fractions from Continuous Tar Distillation[a]

Fraction number	Synonyms	Boiling Range (°C)	% Crude Tar (by Weight)
1	Crude benzene, Light oil	106–107	2.4
2	Naphtha, Carbolic oil, Phenolic oil	167–194	3.1
3	Heavy naphtha, Carbolic oil, Naphthalene oil	203–240	9.3
4	Naphthalene oil	215–254	3.5
5	Wash oil, Benzene absorbing oil, Light creosote	238–291	10.2
6	Creosote	271–362	11.5

7	Heavy creosote, Heavy oil	285–395	12.1
Residue	Medium-soft pitch	—	40.5
Liquor and losses	—	—	7.4

[a] From NIOSH (9).

Table 22.2. Occupations with Potential Exposure to Coal Tar Products[a]

Artificial stone makers	Impregnated felt makers
Asbestos goods workers	Insecticide-bomb makers
Asphalt workers	Insulation-board makers
Battery box makers	Insulators
Battery workers, dry	Lens grinders
Boatbuilders	Linemen
Brickmasons	Miners
Brick pressers	Painters
Brickyard workers	Paper conduit makers
Briquette makers	Pavers
Brushmakers	Pipeline workers
Cable makers	Pipe pressers
Carpenters	Pitch workers
Coal tar still cleaners	Railroad track workers
Coal tar workers	Riveters
Coke-oven workers	Road workers
Corkstone makers	Roofers
Creosoters	Roofing-paper workers
Diesel engine engineers	Ropemakers
Electric equipment makers	Rubber workers
Electricians	Shingle makers
Electrode makers	Shipyard workers
Electrometallurgic workers	Soapmakers
Farmers	Smokeless fuel makers
Fishermen	Stokers
Flue cleaners	Tar paintmakers
Fuel pitch workers	Tile pressers
Furnace men	Waterproof-concrete workers
Gashouse workers	Waterproofers
Glassblowers	Wood preservers

[a] NIOSH (9).

Table 22.3. Types of Industrial Processes Using Coal Tar Products[a]

Type of Coal Tar Product	Industry	Industrial Process	Products
COAL TAR PITCH	Aluminum	Aluminum production	Aerospace equipment parts
			Siding, windows, doors
			Packaging
			Foil, wires, cans
			Hardware
	Steel	Electric steel	Automobiles
			Appliances
			Hardware
			Furniture
		Oxygen furnace steel	Construction material
			Transportation
	Foundry	Large casting production	Machine tools for consumer products
	Carbon-graphite	Carbon and graphite products	Batteries for portable equipment
			Pencils
			Streetlighting arcs
			Movie projector arcs
			Clay targets
	Electrical	Electrical conduit production	Motors and parts for household appliances, TV sets, pumps, power tools, construction
CREOSOTE	Construction	Treatment of construction and marine pilings	Construction of buildings, factories, pipelines, roads, etc.
		Tar-based pipeline coatings	
		Tar road, roofing, and waterproofing material	
Railway	Treatment of railway ties	Rails, roadways	
Utility	Treatment of utility poles	Poles for power and telephone utilities	

[a] Adapted from NIOSH (9).

Table 22.4. Petroleum Distillates and Their Uses[a]

Fraction	Carbon Atoms	Boiling Range (°C)	Class of Compounds	Synonyms[b]	Use
Crude oil	C_1–>C_{50}	<0–>1000	More than 300 organic substances, some heavy metals	Earth oil, petroleum	Petrochemicals and petroleum distillates
Natural gas	C_1–C_2	–164 to –88	Methane (83–99%), ethane (1–13%), propane (0.1–3%), and butane (0.4–1%)		Fuel, chemical
Liquefied gas	C_3–C_4	–44.4 to +1.0	Propane and butane with mercaptans added for odorant warning properties	Bottled gas, LPG (liquefied petroleum gas)	Fuel gas, stock for petrochemicals
Petroleum ether	C_5–C_6	30–60	Paraffins (pentanes, hexanes, isohexanes); principally 80% *n*-pentane and 20% isohexane	Petroleum benzine, ligroine, Skellysolve	Dry cleaning, thinner, solvents
Naphthas	C_5–C_{11}	95–160	55.4% paraffins, 30.3% mono- and 2.4% dicycloparaffins, 0.1% benzene, 11.7% alkylbenzenes, 0.1% indans and tetralins.	VM&P naphtha, varnish makers and painters naphtha, light naphtha, dry-cleaner naphtha, and spotting napththa	Cleaning fluids, solvents, thinner, polish, refining stock
	C_7–C_{12}	150–204	Paraffins, naphthenes, aromatics	High flash naphtha	
	C_5–C_{12}	185–207	60.8% paraffins, 24.5% mono- and 11.2% dicycloparaffins, 0.07% benzene, 3% alkylbenzene, 0.3% indans and tetralins	140° flash naphtha, aliphatic solvent naphtha	

	C_8–C_{13}	93–315	Paraffins, alkylbenzenes	Aromatic petroleum naphtha, Coal tar naphtha	
				High aromatic naphtha, high	
	C_8–C_{13}	184–206	Paraffins, mono-, di- and tricyclic naphthenes, alkylbenzenes, naphthalenes, and olefins	Aromatic solvent	
Rubber solvent	C_5–C_7	45–125	41.4% paraffins, 53.6% monocycloparaffins, 0.1% olefins, 1.5% benzene, 3.4% alkylbenzenes	—	Rubber solvent
Gasoline	C_4–C_{12}	32–210	Isoparaffins, olefins- and aromatics	Petrol, benzin, petroleum spirits, motor or aviation gasoline	Aviation fuel automobile fuel, thinner
Mineral spirits	C_6	150–200	80–86% paraffins, 1% olefins, 13–19% aromatics and naphthenes	White spirits, petroleum spirits, refined petroleum solvent	Solvent, degreasing, dry cleaning
Stoddard solvent	C_7–C_{12}	160–210	47.7% paraffins, 26% mono- and 11.6% dicycloparaffins, 0.1% benzene, 14.1% alkylbenzenes, 0.5% indans and tetralins	White spirits	Solvent
Kerosene	C_5–C_{16}	175–325	Alkylbenzenes, 25% normal paraffins, 11% branched paraffins, 30% mono- and 12% dicycloparaffins, 1% tricycloparaffins,	Gas turbine fuel, jet fuels (JP1–6)	Jet and turbofuel

			16% mononuclear aromatics, and 5% dinuclear aromatics		
			Aliphatic, olefins, mono- and dicycloparaffins, alkylbenzenes	Tractor fuel, coal oil, stove oil	
Diesel fuel	C_5–C_{16}	177–400			Fuels, solvent, lighter fluid
Deodorized kerosene	C_6–C_{14}	209–274	55% paraffins, 41% naphthenes, 4% aromatics		Solvent
Fuel oil	C_9–C_{16}	184–334		Gas oil, heating oil, furnace oil	Fuel
Lubricating oil	C_7–C_{20}	204–400		Oil, white oil, mineral oil	Lubricating oils and greases, laxative, ointment
		260–370	Predominantly paraffinic, but may contains some naphthenic and alkyl aromatic hydrocarbons	Mineral seal oil	
	C_{17}–higher	366–588		Grease, petroleum jelly, petrolatum	
Paraffin wax	C_{20}–higher	204–400	*n*-Alkanes with varying proportions of iso- and cycloalkanes	Paraffin, waxes, petroleum waxes	Sealant, polish, food component, sealing wax
Asphalt	C_{20}–higher	400–higher		Road oil, tar, bitumen, bottoms	Sealant, construction

[a] Adapted from Cavender (21), NIOSH (110), and Sandmeyer (111).
[b] A complete listing of synonyms is given in each topic section.

Table 22.5. Some Occupations with Potential Exposures to Petroleum Distillate Solvents[a]

Adhesive makers	Leather japanners
Ammonia synthesis workers	Metal cleaners
Asphalt coating workers	Naphtha workers

Ceramic production workers	Oil processors
Degreasers, metal	Painters
Detergent makers	Paint makers
Dry cleaners	Perfume extraction workers
Enamel makers, synthetic	Petrochemical workers
Farmers	Petroleum refinery workers
Fat and oil processors	Photographic chemical makers
Fungicide handlers	Printers
Garage workers	Resin makers
Heating fuel handlers	Rocket fuel handlers and makers
Herbicide handlers	Rubber coaters and makers
Hydrogen manufacturing workers	Stainers
Ink production workers	Stain makers
Insecticide handlers	Typesetters
Jet fuel handlers and makers	Varnish makers
Kerosene handlers	Wax makers
Laboratory workers, chemical	Wood preservative makers
Lacquers	Wool process workers

[a] Adapted from NIOSH (9).

Petroleum, Coal Tar, and Related Products
Richard W. Niemeier, Ph.D.

Petroleum Distillates

Petroleum distillates is a very complex topic which has been described by many authors (21, 110–112, 134). Much variation is found in the literature in describing the various fractions tested and/or described, and these descriptions have been made by classes of usage (i.e., diesel oil, jet fuel, thinners), distillation fraction cuts usually classified by boiling ranges, refining categories, such as hydrotreated, catalytic cracking, or clay treated, or viscosity ranges in the case of refined oils. For example, NIOSH (110) considered only the refined petroleum solvents that have a total aromatic content of less than 20%. Other hydrocarbon solvents such as thinners, whose total aromatic content may exceed 20%, were not discussed in this document. In another criteria document, NIOSH (143) described only alkanes. Tomes (15), HSDB (3), REPROTOX (19), TERIS (87), and the Canadian Domestic Substances List (144) list petroleum distillates by distillation treatment and refining categories. Many synonyms have been listed for each component. However, there may be overlap in names from one CAS Number to another. This is especially evident for the naphthas and fuel oils. In RTECS (18), data from both refining categories and primary chemical names, including the Chemical Abstracts Number (CAS) and other related information such as commercial uses (145, 146) can be found. This review will not attempt to weave all of these categories into one unified presentation but will convey what is available in the literature.

Table 22.6 illustrates the complexity of products that are available through distillation, cracking, and secondary refining proceses (134) leading only to the high boiling petroleum products.

Table 22.6. High Boiling Petroleum Products

- **Products of distillation and cracking processes**
  - Light and uncracked distillates
    - *Heavy aromatic naphthas*
    - *Spraying oils*
    - *Diesel fuels*
  - Heavy and cracked distillates
    - *Industrial fuels*
    - *Heat transfer oils*
    - *Pyrolysis fuel oils*
  - Uncracked residues
    - *Asphalt*
  - Cracked residues
    - *Petroleum pitch*
    - *Petroleum coke*
- **Products of secondary refining processes**
  - Raffinates
    - *White oils*
    - *Mineral seal oils*
    - *Petroleum waxes*
    - *Petrolatum*
    - *Lubricating oils*
      - Cutting and grinding oils
      - Motor oils
    - *Metallurgic oils*
      - Quenching oils
      - Tempering oils
    - *Insulating oils*
      - Transformer oils
      - Cable oils
    - *Hydraulic oils*
      - Transmission fluids
    - *Textile oils*
    - *Printing oils*
  - Aromatic extracts
    - *Rubber extension oils*
    - *Printing ink vehicles*
    - *Textile oils*
    - *Foundry core oils*
    - *Heat transfer fluids*

Table 22.7. Alkane Isomers[a]

Alkane	Formula	Isomer Name
Pentane	C_5H_{12}	*n*-Pentane
		2-Methylbutane
		2,2-Dimethylpropane
Hexane	C_6H_{14}	*n*-Hexane
		2-Methylpentane
		3-Methylpentane
		2,2-Dimethylbutane
		2,3-Dimethylbutane
Heptane	C_7H_{16}	*n*-Heptane
		2-Methylhexane
		3-Methylhexane
		3-Ethylpentane
		2,2-Dimethylpentane
		2,3-Dimethylpentane
		2,4-Dimethylpentane
		3,3-Dimethylpentane
		2,3,3-Trimethylbutane
Octane	C_8H_{18}	*n*-Octane
		2-Methylheptane
		3-Methylheptane
		4-Methylheptane
		2,3-Dimethylhexane
		2,4-Dimethylhexane
		2,5-Dimethylhexane
		2,2-Dimethylhexane
		3,4-Dimethylhexane
		3,3-Dimethylhexane
		3-Ethylhexane
		2-Methyl,3-ethylpentane
		3-Methyl,3-ethylpentane
		2,2,3-Trimethylpentane
		2,3,3-Trimethylpentane
		2,3,4-Trimethylpentane
		2,2,4-Trimethylpentane
		2,2,3,3-Tetramethylbutane

[a] From NIOSH (143).

Table 22.8. Potential Occupational Exposures to Pentane, Hexane, Heptane, and Octane[a]

Adhesive workers	Petroleum refinery workers
Automobile fuel handlers	Plastics manufacturing workers
Aviation fuel handlers	Polyethylene laminating workers
Cabinet finishers	Printers
Degreasing workers	Printing ink production workers
Farm fuel handlers	Resin makers
Furniture makers	Rubber cement workers
Glue fabrication workers	Shoe factory workers
Gluing machine operators	Solvent workers
Laboratory workers, chemical	Spray painters
Lacquerers	Stainers
Lacquer makers	Stain makers
Laminators	Synthetic chemical production workers
Leather cementers	Synthetic rubber workers
Metal degreasers	Thermometer makers, low temperature
Petrochemical process workers	Varnish makers
Petroleum distillation workers	Vegetable oil extraction workers
Petroleum extraction workers	Vinyl production workers

[a] From NIOSH (143).

Table 22.9. Summary of U.S. Occupational Exposure Limits and Recommendations for Pet Distillates[a]

Compound	CAS Number	OSHA PEL	NIOSH REL	NIOSH Ceiling	IDLH
Crude oil	[*8002-05-9*]	500 ppm 2000 mg/m^3	350 mg/m^3	1800 mg/m^3	1100 mg/m^3
Natural and liquefied gas	[*8006-14-2*][*74-82-8*]	None	None	None	None
Gasoline	[8006-61-9; 86290-81-5]	None	Carcinogen (CA)	None (CA)	None (CA)
Alkanes (see test)					
Petroleum distillates (naphtha)	[*8002-05-9*]	500 ppm 2000 mg/m^3	350 mg/m^3	1800 mg/m^3	1,100 mg/m^3
Petroleum ether	[8032-32-4; 68476-50-6]	None	350 mg/m^3	1800 mg/m^3	None
Rubber solvent	[*8030-30-6*]	100 ppm	100 ppm		1,000 ppm

		(400 mg/m^3)	(400 mg/m^3)		
VM&P naphtha	[*8030-30-6*]	100 ppm (400 mg/m^3)	100 ppm (400 mg/m^3)		1,000 ppm
Petroleum spirits	[*64475-85-0*]		350 mg/m^3	500 mg/m^3	
Stoddard solvent	[*8052-41-3*]	500 ppm 2000 mg/m^3	350 mg/m^3	1,800 mg/m^3	20,000 mg/m^3
140 ° flash naphtha	[*8030-30-6*]	100 ppm (400 mg/m^3)	100 ppm (400 mg/m^3)		1,000 ppm
Aromatic petroleum Naphthas		100 ppm (400 mg/m^3)	100 ppm (400 mg/m^3)		1,000 ppm
Kerosene	[*8008-20-6*]	None	100 ppm (400 mg/m^3)		None
(hydrodesulfurized)	[*64742-81-0*]				
Jet fuels	[*94114-58-6*]	None	None		
Diesel fuel	[*68334-30-5*]	None	None		
Heating Oils	see text		See kerosene		
White oils	[*8012-95-1*]	5 mg/m^3	5 mg/m^3	10 mg/m^3	2,500 mg/m^3
Metallurgical oils					
Insulating oils					
Hydraulic oils					
Textile oils					
Printing oils					
Lubricating oils					
Paraffin (waxes)	[*8002-74-2*]	None	2 mg/m^3	None	None
Cutting oils (metalworking fluids)	[*64771-79-5*]		0.4 mg/m^3 (thoracic particulate mass) ≅0.5 mg/m^3 (total particulate mass)		
Petrolatum	[8009-03-8; 8020-83-5]	None	None		
Residual oils	see text	None	None		
Asphalt	[*8052-42-4*]	None	1 mg/m^3 total particulates and 0.3 mg/m^3 benzene solubles	None	None

[a] Occupational exposure limits, sampling, and analytical methods were based on the CAS Number because of discrepancies and confusion in using synonyms.

Lubricating Stock Distillates

Petroleum, Coal Tar, and Related Products
Richard W. Niemeier, Ph.D.

Other Descriptions of Distillate Fractions

Table 22.10 lists characteristics of higher molecular weight petroleum distillate products processed by various methods. Some toxicity information is provided where available. It is assumed that many of these fractions would be similar to other higher viscosity cuts. Severe solvent or hydrogen treatment has been found to remove many impurities found to be more carcinogenic in the less refined fractions.

Table 22.10. Fractionation of Various High Molecular Weight Petroleum Distillates[a]

Petroleum Fraction	CAS Number	Carbon Content	Boiling range °C (°F)	Viscosity	Method of Production	Principal Components
Catalytic, reformer fractionator residue, low-boiling	[*68477-31-6*]		<288° C (550° F)		Distillation of catalytic reformer fractionator residue	Complex combination of hydrocarbons
Clay-treated heavy naphthenic	[*64742-44-5*]	C_{20}–C_{50}	NA	>100 SUS at 100°F	Treatment with natural or modified clay through contact or percolation to remove the trace amounts of polar compounds and	Complex combination of hydrocarbons containing few normal paraffins

					impurities	
Clay-treated light naphthenic	[*64742-45-6*]	C_{15}–C_{30}	NA	<100 SUS at 100°F	Same as for clay-treated heavy naphthenic	Complex combination of hydrocarbons containing few normal parafins
Clay-treated heavy paraffinic	[*64742-36-5*]				Same as for clay-treated heavy naphthenic	Lower content of aromatic compounds.
Hydrodesulfurized middle	[*64742-80-9*]	C_{11}–C_{25}	205 to 400°C (401 to 752°F)		H_2 to convert organic S to H_2S for removal	
Hydrotreated heavy naphthenic	[*64742-52-5*]	C_{20}–C_{50}	NA	>100 SUS at 100°F	H_2 in presence of catalyst	Few normal paraffins
Hydrotreated heavy paraffinic	[*64742-54-7*]	C_{20}–C_{50}	NA	>100 SUS at 100°F	H_2 in presence ofcatalyst	Large portion of saturatedhydrocarbons
Hydrotreated light	[*64742-47-8*]	C_9–C_{16}	150 to 290°C (302 to 554°F)		H_2 in presence of catalyst	
Hydrotreated light naphthenic	[*64742-53-6*]					
Hydrotreated light paraffinic	[*64742-55-8*]	C_{15}–C_{30}	NA	<100 SUS at 100°F	H_2 in presence of catalyst	Large portion of saturated hydrocarbons
Hydrotreated middle	[*64742-46-7*]	C_{11}–C_{25}	205–400°C (401–752°F)		H_2 in presence of catalyst	
Hydrotreated (mild) heavy naphthenic	[*64742-52-5*]	C_{20}–C_{50}	NA	>100 SUS at 100°F	H_2 in presence of catalyst	Contains relatively few normal paraffins
Hydrotreated (severe) heavy naphthenic	[*64742-52-5*]				H_2 in presence of catalyst	
Light catalytic cracked	[*64741-59-9*]	C_9–C_{25}	150–400°C (302–752°F)		Catalytic cracking	Large portion of bicyclic aromatic hydrocarbons

[a] Adapted fom TOMES (15) and Canadian Environmental Protection Act (144).

33.0 Petroleum Distillates, Catalytic, Reformer Fractionator Residue, Low-Boiling

33.0.1 CAS Number: See Table 22.10.

33.0.2 Synonyms: Petroleum distillates; distillates, petroleum; catalytic reformed naphtha; catalytic reformer fractionator residue, low-boiling; low-boiling catalytic reformer fractionator residue; naphtha, catalytic reformed; reformate

33.1 General

Commonly used as pesticide diluents. In subchronic inhalation studies with petroleum distillates in the form of full-range catalytically reformed naphtha (reformate), rats were exposed to the partially vaporized material at concentrations up to 8050 mg/m^3 for 13 weeks. The highest exposure group had reduced body weights and liver and kidney weights (284).

Chronic exposure to some low-boiling petroleum fractions has been associated with permanent central and/or peripheral nerve damage. No studies were found on the possible genetic or carcinogenic activity of these petroleum distillate fractions in humans or experimental animals. Petroleum distillates in the form of full-range catalytically reformed naphtha (reformate) were not teratogenic or fetotoxic in rats exposed at airborne levels up to 7,800 mg/m^3 of vapors on days 6 through 19 of gestation (284).

34.0 Petroleum Distillates, Clay-treated Heavy Naphthenic

RTECS (18) reported equivocal tumorigenic effects on the skin of mice of 410 gm/kg/78 weeks or 406 gm/kg/22 weeks at the site of application.

35.0 Petroleum Distillates, Clay-Treated Light Naphthenic

RTECS (18) reported that this material is an equivocal tumorigenic agent in mice at 577 gm/kg/78 week, and tumors were found at the site of application.

36.0 Petroleum Distillates, Heavy Paraffinic, Clay-Treated

This product may be a mild skin and eye irritant. Inhalation of large amounts of vapor may produce symptoms of CNS depression, including nausea, headache, weakness, dizziness, loss of coordination, and coma. It is unlikely that high enough concentrations of the vapors would be present to cause death unless bulk quantities of this product are handled under conditions of poor ventilation.

36.4 Toxic Effects

Repeated skin contact with this product may produce dermatitis or oil acne. Inhalation of large amounts of the mist may result in accumulations of mineral oil in the lungs, accompanied by pulmonary fibrosis. It is possible that this product may contain substances which have caused cancer in laboratory animals. It may be noted that used lubricating oils tend to contain higher amounts of cancer-causing substances than new oils. Mineral oils that have high levels of aromatic compounds have been linked with scrotal and lung cancer in humans. Newer mineral oils generally do not contain high levels of these aromatic compounds.

37.0 Petroleum Distillates, Hydrodesulfurized Middle

No information was available on the toxicity of this fraction.

38.0 Petroleum Distillates, Hydrotreated Heavy Naphthenic

No information was available on the toxicity of this fraction.

39.0 Petroleum Distillates, Hydrotreated Heavy Paraffinic

RTECS reported (18) an oral LD_{50} in rat of >15 gm/kg and a dermal LD_{50} in rabbit of >5 gm/kg. This product, listed by EPA, is used frequently as a spray oil in pesticide preparations (146).

40.0 Petroleum Distillates, Hydrotreated Light

No information was available on the toxicity of this fraction.

41.0 Petroleum Distillates, Hydrotreated Light Naphthenic

No information was available on the toxicity of this fraction. This product, listed by EPA, is used frequently as a spray oil in pesticide preparations (146).

42.0 Petroleum Distillates, Hydrotreated Light Paraffinic

No information was available on the toxicity of this fraction.

43.0 Petroleum Distillates, Hydrotreated Middle

No information was available on the toxicity of this fraction.

44.0 Petroleum Distillates, Hydrotreated (Mild) Heavy Naphthenic

44.0.1 CAS Number: See Table 22.10

44.0.2 Synonyms: Distillates (petroleum), hydrotreated (mild) heavy naphthenic; hydrotreated (mild) heavy naphthenic distillate; hydrotreated (mild) heavy naphthenic distillates (petroleum); petroleum distillates, hydrotreated (mild) heavy naphthenic
44.4 Toxic Effects
RTECS (18) listed a rat LD_{50} by the oral route at >15 gm/kg, and dermal application in rabbits resulted in a LD_{50} >5 gm/kg. Skin irritation in rabbits was severe at 500 mg. An IARC review of animal data led to the conclusion that there was sufficient evidence for carcinogenicity (Group I). RTECS listed a mouse skin-painting study with an dose intermittent of 398 gm/kg/22 weeks which resulted in classifying it as an equivocal tumorigenic agent by RTECS criteria, and skin and appendage tumors were at the site of application. Another study cited by RTECS in a mouse skin-painting study with an dose intermittent of 402 gm/kg/78 weeks led to the conclusion that it is an equivocal tumorigenic agent by RTECS criteria, and skin and appendage tumors were at the site of application. An additional mouse skin-painting study was cited where the intermittent dose was 480 gm/kg/80 weeks, the results were considered neoplastic by RTECS criteria, and skin and appendage tumors were at the site of application.
45.0 Petroleum Distillates, Hydrotreated (Severe) Heavy Naphthenic
45.0.1 CAS Number: See Table 22.10

45.0.2 Synonyms: Distillates (petroleum), hydrotreated (severe) heavy naphthenic; hydrotreated (severe) heavy naphthenic distillate; hydrotreated (severe) heavy naphthenic distillates (petroleum); petroleum distillates, hydrotreated (severe) heavy naphthenic
45.4 Toxic Effects
RTECS (18) listed a rat LD_{50} by the oral route at >15 gm/kg, and dermal application in rabbits resulted in a LD_{50} >5 gm/kg. IARC determined that the evidence in animal studies was inadequate (Group 3).
46.0 Petroleum Distillates, Light Catalytic Cracked (Light Catalytic Cycle Oil)
RTECS (18) listed an inhalation LC_{50} in the rat at 3400 mg/m^3/4h and an oral LD_{50} in the rat as 3200 mg/kg.

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Ionizing Radiation
Roy E. Albert, MD

1 Introduction

Ionizing radiation is undoubtedly one of the most intensely studied of all toxic agents. The impetus for understanding its manifold effects came from its extensive use since the beginning of the century in medical diagnosis and in treating cancer. With the development of atomic energy during World War II, the field expanded dramatically. Atomic energy became one of the country's largest industries. The potential health hazards from occupational and environmental sources of radiation became an important area for research; it spawned a new field in the post-World War II era of measurement and control called health physics.

Under the Atomic Energy Commission (AEC), a great national laboratory complex was established for research on weapons and power production and for biomedical and physics research. Long-term biomedical research was also initiated at large university-based facilities and by the support of individual grants. The development and sale of radioisotopes and radiation measuring instruments was subsidized by the AEC to the great benefit of biomedical research in general. Radiation biology has its own society, (the Radiation Research Society), and its own journal, the *Journal of Radiation Research*. In recent years, radiation has become an integral tool for understanding cellular function at the molecular level, for example, the tumor suppressor gene, p53. However, the level of biomedical research on radiation is much lower in the last few decades than earlier.

This chapter gives the toxicologist the basic features of radiation biology. Because of the scope of the field, only the essential concepts are presented. The reader is referred to textbooks (1–6) and other publications cited for more details.

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2 Physical Considerations
There are two forms of ionizing radiation: high energy electromagnetic waves and subatomic particles. Their common property is the ability to eject electrons from molecules, a phenomenon called ionization. At levels of lesser energy deposition, they are also capable of raising electrons to higher energy levels which are called excitation. Both ionization and excitation can lead to chemical change. Thermal effects are of no consequence in the biological effects of ionizing radiation. A whole body exposure of 2000 rads enough to kill everyone twice, would raise the body temperature by only 0.01°C.

The energy of ionizing radiation is expressed in electron volts. The energy range of ionizing radiation is large, from a few electron volts to billions of electron volts. Most commonly encountered is the kilovolt (keV) and megavolt (MeV) domain. The average energy that causes ionization in tissue is about 75 eV.
2.1 Electromagnetic Radiation
Electromagnetic radiation is propagated in packets called photons. The energy of photons is a function of the wave frequency. These frequencies range through many decades. Electromagnetic radiation, in order of increasing frequency and energy, includes radio waves, infrared radiation, visible radiation, ultraviolet radiation and ionizing radiation. Among the nonionizing radiation, ultraviolet light can cause excitation but not ionization, and infrared radiation causes heating.

There are two kinds of electromagnetic ionizing radiation (photons): gamma rays and X rays. They have identical properties but different sources. X rays are generated by machines that accelerate a beam of electrons so that it impacts a metallic target releasing X rays whose energy depends on the speed (energy) of the impacting electrons. This is the bremsstrahlung (braking radiation). Gamma rays are emitted by disintegrating atomic nuclei of radioactive isotopes. The energies of the gamma radiations released by the disintegration process are unique to each radioactive isotope.

There are three modes of interaction of electromagnetic radiation with matter: pair production, compton scattering, and the photoelectric effect.

2.1.1 Pair Production Pair production occurs when a photon whose energy is in excess of 1.02 MeV, passes near an atomic nucleus and is transformed into an electron and a positron. The probability of pair production increases rapidly above the threshold of 1.02 MeV and is a function of the square of the atomic number of the irradiated material. When the positron loses energy to about 1.022 MeV by interactions with the absorbing medium, it undergoes an “annihilation” reaction when it contacts an electron. This results in the release of two photons in opposite directions each with an energy of 511 keV. Pair production is not important in tissue-equivalent materials at photon energies less than 10 MeV.

2.1.2 Compton Scattering Compton scattering is the dominant form of interaction in tissue-equivalent materials at photon energies in the MeV range, such as the gamma radiation from radioactive cobalt-60. The process involves loosely bound electrons. With Compton scattering, the incident photon causes the ejection of an electron and the emission of a photon whose energy is lower than the incident photon. The amount of energy lost by incident photons covers a broad range from virtually zero to 80%. The scattered electrons form a continuous spectrum of energies with a maximum somewhat below the energy of the incident photon and with a peak at both high and low energies. The process is independent of atomic number and is important in the energy range of 100 keV to 10 MeV.

2.1.3 The Photoelectric Effect The photoelectric effect predominates over Compton scattering in the kilovolt energy range used in diagnostic X ray. The photoelectric effect involves only bound electrons in the K, L, and M shells of the atoms in the absorbing material. This is in contrast with Compton scattering that involves loosely bound electrons. The incident photon gives all of its energy to the electron. Some energy is required to overcome the binding energy of the electron; the rest is given to the electron in the form of kinetic energy. When the orbital electron is ejected from the atom, it is replaced by an electron from an outer shell. The difference in the binding energies of the two shells is released as a fluorescent X ray with the characteristic energy of the electron shell. For example, a device for measuring the amount of lead paint in walls is based on the photoelectric effect; it works by shining a source of gamma radiation from cadmium-108 on the wall and measuring the intensity of one of the fluorescent X rays characteristic of lead (7). The intensity is a function of the amount of lead in the paint.

Both Compton scattering and the photoelectric effect occur in the kilovolt range X rays used for diagnostic purposes; the former is dominant at the higher energy range, and the latter at the lower energies. The photoelectric effect is strongly dependent on the atomic number (Z) of the absorber, namely Z^3; hence, diagnostic X rays display bone shadows because of the higher Z of bone compared to soft tissues. Energies in the MeV range are desirable for radiation therapy because Compton scattering predominates, and there is an advantage of having equal absorption by bone and soft tissue.

The radiobiological effects of absorption by the Compton and photoelectric processes are similar because they both result in converting the energy of the photons to electrons. However, the energy of fluorescent photons is small, in the range of 500 eV, and has little biological effect.

In fact, the final common pathway for biological effects for both particulate and electromagnetic radiation, that is, all forms of radiation, is the production of electrons.

2.2 Particulate Radiations

There are two types of particulate radiation: those that are charged and eject electrons by collision and those that are uncharged and interact with matter to form charged particles. The important particulate forms of ionizing radiation that are charged include alpha rays (helium nuclei), protons (hydrogen nuclei), and beta rays (electrons). Neutrons are uncharged atomic nuclear particles that eject protons by collision with hydrogen nuclei.

Alpha and beta particles can be released by the decay of radioisotopes. Neutrons are produced mainly by nuclear fission in reactors or nuclear weapons. Charged particles such as electrons and protons, as well as heavier ones such as carbon, neon, and argon, can be produced in accelerators.

There are two important mechanisms for energy loss by electrons. The first is by scattering. This involves ionization and excitation. The second, bremsstrahlung, involves passage of the electron near an atomic nucleus. Electrostatic forces around the nucleus bend the path of the electron; the consequent acceleration causes the release of a photon. Bremsstrahlung has a broad continuous spectrum of energies characterized by its peak energy; for example, a 250-keV X ray machine produces X rays that range continuously in energy from a few hundred electron volts to a peak of 250 keV.

Electrons undergo multiple collisions in an absorbing material, and each electron has a zigzag track. Secondary electrons that are released by the collision of a primary electron are called delta rays; each has its own zigzag track. The penetration of electrons, for example, into the skin from an isotopic source applied to the surface of the skin, resembles the diffusion of a gas. The dose varies with depth. There is an initial increase due to the buildup of scattered electrons and then a monotonic decrease with increasing depth in skin down to the maximum range.

In the zigzag paths of electrons, short branching tracks are called “spurs”; these contain an average

of three ion pairs. In the case of gamma or X rays, 95% of the energy is deposited in spurs. Larger and more densely ionizing tracks are called “blobs,” and when they overlap the DNA molecule, they produce sites of multiple damage.

With all particulate radiations, the energy transferred is proportional to its charge, the Z of the absorber, and inversely proportional to the square of its velocity. Hence, the rate of energy transfer from particulate radiations per unit path length rises toward the end of its track when the kinetic energy approaches zero. This terminal rise in energy deposition, the Bragg peak, is most important with heavy charged particles whose tracks are straight. It is the basis for selective irradiation of deep tissues within the body, such as the pituitary gland, by highly energetic accelerator-produced particles.

Neutrons are generated over a very wide range of energies, depending on their source. They do not interact electrically with matter but are scattered or absorbed. The modes of interaction are complex and energy dependent. For example, one important mode of interaction is elastic scattering. This is particularly important with hydrogenous material. Both the neutron and the hydrogen nucleus recoil. The recoiling hydrogen nucleus, which is a proton, causes ionization over a distance of microns and the recoiled neutron, now at lower energy, undergoes further collisions. This is the reason that hydrogenous material such as paraffin can be used as a neutron shield.

Another important neutron reaction is absorption by an atomic nucleus, in which the nucleus with its added neutron becomes unstable and undergoes radioactive decay and releases ionizing radiation. Neutron bombardment in a nuclear reactor is one method of producing radioisotopes commercially. The formation of radioactive isotopes in a neutron-irradiated body can also be used to estimate the neutron dose from radiation accidents.

The penetration into tissue of charged particles such as alpha, beta, and protons is very limited. Heavily charged particles produce densely ionizing tracks of short length because their energy deposition per unit path length is so high. Alpha particles deposit energy in short tracks whose length depends on the energy but commonly is on the order of 35 to 50 microns long and a few microns wide. Alpha particles and protons are blocked by tissue-equivalent material no thicker than a sheet of paper. Electrons penetrate one or two centimeters depending on their energy. Electromagnetic radiation and neutrons easily pass through the entire human body because they deposit energy in a widely scattered fashion.

The energy deposition per unit path length, called “linear energy transfer” (LET), has significant consequences with respect to biological effects. There is great inhomogeneity in the dose distribution of high-LET radiation at the microscopic level: many cells receive no radiation at all, and others receive very high doses. A cell can be killed by a single alpha track that traverses its nucleus in sharp contrast with the more diffuse radiation patterns from the low-LET electrons and gamma or X rays.

Densely ionized tracks produced by alpha and protons are qualitatively different from X or gamma rays because the damage, although focal, is so intense that it is difficult for the cells to accomplish repair. The temperature within alpha tracks is several million degrees.

2.3 Dose

Because all forms of ionizing radiation have the final common pathway of ionization and excitation caused by electrons, the important determinant of the way they produce biological damage is the pattern and energy of electron release. Radiation dosimetry can be exceedingly complicated (8). The concept of dose is energy deposition per unit mass of the absorber. The pattern of energy deposition depends on (1) the type of radiation, particulate or electromagnetic; (2) the energy of the radiation; and (3) the geometrical characteristics of the applied radiation. The whole human body can be exposed more or less uniformly throughout all of its tissues by exposure to a broad beam, high-energy external source of gamma or X rays. By contrast, an equal dose can be delivered to the surface epithelium of the tip of one finger by an external isotopic source of alpha radiation. The biological consequences in this example are very different. Hence, the biological effects depend on

both the magnitude and location of the dose.

The basic unit of absorbed dose is the rad, which is 100 ergs per gram. This assumes that one gram units of tissue have a uniform deposition of energy. Since 1977, with the introduction of the SI system (Systeme Internationale), the gray (Gy) has been introduced to supplant the rad as the unit of dose. One gray equals 100 rads. Thus a bridge between the rad and the gray that is commonly used by those who think in terms of rads is one centiGray (cGy) which equals one rad.

Because the biological effects of the various kinds of radiation can be different at equal average tissue doses due to the differences in the microscopic pattern of energy distribution, it has been useful to introduce a weighting factor that makes doses from different types of radiation equivalent in terms of biological effect. Multiplying the dose in rads or grays by a weighting factor yields a dose in terms of rem (roentgen equivalent man) or the sievert. One sievert equals 100 rem just as one gray equals 100 rads. The weighting factor for a specific type of radiation is its relative biological effectiveness (RBE) in relation to a reference type of radiation, namely 250 keV X rays. RBE is commonly used in radiobiological research. In radiation protection, the weighting factor is called a quality factor. As a matter of practicality the RBE is constrained to a specific biological effect, but the quality factor applies to a given type of radiation without reference to a specific biological effect.

2.4 Radionuclides

In its gross structure, the atomic nucleus consists of protons and neutrons (4). The number of protons determines the atomic number (Z) which is the net positive charge of the atom. The negative orbital electrons balance the positive charge. The number of neutrons contributes to the atomic mass number (A). Each element has a unique value of Z. Each nuclide of an element has specific value of Z and A, and is designated by its name and A, for example, Chromium-51. If a nuclide is unstable, it is called a radionuclide. Isotopes of a given element can have different values of A due to different numbers of neutrons. The terms radioactive isotopes and radionuclides are used synonymously.

Unstable nuclides undergo nuclear rearrangements called radioactive decay because they result in the emission of radiation and transmutation to a different element. Generally, the greater the ratio of neutrons to protons, the more unstable; nuclides of A>200 are all radioactive. Ultimately, radioactive decay reduces the ratio of neutrons to protons, but in chain decay there may be a temporary increase in the ratio due to electron emission.

Alpha decay involves the emission of helium nuclei, each consisting of two protons and two neutrons. This reduces Z by 2 and A by 4. Beta decay is equivalent to converting a neutron to a proton, and it results in an increase in Z. The resulting nuclide may be stable or in a excited state which is relieved by the emission of a gamma ray. The energy of alpha radiation emitted by a given radionuclide is constant; usually, the shorter the half-life, the more energetic. However, beta rays are not monoenergetic but exhibit a spectrum of energies which is characteristic of the radionuclide.

More unusual forms of decay involve (1) positron emission (positive electrons) which is the equivalent of converting a proton to a neutron, (2) electron capture with the apparent engulfment of a K orbital electron by the nucleus to convert a proton to a neutron and with the emission of a K electron X ray, (3) Auger electron emission which is the equivalent of electron capture where the fluorescent X ray itself is captured by an orbital electron which is then ejected from the M shell of the decayed atom. Both electron capture and Auger emission reduce the value of Z by one.

Radionuclides undergo decay by a number of alternative pathways so that mixed forms of decay are frequent. The relative frequency and energies of gamma radiation constitute a signature that can be used to identify radionuclides by gamma spectroscopy.

Radionuclides have the property of decaying on a probabilistic basis. Each radioactive atom has a 50% chance of decaying in a fixed period of time, called a “half-life.” In each successive half-life, the number of undecayed radioactive atoms is reduced by a factor of 2. Half-lives range from fractions of a second to billions of years. Most of the stable lead in the world came from the decay of

the uranium and thorium series. The parent isotopes, uranium-238 and thorium-232, have half-lives in the billions of years (9).

Radioactive decay series involve two or more sequential decays before a stable isotope is reached. Starting with a pure sample of the parent isotope, the buildup and decay of the successive daughter isotopes can have complex patterns that are a function of their respective half-lives. These patterns are readily calculable by using partial differential (Bateman) equations. When a decay series reaches equilibrium, the decay rate (e.g., disintegrations/second) is equal for each member of the series; the number of radioactive atoms of each member is proportional to its half-life. The mean life of an isotope is 1.44 times its half-life. The mean life is useful for calculating the total number of atoms of an isotope at time zero; the number of atoms of an isotope is the disintegration rate (disintegrations/minute) multiplied by the mean life (in minutes).

The dose rate from radionuclides deposited in the body decreases as the radioactive atoms decay and because the radionuclide is excreted. If the excretion is exponential, there is an "effective half-life" of the radionuclide in the body which is the product of the radiological and biological half-lives divided by their sum. For example, if the radiological and biological half-lives are each 2 hours, the effective half-life in hours $2 \times 2/2 + 2 = 1$.

The original metric for radioactive decay rate was the curie (Ci) which is the number of disintegrations per second in a gram of radium-226. One Ci = 3.7×10^{10} d/s. One mCi = 3.7×10^{7} d/s. One mCi = 3.7×10^{4} d/s or 2.2×10^{6} dpm. A more recent unit for radioactivity is the becquerel (Bq) which is 1 disintegration per second.

Isotopes of a given element differ chemically only in atomic mass which affects the diffusion rate. The fissionable isotope, uranium-235, was isolated from its parent uranium-238 by gaseous diffusion despite the small mass differential; this was the essential step in the development of atomic energy. Biologically, the mass differences are significant only with the lightest elements. Significant diffusion differences exist between stable hydrogen and heavy hydrogen (deuterium) and tritium (hydrogen-3). Otherwise the behavior of radionuclides is essentially identical to the normal stable isotopes found in living organisms. This is the reason that they can be used as biological tracers.

2.5 Measurement of Radiation

Many commercial instruments are used for measuring ionizing radiation, but the basic principles behind their operation are relatively few. Ionization devices depend on the ionization of air or other gases by radiation. One of the oldest instruments is the gold leaf electroscope, in which a strip of gold foil is hung over an insulated arm, forming two adjacent but connected leaves. The application of an electrostatic charge to the foil causes the leaves to fly apart where they remain until ionization of the air discharges them and causes them to fall toward each other. The extent to which they do so in a given time is a measure of the radiation dose. The loss of a static charge is the basis for the commonly used pocket dosimeters. Ionization chambers measure current flow from ionized gas in a voltage field applied to parallel conducting plates. A cascade of ions in a high-voltage field between a cylinder wall and a central electrode is the basis for the Geiger counter which records individual ionization as clicks or as current flow. Depending on the thickness of the walls of an ionization chamber, they can be adapted to measuring gamma rays, beta rays of different energies, or alpha particles.

Photographic film responds to ionizing radiation much as it does to visible light. A piece of uranium ore unwittingly placed on a wrapped sheet of unexposed film led to the discovery of radioactive isotopes by Becquerel. Film packs are commonly used as personal dosimeters.

Single crystals of sodium or cesium iodide are commonly used scintillation detectors. When struck by penetrating radiation, they emit a flash of light whose intensity is proportional to the energy of the radiation. Photomultiplier tube(s) placed against the scintillation detectors convert the flash of light into an electrical impulse whose size is proportional to the intensity of the flash. Scintillation

detectors count both the number and energy of the detected radiation, providing an energy spectrum that can be useful in identifying the radiation source, generally of gamma-emitting isotopes. These devices are used extensively for imaging in nuclear medicine by using multiple, small, columnated scintillation detectors for gamma radiation and for coincidence counting of positrons that annihilate to form 0.511 MeV gamma rays that are released back-to-back, 180° apart.

Liquid scintillation counters are widely used to measure radionuclides whose radiations are too weak to penetrate the light seal around solid scintillation detectors. The radiation-emitting samples are suspended or dissolved in the fluorescent liquid. As with solid detectors, the intensity of the light signal can be used to count isotopes with different energies, such as tritium-3 and carbon-14, simultaneously.

Thermoluminescent detectors, such as lithium fluoride pellets, store radiation energy during exposure; heating releases the stored energy in the form of light. The intensity of the light is a function of the amount of absorbed energy. Because of their small size, thermoluminescent dosimeters can be very useful in determining the dose distribution in tissue-equivalent phantoms that simulate the radiation of body parts.

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3 Radiation Damage at the Molecular Level
The biological effects of radiation result principally from damage to DNA. Other molecules in the cell are also damaged but they are either present in large numbers or can easily be replaced. DNA may be damaged directly by deposition of ionizing energy within the molecule itself or indirectly by the diffusion of radiation-induced free radical ionization products of water into the DNA molecule.
3.1 Radiation Chemistry
The radiative chemistry of water is extremely complicated (10). However, the most important sequence of reactions between water and radiation is the production of an ionized (charged) water radical, H_2O^+, which reacts with a normal water molecule to yield a free OH^* (hydroxyl) radical. The hydroxyl radical accounts for most of the indirect radiative damage and has a lifetime of only about 10^{-5} seconds. Its short lifetime limits the diffusion distance to a cylinder of about twice the diameter of the DNA molecule. Hence, free water radicals have to be produced in the immediate vicinity of DNA molecules to do damage. About two-thirds of the radiation damage is indirect, caused by water radicals.

Molecular radiation damage can be reversed by several mechanisms. Recombination of radicals and ions can occur before they diffuse apart, within the first 10^{-11} seconds. This is the coming together of the ion and radical pairs to produce the original molecule. A molecule such as DNA can be restituted by reaction of the free radical on DNA with a sulfhydryl molecule, yielding a sulfide radical and normal DNA.

$$\mathrm{DNA^* + RSH \rightarrow DNA + RS^*}$$

The free radical on DNA is thereby transferred to the sulfhydryl moiety restoring the DNA to a normal state. Enzymatic repair, as discussed later, can also reconstitute DNA to its normal state.

The OH^* radical can react by extraction of hydrogen atoms as in

$$\mathrm{R - H + OH^* \rightarrow R^* + H_2O}$$

The OH^* radical can undergo addition reactions as in

$$R - C = C - R + OH^* \rightarrow RCHOH - C^* - R$$

with the formation of a carbonium ion.

Oxygen can play an important role in the fixation of radiation damage as in

$$R^* + O_2 \rightarrow RO_2^*$$

This peroxidation radical is relatively stable and, more importantly, prevents chemical restitution. The presence of oxygen has a dramatic effect in increasing the biological damage from ionizing radiation, as discussed later.

3.2 DNA Damage

Radiation of DNA can damage purine and pyrimidine bases, as well as the sugar backbone (11). The most important mode of radiative damage is to the sugar backbone and results in either single- or double-strand breaks. The single-strand breaks are repaired rapidly within a period of minutes and so efficiently that the DNA is restored to normal with a high degree of freedom from errors in the sequence of base pairs. Single-strand breaks undergo excision repair in which the gap is trimmed back and then reconstituted by polymerase enzymes using the intact strand as a template. Damaged bases per se are removed by glycoylase enzymes, and then the strand is reconstructed by an excision repair process.

Double-strand breaks are much more serious because rejoining the broken ends can result in abnormalities of chromosomal structure. Double-strand breaks can be formed when two single-strand breaks occur simultaneously from an ionization track or if the two single-strand breaks are formed sequentially within ten bases of each other in a period less than that required for repair. Double-strand breaks take hours to be rejoined. With low-LET radiation, single-strand breaks occur about one hundred times more frequently than double-strand breaks. Double-strand breaks are much more common with high-LET radiation.

The principal form of nonlethal genetic damage caused by radiation is the loss (deletion) of chromosomal segments. Less important is single base pair damage that results in point mutations, that is, altered base sequences.

One double-strand break on an unreplicated chromosome results in a broken arm that can rejoin (with some loss of DNA) or remain fragmented either in the form of a rod or, when the ends fuse, as a ring (12). Both the damaged chromosome and the fragment can replicate to form two short-arm chromosomes and acentric fragments. The acentric fragments remain in the parent cell, and the short-armed chromosome segregates into the parent and daughter cells. Two double-strand breaks on one arm of a prereplicated chromosome can lead to the displacement and loss of the segment between the breaks and also results in a short-armed chromosome and a fragment. Acentric fragments, those that have no centromeres, can become encapsulated in a membrane. Such structures are called microsomes and are useful quantitative markers for the action of genotoxic agents, including chemicals and radiation. The microsomes eventually disappear.

When multiple double-strand breaks occur on different chromosomes in close proximity, rejoining can lead to a wide variety of chromosomal abnormalities. Lethal abnormalities include dicentric and ring lesions. Abnormalities that are not necessarily lethal include deletions and translocations.

A double-strand break on each arm of two nearby unreplicated chromosomes can result in a translocation in which the chromosomal fragments switch places. Alternatively, the amputated arm of each unreplicated chromosome can anneal to form a single chromosome with two centromeres. The dicentric chromosome can replicate and become observable in metaphase preparations during

mitosis.

If cells are irradiated after the chromosomes have replicated (during the G2 period) but before being separated during mitosis, a lethal lesion can be formed that is called an anaphase bridge. This is caused by a simultaneous break in the arms of the paired (replicated) chromosomes and subsequent annealing of the stumps. The parent and daughter cells cannot separate during anaphase because of the chromosomal bridge, and they die.

These chromosomal abnormalities are important because they are a mechanism of cell killing and genotoxicity. They can be quantitated in metaphase spreads giving informative dose–response relationships. The shape of the dose–response curve for dicentrics and rings is linear-quadratic. At low doses, the curve is linear because some of the two double-strand breaks are produced simultaneously by a single ionization track. The quadratic higher dose portion of the curve is due to production of each of the two double-strand breaks by separate ionization tracks. Here the probability that two chromosomes are hit by separate tracks within a short time in about the same location is a function of the square of the dose. These relationships make it possible to reconstruct the radiation dose received by an individual by quantitating chromosomal abnormalities in circulating lymphocytes; some lymphocytes have a long residence time in the blood and can be stimulated to undergo cell replication.

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4 Radiation Effects at the Cellular Level
Cell death is reproductive in nature. This means that cells die when they try to divide. This phenomenon was shown in the classic studies of Spear with X irradiation of fibroblast cultures (13). The number of mitotic cells falls promptly after radiation. The magnitude and duration of the decrease in mitosis increases with dose. The presence of necrotic cells first makes its appearance at about the time when there is recovery from mitotic depression. It follows that the first appearance of radiation damage is a function of the proliferative rate of tissues. For example, white blood cells have a rapid turnover of precursors in the bone marrow and a short life in the peripheral circulation. There is a prompt decrease in white blood cell counts shortly after radiation in contrast to red blood cells whose precursors have a slower reproductive rate in the marrow, and the red cells have a relatively long life in circulation.
4.1 Cell Survival Curves
A great deal of quantitative information about reproductive cell killing, cellular repair, and dose–response relationships has been obtained by using the colony formation method developed by Puck (14). This approach involves dispersing cultured cells into single-cell suspensions. Aliquots are loaded into petrie dishes where they settle and attach. The petrie dishes may have a “feeder” layer of lethally irradiated cells that cannot multiply but are metabolically active and facilitate the growth of the single-cell aliquots. After attaching, the reproductively competent cells grow to form colonies several millimeters in diameter in a few weeks. Irradiation of the petrie dishes at the single-cell stage reduces the number of reproductively viable cells monotonically with increasing dose. Colony counts at two weeks give the fraction of cells, corrected for the plating efficiency of controls, that are rendered sterile. Those cells that are “reproductively dead” actually survive and multiply a few times but cannot form colonies. A plot of the log of the fraction of the plated cells, normalized to unity on the basis of the plating efficiency of the controls plotted against the dose on an arithmetic scale, gives a survival curve. The survival curve for high-LET radiation is exponential, a straight line on a semilog plot. The slope is a function of the sensitivity of the types of cells that are exposed to a given type of radiation. The slope is expressed as the D_0 dose, a reduction of survival to 37% which is equivalent to an average of one “hit” per cell. Typical D_0 values are on the order of 1–2 Gy.

The survival curves for low-LET radiation have a flat shoulder in the low-dose region, where relatively little cell killing occurs (15). At higher doses, the curves tend to become exponential, a straight line on a semilog plot. The shoulder reflects repair of the radiative damage. This can be shown by irradiating cells twice with an increasing amount of time between the two exposures. With increasing intervals and replating the cells soon after the second exposure, the shoulder reappears, growing from a small size to the magnitude encountered with single radiative exposures. The repair is complete in a few hours and likely represents the repair of single-strand breaks. After sufficient time for repair, the surviving cells behave as if they had not been previously irradiated. They show the same shoulder and the same survival slope as cells that are irradiated for the first time. This kind of radiative damage, called "sublethal" refers to damage that will be repaired unless additional radiation is administered before the repair period is over. The lack of a shoulder with high-LET radiation indicates that there is no repair, and the interval between split radiative exposures has no effect on the kinetics of survival. There is another kind of damage that is called "potentially lethal." It is a form of damage that is inevitably lethal unless circumstances interfere with the progress of the cell cycle, as with confluent growth in tissue culture where cell-to-cell contact inhibits proliferation. Under these circumstances, the irradiated cells have a chance to recover somewhat from the potentially lethal damage, probably by repairing double-strand breaks. The repair of potentially lethal damage is considerably slower that of sublethal damage.

Back-extrapolation (from high dose to low dose) of the exponential slope to a survival of unity gives a quasi-threshold measure of the width of the shoulder. This varies according to cell type by a factor of 2–3. Some survival curves with a "true" exponential high-dose region can be construed to reflect a multihit process; back-extrapolation of the linear slope to zero dose gives an intercept that can be interpreted as a "hit" number, the number of hits required to render the cell reproductively sterile. The magnitude of the hit number is also an indication of the size of the shoulder.

Some survival curves show a gradually increasing slope without a convincing linear exponential portion. These curves are better interpreted as linear-quadratic in nature. There is a low-dose linear portion and a quadratic portion in the higher dose range.

The equation for the linear quadratic dose response, where R is reproductive cell death, D is dose, and A and B are constants, is

$$R = AD + BD^2$$

This is the same equation used to describe the dose response for the induction of chromosomal damage discussed earlier, and the same interpretation holds that the cell killing has a single-hit component and a two-hit component.

The linear and quadratic components of the cell killing are equal when the dose D is equal to the ratio of the constants A and B:

$$AD = BD^2$$

or

$$D = A/B$$

There is compelling evidence that cell death is a function of chromosomal damage, for example, in terms of a linear relationship between the number of chromosomal aberations (dicentrics and rings) per cell and the log of the cell survival. Other evidence includes cell lethality by tritiated thymidine which is incorporated in DNA and which irradiates only DNA, the increased sensitivity to cell killing by halogenated pyrimidines that are incorporated into DNA, etc.

Tissues of a given type tend to show a relatively narrow range of sensitivities. However, tumors that arise in a given tissue tend to show a broader range of radiosensitivities, some higher and others lower than normal but with considerable overlap. This is an impediment to effective radiative treatment.

The kinetics of cell killing with the Puck technique have proved to be comparable to the kinetics observed *in vivo*. Estimates of cell survival in cancer radiotherapy have some utility. Because single-cell preparations from freshly excised tissue do not do well in the Puck technique, surrogates based on cell numbers in agar suspensions and total DNA content of tumors have been used as measures of reproductive survival.

Radiotherapy involves repeated exposures at intervals that allow for repair in normal tissues. Survival curves for repeated irradiation are exponential without a shoulder because the cell killing from each radiative fraction combines with subsequent fractions multiplicatively. For example, four successive fractions, each reducing survival by a factor of 0.6 will combine to reduce survival to $0.6 \times 0.6 \times 0.6 \times 0.6 = 0.13$. This type of multiplicative interaction yields an exponential survival curve.

Survival curves provide the basis for useful radiotherapeutic calculations. For example with a tumor of 10^9 cells, a 90% chance of cure would involve reducing the population by a factor of 10^{-10}. This target would be achieved with an estimated dose of 69 Gy. This estimate is based on a survival curve without a shoulder, a D_0 of 3 Gy and daily dose fractions of 2 Gy. A tenfold reduction in survival would be equal to $2.3 \times D_0$. Therefore a dose required to reduce survival by ten orders of magnitude (D_{10}) would be $D_{10} = 2.3 \times 3 = 6.9$ Gy $\times$ 10 = 69 Gy.

4.2 Modifiers of Radiation Damage

Survival curves provide a useful means of quantifying the effects of modifiers of radiation damage. For example, the oxygen effect increases the slope of the survival curve by a factor of about 2–4 from the hypoxic to the aerated state (16). The character of the survival curve stays the same, but the effect of oxygen is to decrease the dose by a constant factor for the same level of effect. This applies to both the high-dose quadratic and the low-dose linear portion of the survival curve, although the factor, called the “oxygen enhancement ratio” (OER), is 3.5 for the former and 2.5 for the latter. By contrast, the (OER) is smaller for the higher LET radiations. For example, for alpha radiation, it is 1.0 (no effect), and the OER is 1.6 for 15 MeV neutrons.

Equal total doses given at low dose rates for low-LET radiation have a smaller effect than higher dose rates because the lower dose rates permit repair. This is not true for high-LET radiation. However, if the dose protraction becomes large, the mitotic cycle has an effect because different parts of the mitotic cycle have different radiosensitivities.

The mitotic cycle has a quiescent phase, called G1, which, depending on the proliferative rate, can last for a matter of hours to weeks. Then cells given appropriate stimulation enter the phase of DNA replication, called the S period, which lasts on the order of ten hours. A short period, called G2, follows that lasts a few hours, in which the chromosomes condense. Finally the mitotic phase, called M, takes place which also lasts a few hours; here, the chromosomes line up at an equatorial plate and are pulled by spindle fibers to opposite sides of the cell which then divides in the middle to form two cells. Then the divided cells are either in the G1 phase, and the cycle repeats itself, or are in a G_0 phase which is out of the cell cycle.

The influence of the cell cycle on radiation sensitivity can be easily studied in tissue culture because cells in mitosis round up and are easily detached from the surface of the culture dish by gently agitating the medium. Then the harvest of synchronized mitotic cells can be studied by the Puck technique of colony formation after radiation. The pattern varies with cell type, but the constant feature is that the sensitivity is highest in the G2 and M phases and lowest at the end of the S period.

In some cell types sensitivity is increased at the begining of the G1 period as well (17).

Radiative sensitivity, according to cell cycle, plays a role in the effects of dose rate on cell survival. The effect of dose rate on cell survival is complicated but predictable on the basis of what is known about the dynamics of DNA repair and the effects of the cell cycle on radiative sensitivity. When low-LET radiation is given in a short period at relatively high dose rates, the typical survival curve is obtained with its shoulder and high-dose exponential fall-off. As the dose rate is decreased, the first effect is an increase in the size of the shoulder and a more shallow exponential drop, that is, the D_0 increases. This is due to the fact that DNA repair proceeds during the radiative exposure and nullifies some of its damaging effects. At this level of dose rate, cells are substantially arrested at the junction between G1 and S and between S and G2. The rate of mitosis is much depressed. The reason for the arrest at these checkpoints is the action of the p53 gene. DNA damage activates the p53 gene which then expresses more of its protein. The p53 protein interacts with proteins of related genes to activate the checkpoints that arrest the flow of cells through the mitotic cycle. The effect of this arrest is to give more time for DNA repair, which, if inadequate, triggers cell death by apoptosis.

With a further lowering of dose rate, the checkpoint block is only partial, and cells move through the cycle into G2 and M, where they are more radiation sensitive. This reverses the trend toward shallower survival curves, and the slope of the survival curve increases toward those of the higher dose rates. As the dose rate further decreases, the flow of cells into mitoses is further increased toward normal, and cell proliferation counterbalances the losses due to reproductive death. This further decreases the slope of the survival curve, and it may be flat or have a positive slope indicating that the number of cells increases during radiation.

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5 Cell Survival in Tissues
A number of assays have been developed to determine the survival of clonogenic cells in tissues. These cells include the skin, the villi of the small intestine, the testes, the tubules of the kidney, and cells of the bone marrow and thyroid. The skin assay depends on the formation of regenerating nodules on the skin surface arising from cells that have migrated upward from the underlying hair follicles that have survived the radiative exposure (18). The intestine assay examines the proportion of the villi that are regenerating after irradiation (19). The bone marrow assay looks at colony formation in the spleen after irradiated cells have been injected into the bloodstream and have been deposited there (20). The testes assay determines the proportion of tubules that contain spermatogenic epithelium (21). These assays are done with graded doses of single, multiple, or split exposures. The results of these studies resemble those with cell cultures in terms of a wide range of widths of the shoulders and fairly uniform high-dose slopes.

Assays have been done on functional end points in contrast to cell survival. Typical of such studies are the effects of X rays on skin reactions in the mouse (erythema, desquamation, and ulceration) with single and fractionated exposures. It is evident that fractionation permits a great deal of radiative repair in the skin. As shown later, this holds true for skin carcinogenesis as well.

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6 Radiation Sensitivity According to Cell Type

As early as 1906, Bergonie and Tribondeau (22) noted that different kinds of mammalian tissues have very different radiation sensitivities. The most sensitive were those that have a high mitotic rate, undergo many cell divisions, and are primitive in character, that is, are undifferentiated.

Rubin and Casarett's categorization of types of cells according to decreasing levels of radiosensitivity is still used (23). Category I includes the most radiosensitive: these are cells like the basal cells of the epidermis that undergo regular cell division and show no differentiation between divisions. Category II cells are like myelocytes in the bone marrow that also divide regularly but do undergo some differentiation between divisions. Category III cells are relatively resistant like the hepatocytes in the liver that normally divide very infrequently but can be triggered into rapid mitosis. In the case of the liver, this occurs with toxic liver damage or partial hepatectomy. Category IV has the most resistant cells, including muscle cells and the neurons of the central nervous system. These cells are highly differentiated, and it is questionable that they divide at all once the organism reaches maturity.

Cell death is reproductive in nature. It follows that the first appearance of radiation damage is a function of the proliferative rate of tissues. For example, white blood cells have a rapid turnover of precursors in the bone marrow and a short life in the peripheral circulation. There is a prompt decrease in white blood cell count shortly after radiation, in contrast to red blood cells whose precursors have a slower reproductive rate in the marrow, and the red cells have a relatively long life in the circulation (24).

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7 Chemicals that Modulate Radiation Effects

Some chemicals increase and others decrease radiation effects. One class of chemicals that increases radiosensitivity is the halogenated pyrimidines, including 5-bromodeoxyuridine (BUdR) and 5-iododeoxyuridine (IUdR) (25). The halogen is recognized as a methyl group, and these chemicals are treated metabolically as if they were thymidine and are incorporated into DNA. The DNA bonds are weaker with the halogen moieties, and radiation-induced strand breakage occurs more readily. The degree of incorporation is a function of the rate of cell proliferation. Therapeutic effectiveness for cancer depends on the relative rates of turnover of cancer cells compared to normal surrounding tissues. In cultured cells, the dose required to reduce survival to a given level of reproductive death is about one-half in halogenated pyrimidine treated cells compared to untreated cells. The use of these agents has received some clinical attention.

There are chemicals that increase the radiation sensitivity of hypoxic cells but not those that are well oxygenated (26). Their potential use in cancer radiotherapy depends on the presence of hypoxic cells in tumors because such cells are relatively radioresistant. These chemicals belong to the class of nitroimidazoles such as etanidazole. They mimic the action of oxygen and fix radiative damage by preventing chemical restitution of the damaged molecules. They have an enhancement ratio of about 2. Their use is limited by neurotoxicity. They also sensitize cells to cancer chemotherapeutic drugs, particularly alkylating agents.

Chemicals that decrease radiation effects are called radioprotectors. The sulfhydryl compounds are an important class of radioprotectors, including the natural amino acid cysteine and its metabolite cysteamine (27). The factor for dose reduction (the ratio of doses for equal effect) is about 2 for these compounds. They work by scavenging free radicals and promote chemical repair by restitution. Because of the short life of free radicals, the radio protector must be present at the time of irradiation. Their behavior with respect to LET is analogous to the oxygen effect, strong for the low-

LET radiations and minimal for the high-LET radiations. Like the oxygen effect, the maximum dose reduction factor would be 3. The nausea and vomiting produced by cysteine and cysteamine are reduced by covering the SH moiety with a phosphate. Such a compound is activated intracellularly by metabolic removal of the phosphate. The best of the synthetic compounds is WR2721 which is S-(2-(3-amino propylamino)) ethylphosphothioic acid (28). Its effectiveness depends on penetration of cells. Its failure to protect the central nervous system is due to the blood–brain barrier. Radioprotective agents do not have important uses. For practical reasons they are of no help in radiation accidents, where the administration is necessarily delayed. Their use for anticipated exposure is limited by hypotensive toxicity. Use in cancer radiotherapy is problematic because benefit requires protection of normal tissues but not the tumor which cannot be readily determined except after the fact.

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8 Let and RBE
As indicated earlier, gamma and X rays are sparsely ionizing; there is substantial separation of the ionization in tissue. Particulate radiation such as alphas, protons, and neutrons are densely ionizing because they produce dense columns of ionization (29). LET refers to the energy deposition per micron of path length. Typical values are 0.3 keV/mm for 1 MeV gamma rays, 2 keV/mm for 250 keV X rays and 100–2,000 keV/mm for heavy charged particles. The relative biological effect (RBE) is the ratio of doses for equal biological effect for a given type of radiation relative to the benchmark radiation of 250 keg X rays. RBE increases with LET to a peak of 100 keV/mm and decreases at higher LETs (30). The reason for this pattern is that at 100 keg/mm the average separation between ionizations is about 2 nm which is similar to the diameter of the DNA helix, thus maximizing the efficiency of a double-strand break. LETs less than 100 keg are more likely to produce single-strand breaks that are more readily repaired than double-strand breaks. LETs higher than 100 keg represent overkill for double-strand breaks and are less efficient and more wasteful of radiation dose.

The RBE for high-LET radiation compared to low-LET radiation increases at lower doses because of the shoulder in the dose–response curve for low-LET radiation, whereas the high-LET radiation is linear. Hence, RBEs are not dose invariant. RBEs differ according to tissue type and tend to be higher where DNA repair is rapid for sublethal damage so that the shoulder on the dose–response curve is broad. The oxygen enhancement ratio (OER) is about 3 for low-LET radiation. It decreases when the LET reaches 30 keV/mm and reaches unity at 160 keV/mm (31).

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9 Whole Body Radiation Syndrome
The duration of survival and the nature of the effects of brief whole body exposure to penetrating ionizing radiation is related to dose. Most of our information on the whole body radiation syndrome in humans has been the result of accidental nuclear criticality incidents and the study of atom bomb survivors (32).

At the highest doses in the domain of ten thousand rads (100 gray), the reaction is immediate. One example is that of an individual who worked in a uranium-235 recovery plant. Uranium 235 is the fissionable isotope of the uranium-238 decay chain. Late Friday afternoon, he inadvertently poured a

container held under his left arm, filled with a solution of ^{235}U-enriched uranium, into a barrel already containing a similar solution. He apparently lost track of how much fissionable material the barrel contained. The amount he added exceeded criticality. There was a blue flash as the liquid exploded, and he was drenched with the radioactive fluid. He immediately became disoriented. His coworkers did a partial decontamination. He was taken by ambulance to a series of hospitals which refused admission. An admitting hospital was finally located, and he was installed in an evacuated emergency ward, placed on a rubber sheet and further decontaminated by sponging with wet towels. During the night, his blood pressure dropped sufficiently to warrant continuous intravenous vasopressor medication. The next morning, his left arm and the left side of his face abruptly became severely edematous. In spite of the vasopressor medication, he went into irreversible shock and died that afternoon about 22 hours after exposure. This pattern is known as the central nervous system/cardiovascular syndrome. The disabling effect of high doses of radiation on the function of the nervous system was the basis for considering the wartime use of atomic weapons to disable pilots.

The gastrointestinal syndrome predominates at doses of about 1000 rads (10 gray). It is expressed as a cholera-like syndrome that results from denuding the lining of the small intestine. Nausea and vomiting are immediate and intense. Diarrhea begins in a day or two. If not treated, the outcome is fatal in about 9 days. The reason for the GI syndrome is the radiosensitivity of the stem cells of the crypts of the intestinal villi. These villi are numerous finger-like projections of the intestinal mucosa that enormously increase the absorptive capacity of the small intestine. As the stem cells reproduce, the daughter cells move up the villi, undergo differentiation, and eventually slough off the tips of the villi. The proliferating stem cells at the base of the villi are more radiosensitive than the postmitotic cells on the villi. The effect of the radiation is to cut off the supply of new cells on the villi. After a number of days, the surface of the intestine is denuded. Transmucosal water transport is deranged, and fluids pour into the lumen of the intestine causing diarrhea which can be bloody. Supportive therapy with fluid replacement and antibiotics to restrain bacterial growth in the gut can be helpful but the damage at doses of 1000 rads or greater is too severe to permit survival. Death can supervene before the lethal consequences of hemopoietic damage take effect.

The radiation dose required to kill half the population of humans (LD_{50}) is about 400 rads if no medical treatment is used. With treatment by antibiotics and the use of sterilized environments, the LD_{50} is about 800 rads. The cause of death is the hemopoietic syndrome or bone marrow death.

The mechanism is similar to the GI syndrome. The stem cells in the bone marrow are more radiosensitive than their differentiated offspring, and they stop replicating. There is a drop in the concentration of circulating blood cells which is a function of the life spans of the various types of blood cells. The drop in red blood cells is slow because of the 120-day life span of mature erythrocytes. Adult lymphocytes are unusual in being directly destroyed by radiation, and their disappearance from the blood is precipitous. Leukocytes and platelets fall in a matter of 2–3 weeks. When the concentration of leukocytes and platelets falls to critical levels, the irradiated individual develops infection particularly in the mouth and oropharynx and bleeding of the skin (petechia) and from the kidney into the urine. Transfusion of bone marrow cells has been used to treat the hemopoietic syndrome by replacing stem cells of the marrow. There is a relatively narrow window for success. Doses at or greater than 1000 rads are lethal because of the GI syndrome, and doses up to double the LD_{50}, 800 rads, are recoverable with medical treatment. So the dose range where bone marrow transfusion is life-saving is between 800–1000 rads. The dosimetry of radiative accidents is generally uncertain, so the need for bone marrow transfusion is mostly with high-dose radiotherapy of disseminated cancer such as leukemia. The required bone marrow dose is on the order of 2×10^9 cells.

Ancillary damage with the whole body radiation syndrome on the order of the LD_{50} is hair loss because of the relatively high sensitivity of cells in hair follicles. This sensitivity was the basis for

the Adamson–Keinbock method of depilation of the scalp by X radiation for treating scalp ringworm (*Tinea capitis*). Previous to this, the hair was pulled out manually to decontaminate the scalp of the fungus. Hair grew back in a few months.

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10 Heritable Effects
As indicated earlier, ionizing radiation can produce genetic damage by chromosomal breakage or single base pair changes (point mutations). Classic studies by Muller in the 1920s on *Drosophila* demonstrated the linearity of the dose–response for mutations (33). There was no effect of dose rate or fractionation. Effects on the male gametes depend on the stage of sperm development, and mature sperm (spermatogonia) are the least sensitive, and dividing meiotic cells are eight times more sensitive. Oocytes are relatively insensitive. Concern about the applicability of these data to humans led to massive studies of millions of mice by the Russells at Oak Ridge (34). Using a number of specific traits such as various hair colors, they confirmed the linearity of the dose–response but found that, unlike *Drosophila*, there is a pronounced dose–rate effect that amounts to a reduction factor of 3 in dose for a given level of mutagenic effect.

The female is so much less sensitive than the male that for practical purposes almost the entire burden of radiation-induced mutations falls on the male. It was found that a delay of a few months in conception after radiation in the mouse markedly reduced the number of mutations. Humans are advised to delay conception for 6 months after heavy radiation. This reduction is presumed to be due to a repair mechanism.

Based on the mouse data, the estimated doubling dose in humans, the dose required to double the background incidence of mutations, is about 100 rads (1 gray) (35). Using a variety of indicators, the doubling dose in A-bomb survivors was in the same domain, about 156 rads although the data were not statistically significant (36). The ICRP uses an estimate of 0.6×10^{-4} per rem for radiation-induced hereditary disorders in a working population. The effect of radiation on the induction of congenital malformations is far more important than on heritable effects.

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11 In Utero Effects
Radiation damage at the preimplantation stage leads to fetal death. In the period of organogenesis, radiation causes structural malformations. In the stage after organogenesis, called the period of fetal development, radiation causes growth retardation manifested by low birth weight which may or may not be reversible during childhood. The stages of preimplantation, organogenesis, and the fetal period corresponds to 0–9 days, 10 days to 6 weeks, and 6 weeks to term, respectively, in humans. All in utero effects are due to cell killing, abnormal differentiation, and impairment of cell migration in the brain (37).

Irradiation during organogenesis in mice results in major malformations such as anencephaly, evisceration, and spinal bifida, as well as minor terata such as extra ribs. Humans are apparently not as susceptible as mice to the induction of malformations although some have been reported anecdotally from clinical experience. In the study of Japanese survivors of the A-bomb, growth

retardation, microcephaly, and mental retardation have been encountered (38). The occurrence of mental retardation peaked at 8–15 weeks (fetal age) of irradiation. There was a fairly linear dose–response relationship that reached 60% at doses in the range of 135 rads (39). Before and after this period of fetal development, radiation produced little mental retardation. Radiation before 8 weeks can lead to microcephaly without mental retardation. The dose response for mental retardation suggests a threshold at 25 rem.

Minimal doses with effects on the embryo and fetus include oocyte death in primates (LD_{50} = 5 rads), CNS damage in mice at 10 rads, brain damage in rats at 6 rads, small head circumference in humans at 6 rads (38).

The NCRP recommends that the maximum permissible dose during the entire gestation period in women should not exceed 0.5 rem and the monthly exposure should not exceed 0.05 rem (40). The data on mental retardation suggest that a reduction in IQ would be undetectable at 10 rads. Exposure of the conceptus/fetus during the period 10 days to 26 weeks, which is the period of sensitivity to malformations, reduction in head circumference, and mental retardation, to radiation above 10 rads should raise concern about the advisability of therapeutic abortion.

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12 Carcinogenesis
Radiation is probably the most thoroughly studied of all known carcinogens in both animals and humans. The impetus for this effort stemmed from the frequent appearance of cancer in X ray pioneers at the beginning of this century, soon followed by the demonstration that radiation can induce cancer in animals. These findings made it clear that radiation is dangerous and that there is a need to protect the large numbers of individuals involved in the extensive use of radiation in medicine and in the atomic energy industry that was developed during and after World War II.

Some generalizations can be made about radiation in relation to other carcinogens. Radiation can induce cancer in virtually every organ of mammalian species but not necessarily in the same species. It can induce cancer de novo in tissues that do not normally develop cancer, and can accelerate the spontaneous occurrence of cancer. The kinds of cancers that are induced by radiation do not differ from those that occur spontaneously or are induced by other carcinogens. This makes it difficult to detect small carcinogenic effects of radiation. Radiation behaves like other carcinogens. Higher doses elicit tumors faster than low doses. As with other carcinogens, there is a substantial delay from the onset of exposure to the induction of cancer by radiation. As with other carcinogens and with spontaneous cancer, the latency is a function of the life span of the species in which cancer is induced; the shorter the life span, the shorter the latency. Latency in humans is a matter of years and can range from a few years up to about 40 years, depending on the target organ and the level of exposure. For example, leukemia induction in Japanese atom bomb survivors began to appear in a few years, whereas excesses of solid tumors in this group did not begin to appear until several decades after exposure. Most cancers take on the order of 15 years to develop after the onset of exposure. Most cancers induced by radiation or chemicals, once started, continue to appear unabated over the lifetime. Leukemia induction by radiation is an exception because it peaked at 5 years. Among chemical carcinogens, bis-chloromethyl ether was also unusual in having a wave of tumor induction in humans. The cause of either the continuous or limited response pattern is not known.

All of the types of radiation can produce cancer if they penetrate to the target cells of the target organ. Generally, high-LET radiations have a linear dose–response pattern, whereas low-LET radiations generally have a linear quadratic shape. This makes the RBE of high-LET radiation

greater in the low-dose range. Radiation can induce cancer by external exposure or internal exposure from implanted isotopic sources or from inhaled or ingested radioactive isotopes.

The mechanism of action of radiation is similar to that of chemical carcinogens in their ability to damage DNA with the activation of oncogenes or the deactivation of tumor suppressor genes. The former involves a “single hit” process. Activation of an oncogene on one allele is tumorigenically sufficient. By contrast, it is necessary to deactivate both alleles of tumor suppressor genes to induce cancer most effectively.

Radiation interacts with other environmental carcinogens. For example the interaction between irradiation of the lung by radon and cigarette smoking is multiplicative and therefore far larger than the effects of either agent separately.

The induction of cancer by radiation is similar to other biological effects in terms of the importance of repair processes. Generally, there is a comparable reduction in the effectiveness of cell killing and tumorigenesis by low-LET radiation with split-dose or low-dose rate exposures. No such effects occur with high-LET radiation. There are exceptions to this generalization such as the more efficient induction of lymphoma by split X ray doses in mice (41) and increased cell killing and tumorigenesis with neutron radiation.

Radiation is unusual among carcinogens in that a single dose can induce cancer, whereas with chemical carcinogens, repeated doses are required to induce tumors. Tissue damage is a common accompaniment to the induction of malignancy.

Although these generalizations are valid, they do not give the flavor of the complexity of tumor induction in individual tissues, different species, and by different kinds of radiation. We illustrate the point by considering skin cancer induced by radiation in the rat, compared with the mouse and humans.

12.1 Skin Tumorigenesis

With single beta-ray exposures of the back of the rat, radiation induces a wide variety of tumor types, most of which resemble the differentiation patterns of various parts of the hair follicle: the sebaceous glands, the external sheath, the hair germ, and the squamous keratinization pattern (squamous carcinomas) of the upper part of the hair follicle or the surface epidermis (42). There are also tumors whose cells are undifferentiated that arise from the hair follicles and from the surface epithelium. All of these tumor types are seen in humans, but with radiation of the scalp most of the tumors are of the basal cell variety; squamous carcinomas arise from irradiation of relatively nonhaired parts like the hands. Squamous tumors are the only type induced in the mouse skin with radiation (43). Skin tumors in the mouse therefore have a more limited range of differentiation than in either the rat or human.

The dose–response pattern in the rat does not fit any simple formulation, linear quadratic or dose square. The dose–response has a sigmoid shape with a sharp peak and a rapid fall with further increases in dose. The fall is associated loss of viable skin due to increasingly severe and extensive ulceration with progressively narrower scars. The tumor types also change with increasing dose. Hair follicle tumors are not formed in the ulcerating dose range, only squamous carcinomas. The growth rate of the tumors increases with dose even among the squamous carcinomas. In the high-dose range, the rats generally carry one or two large squamous carcinomas on their backs. In the lowest tumorigenic dose range, all of the tumors are sebaceous cysts that look like clusters of mature sebaceous glands. The clumps of overreplicated sebaceous glands are nodular. These quasi-tumors give way at higher doses to the less differentiated hair follicle and squamous tumors. Hence, this rat skin model is not consistent with the stochastic concept of carcinogenesis, namely, that malignancy is independent of dose, that is, only the incidence is a function of dose. Similarly, in the harderian gland tumor model, the lesions are more benign at low dosage, although of the same histological type (44). The relationship of dose to malignancy is insufficiently studied in the field of both radiation and chemical carcinogenesis. Its importance relates to the cancer risks of low levels of

exposure to carcinogens.

The hair follicle tumors in the rat can be seen histologically to arise from atrophic hair follicles at a ratio of about one tumor per 2000 atrophic follicles. The follicles are completely eliminated at higher doses where the tumor type is limited to squamous lesions. This suggests that the differentiation pattern of tumors reflects that of the surviving cells. The shapes of the dose–response for tumors and hair follicle damage are very similar. The both have the typical sigmoid shape of toxic responses.

The mouse is different from the rat. With increasing dose, the hair follicles survive intact up to the point where they are obliterated completely. There is no intermediate form of partially killed (atrophic) follicles. This is apparently the reason that the mouse does not develop hair follicle tumors. The tumor induction in the mouse appears at dose levels that eliminate hair follicles.

Chemical carcinogens show a different response pattern in the rat, as illustrated by a study with the polycyclic aromatic carcinogen, anthramine. No hair follicle killing was observed, but there was a profuse yield of hair follicle tumors and squamous tumors. Thus, the association of hair follicle atrophy would seem to rest on the similarity of the dose response for cell killing and malignant cell transformation, not the role of tissue damage in the cause or enhancement (promotion) of tumor induction (R.E. Albert, personal communication).

The skin is markedly sensitive to the depth of penetration of radiation (45). This was first noted with proton irradiation of rat skin where doses up to 10,000 rads to the skin surface produced no tumors. The penetration of the proton radiation was only about 200 microns. Subsequent studies showed that with electron radiation, tumor formation increased for equal surface doses when the penetration of the radiation was increased by increasing the energy of the electrons. Subsequent studies showed that the effects of penetration depth could be reconciled by relating the tumor responses to the dose at a depth of 330 microns in the skin. This is the location of the hair follicle bulge region that contains the stem cells for the hair follicles. Thus, the tumor response is related only to the dose to the stem cells. This finding has subsequently been confirmed by studies of chemical carcinogenesis. It is now commonly assumed that the target cells for tumor induction in every tissue are its stem cells.

Split doses with low-LET radiation showed dramatic reductions in tumor formation indicating the importance of repair processes. Increasing the intervals between the two doses from 1 to 24 hours demonstrated that the repair has a half-life of about 2 hours (46). This is consistent with the time required to repair double-strand breaks in DNA, suggesting that the dominant process in skin tumorigenesis is chromosomal damage. Skin exposed to high-LET radiation such as accelerator-produced argon nuclei showed no repair with split doses. Apparently, the amount of damage to DNA by high-LET radiation is too great to repair.

The characteristics of tumors are so closely linked with those of the parent tissues that cancer is frequently considered a collection of individual diseases that have some features in common. Although this is an exaggerated idea, it conveys the point that extrapolation of carcinogen-induced responses of one tissue to another should be done with circumspection.

12.2 Epidemiological Studies

Many epidemiological studies have been done to characterize the nature and magnitude of the carcinogenic effects of radiation in humans (47). These populations include Japanese atom bomb survivors and patients treated by X radiation for ankylosing spondylitis, acute mastitis of the breast, tinea capitis infection, and thymic enlargement in infants. Follow-up studies have been done on children whose mothers were given X-ray pelvimetry when they were in utero, as well as women who had repeated fluoroscopic examinations for tuberculosis in relation to their breast cancer experience. Studies have been done on uranium miners and miners of other ores that are contaminated with uranium to determine the effect of radon exposure on lung cancer induction. Women who were occupationally exposed to radium were studied for bone cancer, and a number of studies have been done on radiation workers in the atomic energy industry to determine their cancer experience at low levels of exposure.

Only a relatively few studies characterize dose–response relationships in radiation-induced cancer in humans. The rest are useful for giving estimates of risk at one specific dose level.

Two approaches have been used to characterize cancer incidence or death rates in epidemiological studies. One method is to subtract background cancer from the observed response and to regard the excess as the radiation effect. This is known as the "absolute risk" model. The underlying idea is that the radiation effect is independent of whatever it is that causes background cancer. The alternative method is the "relative risk" model which regards radiation as interacting with whatever it is that causes background cancer. This approach is similar to the doubling dose concept mentioned above in the context of the mutagenic response to radiation. Experience with a wide variety of radiation cancer responses tends to support the use of the relative risk model, although not exclusively.

The kinds of tumor studies that provide dose–response relationships include leukemia, breast cancer, lung cancer from radon and bone cancer from radium.

Leukemia induction has been studied mainly in two populations: atomic bomb survivors in Japan and patients with ankylosing spondylitis, a form of rheumatoid arthritis of the spine, which is treated with X radiation. A wave pattern of leukemia was found in both studies. Leukemia in the Japanese peaked at 10 years after exposure and declined thereafter without returning to normal. The same was true for the spondylitics, except that leukemia began earlier at about 2 years postexposure. Japanese up to 20 years of age at the time of irradiation showed an earlier peak than those over 20 years of age at irradiation with a more rapid decline, so that the overall risk was about the same. The dose–response in the Japanese for leukemia is consistent with a linear nonthreshold pattern with the lowest dose at 40 rem and a peak induction at 300–400 rem. Above this dose range, the incidence declines with increasing dose presumably due to the killing of potentially leukemogenic cells. The relative excess risk was 4.2–5.2. No excess cases of chronic lymphocytic leukemia were observed. The effect was limited mainly to acute and chronic myelogenous leukemia. The leukemia risks in the spondylitics were considerably lower than in the Japanese presumably due to the partial bone marrow exposure, because the radiation was centered over the spine, the radiation was more protracted, and the population was older.

The effect of radiation in inducing breast cancer in women has been studied in Japanese atom bomb survivors, tuberculosis cases that were repeatedly fluoroscoped, and cases of X-irradiated postpartum mastitis. These studies have all shown low-dose linearity of cancer induction. There was no effect of fractionation on the cancer response. The cancer risk was highest in women who were less than 20 at the time of radiation; those over 40 showed no increase in the incidence of cancer. The latency of breast cancer was about 10 years with a peak incidence at 15–20 years after exposure and a peak in mortality about 5 years later. There was no effect of dose on latency. Whether this was due to the relatively short period of exposure is not clear. Short periods of exposure in animals do not show much of a dose effect on latency, compared to chronic lifetime exposure.

Lung cancer has been studied mainly in Japanese atom bomb survivors and uranium miners, as well as in ankylosing spondylitics. There are dose–response data only for the uranium and other underground miners exposed to radon. Here again the dose–response is consistent with a linear nonthreshold character (48).

It is apparent that most of the data on dose–response relationships is linear, suggesting that there is no level of exposure that does not have an associated cancer risk. However, in all of these cases the lowest doses are substantial, for example, 40 rem in the Japanese leukemia data. Hence for radiation protection purposes, it is assumed that the radiative dose response is linear nonthreshold.

A considerable body of information has been accumulated on cancer risks in the absence of dose–response data. There is considerable variation in the radiosensitivity among the various organs, on the order of a factor of 7 at the extremes (47).

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13 Cataracts of the Optic Lens
One of the important nonstochastic late effects of ionizing radiation is damage to the lens of the eye (49). The lens is an onion-structured epithelial tissue located inside a fibrous capsule that is situated immediately behind the pupil. The epithelial cells constitute the outer anterior layer. They divide near the equator of the lens. The replicated cells are displaced inward where they flatten and become transparent fibers. There is no mechanism for removing damaged cells. When the proliferating cells are damaged by radiation, they migrate as opaque granules to the posterior surface of the lens. If the amount of damage is mild as with scattered radiation to the eyeball from tinea capitis radiation, where the dose was about 50 rads, the only observed effect was scattered posterior granules. These had no effect on eyesight. Furthermore, the damage was not progressive (50, 51).

The threshold for sight-impairing cataracts is on the order of 250 rads. Doses of this magnitude and greater produce more extensive opacities on the posterior face of the lens which can become progressive to the point of obscuring eyesight.

The experience with radiation-induced cataracts has been largely with the untoward effects of radiation therapy. Workers around accelerators in the early days were particularly at risk for cataracts because of the high RBE of neutrons (52). The dose response in mice for neutron radiation is linear, unlike that from low-LET radiation. The RBE at high doses is on the order of 10. At low doses, the RBE is in the range of 50.

In humans, the time for developing cataracts depends on the dose and can range from months to decades. The latency is on the order of 8 years for doses between 250 and 650 rads. The reason for the long delay and the progressive nature of some cataracts is not clear. Presumably, it has to do with the delays associated with reproductive cell death, where consecutive normal cell replications can occur before cell death supervenes; the slowly accumulating cellular debris is undoubtedly a factor.
13.1 Other Late Nonstochastic Tissue Effects
Late irreversible and progressive damage to tissues results from clonal depletion of tissue cells with particular reference to blood vessels (53). This process leads to fibrosis and circulatory insufficiency. Depletion of cells can occur in terms of functional subunits, such as, kidney nephrons. Damage to the vasculature can occur at the level of both the larger vessels and the microcirculation. An example of the former is the case of accidental radiation of the lower extremities from cyclotron-produced X rays. This resulted in progressive sclerosis of the major arteries in the lower extremities requiring amputation about 6 months after exposure.

Other examples of late damage include fibrosis and stenosis of the esophagus, fibrous atrophy of the stomach and intestinal mucosa, atrophy of the epidermis of the skin and permanent loss of hair follicles, fibrosis of the lung, and necrosis of the brain. Fractionation and dose protraction generally reduce the effectiveness of low-LET radiation in inducting late tissue damage.

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14 Health Effects of Radionuclides
The health significance of radionuclides lies in their ability to enter the body where their biological

behavior is determined by their chemical properties and their radioactive properties allow them to irradiate tissues in which they localize. Thus alpha- and low energy beta-emitting isotopes, which are essentially innocuous outside the body, can produce radiation damage when taken into the body. The two principle routes of exposure to nuclides are inhalation and ingestion. If the inhaled particles are soluble, they are absorbed promptly from the lung and distributed in the body according to their chemical properties. If insoluble, the particles deposited on the bronchial mucosa are swept out of the lung by ciliary action and swallowed. The particles that are deposited in the air spaces of the lung (alveoli) can remain there for long periods of time if they are sufficiently insoluble, such as thorium dioxide which has a half-life of years. Such particles can be slowly relocated to the pulmonary lymph nodes. Particles that are ingested or swallowed after inhalation can be absorbed from the gut and distributed in the body. Some chemicals such as the actinides, thorium and plutonium, are not absorbed regardless of their solubility.

Of the hundreds of radionuclides only relatively few constitute a source of health concern.

14.1 Nuclear Fission Products

The enormous number of nuclear fragments resulting from the fission of nuclear materials in bombs and fuels in nuclear reactors constitutes a potentially dangerous radioactive source of external and internal exposure. Large-scale release of fission products such as happened at Chernobyl (54) can make large geographic areas uninhabitable for years and is one of the deadliest consequences of nuclear war or reactor accidents. The decay of fission isotopes follows a log-log pattern with a rapid initial disappearance of short-lived isotopes and slower disappearance of the residual long-lived isotopes. Yet the quantities of isotopes are so large in nuclear fuels that liquid storage in tanks requires refrigeration to prevent their boiling and exploding. The core of the earth is molten because of heat from the decay of uranium and thorium. Fallout from atomic weapons testing in this country resulted in the dissemination of two important isotopic health hazards: iodine-131 and strontium-90; these are cancer hazards for the thyroid gland and bone, respectively.

14.2 Radium-226

Radium-226 is one of the elements in the decay chain of the naturally occurring uranium-238 decay chain. Radium-226 has a half-life of 1600 years and decays to the gas Radon-222, and then to a series of bismuth, polonium, and lead isotopes to stable lead (55). Young women painted aircraft instrument dials with luminous paint that contained mainly radium-226 mixed with a phosphor so that the dials would glow in the dark. To paint thin lines, the women tipped the brushes with their tongues and thereby ingested substantial amounts of radium (55).

Metabolically, radium behaves like calcium, and the major site of deposition was in the calcified parts of the bone. Radiation, primarily from the alpha rays, heavily damaged the bone and caused cancer in skeletal and nasal sinuses of the most heavily exposed individuals. Follow-up studies were done on many of the women involving evaluation of the skeletal burdens by measuring radon in exhaled air and direct measurement of the skeletel radium-226 in whole body counters. These coumters are steel chambers on the order of 6 inches thick that reduced the ambient background to very low levels and permit measuring the gamma rays from radium-226 with large sodium iodide scintillation detectors. By following the urinary excretion of radium and successive whole body counts, the effective disappearance of radium from the body was determined to be a log-log function, and back-extrapolation gave the initial body burdens.

The exposure standard for radium-226 was set at 0.1 mCi because no evidence of bone cancer was seen at this level of exposure. The dose–response curve for bone cancer looks like a threshold response (56). When it became evident that strontium-90 from atomic weapons tests was widely disseminated in the environment and from there into milk via grazing cattle, great efforts were made to formulate standards of exposure in relation to radium-226. This was done by comparing skeletal cancer induction by radium-226 with strontium-90 in dogs. It was felt that the dosimetry of these bone-seeking isotopes was too complex to rely on comparisons of the isotopes in terms of absorbed dose. The distribution of the radionuclides was spotty in the bone and partially buried in the calcium matrix, and there was uncertainty about which cells were the targets for cancer induction. Hence the comparison was based on skeletal burdens in relation to tumor induction.

Another isotope of radium, radium-224 (thorium X), a 3.6-day half-life, alpha emitter has been used to treat children with tuberculosis and ankylosing spondylitis. Bone tumors (osteosarcomas) were induced with appearance times of 3–22 years after the initial injection (57).

14.3 Plutonium-239 and Plutonium-238

Plutonium-239 and Plutonium-238 are alpha-emitting man-made elements (48). Plutonium-239 has a half-life of 24,400 years and is the principle fissionable material in atomic weapons. Plutonium 238 has a half-life of 86 years, is intensely radioactive, and is used mainly as a heat source to power thermoelectric devices such as cardiac pacemakers and batteries for use in space vehicles.

Plutonium localizes principally in the liver and skeleton. Like other actinides (thorium), plutonium is taken up on the trabecular and periosteal bone surfaces not in the calcium matrix like radium and strontium. In the bone, plutonium is in relatively close proximity to cancer-inducing target cells and is a formidable bone carcinogen. Both the GI tract and the skin are impermeable even to the soluble forms of plutonium, except for penetrating wounds of the skin, and the main route of exposure is by inhalation. The residence time of insoluble forms of plutonium in the lung is a matter of years, a half-life of 1500 days. With high levels of exposure in dogs, there is induction of pneumonitis, followed by pulmonary fibrosis and lung cancer. With inhalation exposure to soluble plutonium, there is rapid redistribution to the liver and skeleton and induction of cancer in both organs. Although five thousand to ten thousand people have been exposed to plutonium in the atomic energy industry, the levels have not been sufficient to cause perceptible injury to date.

14.4 Iodine-131

Iodine-131 is a beta-gamma emitting fission-product isotope with a half-life of 8 days that attracted a great deal of attention because of its wide dissemination via milk from atomic weapons testing (58). Even with atmospheric tests of atomic weapons as far away as the USSR, iodine-131 was easily measured in the thyroid glands of children living on the east coast of the United States. Like strontium-90, iodine-131 posed a cancer threat to children.

Iodine is a component of the thyroid hormone and is concentrated in the thyroid. Thyroid uptake of radioiodine, as measured by external gamma-ray counting, is used as a diagnostic test of thyroid function. Its localization in the thyroid gland is also the basis for treating hyperthyroidism by destroying thyroid tissue to reduce the production of thyroid hormone. Thyroid tumors can be induced by ionizing radiation, especially in children. This was shown in children whose thyroid glands were exposed in association with irradiation of the thymus gland as infants (59). External exposures of the thyroid gland at doses as low as 5–10 rads in children who were treated by X radiation for ringworm of the scalp showed in the induction of thyroid adenomas and carcinomas (60). However, equivalent average doses of radiation from iodine-131 have not produced tumors of the thyroid gland. This apparent discrepancy may be due to inaccurate dosimetry because some of the beta radiation is lost to the gland when deposited in its outer portions, and much of the radioiodine is in the inert colloid storage areas in the gland where some of the radiation is absorbed. However, there is no question that radioactive iodine can produce cancer of the thyroid gland as evidenced by the study of populations exposed to radioactive fallout in the Marshall Islands and in the USSR from the Chernobyl release.

14.5 Radon-222

Radon-222 and its decay products are the most important radiation hazard to the lungs (61). It was the cause of a mysterious illness known since the Middle Ages as “mountain sickness” among miners in the central European silver mines of Jochimsthal and Schneeberg. The disease was identified as lung cancer only in the 1920s. Since then lung cancer has occurred among domestic uranium miners, Chinese tin miners, and other types of miners of different countries where significant amounts of radon occur.

Radon-222 has a half life of 3.82 days and is the immediate gaseous decay product of radium-226. In turn, it decays through eight daughters of bismuth, polonium, and lead to reach the stable isotope, lead-206. The series has an effective half-life of about 30 minutes down to the sixth daughter, Lead-210, which has a half-life of 22 years and effectively stops radiation in the lung. The series is a

composite of alpha and beta emitters but the alpha radiation accounts for most of the dose. Radon itself, distributes throughout the body and localizes in fat; its dose in the lung is unimportant compared to the radiation dose to the mucosa of the lung from the daughters. Radon decay products are solids and when formed in the air, attach to a considerable extent to smaller airborne particles. The deposition pattern in the lung follows that of the particles to which the daughters are attached except for those that are unattached ions. The ions have a high velocity in air and plate out in the upper part of the respiratory tract, whereas those that are attached to small particles tend to deposit deeper in the lung in the lower part of the tracheobronchial tree and in the alveoli.

Once deposited on the bronchial mucosa, the radon daughters are entrained in the mucus layer that coats the mucosa which is propelled by the beating of the mucosal cilia toward the top of the trachea from whence they are swallowed. The daughters are presumably mixed in with the mucus as it is being transported. The alpha particles are the most important component of the radiation, but their penetration is limited to about 70 microns which barely reaches the basal cells of the mucosa; these cells seem to be the target cells for cancer induction, but this is not known for sure. Inhalation of the analog of radon-222 daughters, namely, the gamma-emitting daughters of thoron-220 which have an effective half-life of 10 hours, did not show any clearance from the lung at all (62). It was not possible with the scintillation counting equipment available at the time to determine whether there was any redistribution in the bronchial tree. It is evident that the dosimetry of radon daughters is complex and uncertain.

Of environmental importance is the fact that some homes are situated on radium-rich soils which emit substantial amounts of radon gas into the homes. Using a linear dose–response model based on the radon cancer data in mines and extrapolating the risk to homes, it can be estimated that at the average indoor radon levels of about 15 Bq/m^3 (0.1–0.2 WLM), about 5–10% of the total lung cancer incidence can be attributed to radon. In homes on radium-rich soils, where the radon concentration can be 20 times higher, close to 50% of the total lung cancer incidence can be attributed to radon (63). The presumed factor of the greater susceptibility of children to the carcinogenic effects of radiation lends concern to these estimates. However, the dosimetry of radon in mines is crude, and there is evidence for a strong interaction with cigarette smoking in the miners which is applicable to children only in terms of passive exposure to cigarette smoke in the households of smokers.

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15 Background Radiation
Background radiation occurs from sources external to and within the body. External sources include cosmic radiation and gamma radiation from uranium and thorium decay chains in soil, rocks, and building material. Radiation from within the body arises from naturally occurring radionuclides, mainly potassium-40. Naturally occurring radioactive isotopes that originate outside the body and enter the body include the gas, radon, and its decay products that arise from radium-226 deposits in soil that are inhaled and carbon-14 which is produced by the interaction of cosmic radiation in the atmosphere. Another source of background radiation stems from the diagnostic and therapeutic uses of radiation.

The effective dose from background sources is the dose in rads (or grays) multiplied by the radiative weighting factor, which is 20 for alpha particles emitted by radon daughters and multiplied by the tissue weighting factor which is 0.12 for the lungs. The annual effective dose to the U.S. population is about 646 millirems of which more than half comes from radon (55%); a total of 82% comes from natural sources: cosmic (8%), terrestrial (8%), and internal (11%). Man-made sources (18%) include

medical X rays (11%), nuclear medicine (4%), and consumer products (3%). Less than 1% comes from other sources, including occupational exposure (0.3%) (64).

The intensity of cosmic radiation is a function of altitude. Radiation in Denver is about twice that of regions at sea level. There are regions of high radiative background on the Colorado Plateau because of the high content of uranium and thorium in the soil and rocks. A number of places around the world have high backgrounds for similar reasons. For example, in Kerala, India, the background is triple that in the United States at 1.3 rem/year. There has been a lack of perceptible increases in cancer or severe heritable defects in such areas, lending credence to the position that restricting excess radiation exposures to levels that are double the background level will ensure that no "detectable" harm will be suffered.

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16 Radiation Protection
Historically, occupational standards were developed separately for radon-222, radium-226, and for whole body exposure.
16.1.1 Radon-222
Setting a standard for radon-222 to prevent lung cancer is complicated by the fact that radon-222 rarely exists in equilibrium with its daughters. The difficulty was circumvented by using, as a unit of radon activity, the *Working Level (WL)*, defined as any combination of radon daughters in one liter of air that releases 1.3×10^5 MeV of alpha energy. This is equivalent to 100 pCi per liter of radon-222 in equilibrium with its daughters. A pCi is 10^{-12} Ci. A Ci is 3.7×10^{10} disintegrations per second (d/s). Therefore 100 pCi is 3.7 d/s for each of the isotopes in the decay chain. Most of the dose to the tracheobronchial mucosa comes from the alpha-emitting isotopes, polonium-218 (Ra A) and polonium-214 (Ra C'). When the disintegration rate equivalent to one WL continues for a working month, which is 170 hours, the cumulative exposure is called a Working Level Month (WLM). So far as the tracheobronchial mucosa is concerned, a WLM is a total dose from about 1.5×10^7 disintegrations of Ra A and Ra C'. This number of disintegrations can occur during any period of time, for example, a year. The dose to the bronchial epithelium is 0.2 mrem/year per pCi/L using a radiation weighting factor of 20. The occupational standard for radon-222 is 4 WLM per year. This is equivalent to a bronchial dose of 80 rem/year (65).

Radon in homes in the United States averages from 0.5–1.6 pCi/L and 2.7 pCi/L in Scandinavia. The U.S.EPA has set an "action level at 4 pCi/L suggesting that remedial action should be taken at levels higher than this. This affects 1 in 12 homes in the United States, a total of about 6 million. The action levels in Europe are 2 to 5 times higher. The EPA action level of 4 pCi/L is 100 times lower than the occupational standard. This action level translates into an effective dose of 0.8 rem/year and a cancer risk of 4×10^{-4}/year. Despite the complexity and uncertainty of the lung dosimetry, these crude dose estimates for the occupational standard are far higher than those permitted for external exposure. The bronchial dose associated with the EPA action level for background radon exposure is far higher than the background exposure from other sources.
16.1.2 Radium-226
A standard for radium-226 was based on studies of radium dial workers. The standard is a maximum body burden of 0.1 mCi. This value was picked because at that body burden, no cases of bone cancer were observed. Subsequently, the standards for other bone-seeking isotopes were derived mainly from dog studies that compared the potency of radium-226 with strontium-90 and plutonium-239. The dosimetry of radioisotopes in bone is so complex that the standards were based on skeletal burdens rather than on dose estimates.
16.1.3 External Radiation Standards

External radiation standards were originally focused on preventing acute responses, first skin erythema in the 1920s. Later, with higher energy X-ray machines, the concern shifted to deeper tissues, particularly the bone marrow, as manifested by depressed white blood counts. Subsequently there was a shift to preventing more sensitive responses, namely, cancer and mutations. Today, standards are based largely on preventing cancer. All of these changes were accompanied by progressively lower standards.

As indicated earlier, the absorbed dose is absorbed energy per gram of tissue (100 ergs/gram). The absorbed dose is expressed in rads or Grays (Gy = 100 rads). The radiation weighting factor (Wr) is based on the RBE combined with judgment factors about the relative effectiveness of different kinds of radiation at low doses. The radiation weighting factor converts the absorbed dose to equivalent dose measured in rems or sieverts (Sv = 100 rems). The radiation weighting factor for gamma rays and electrons = 1; protons = 5; alpha particles, fission fragments and heavy nuclei = 20; neutrons = 5–20, depending on energy (66).

The concept of effective dose is used for stochastic effects (cancer and hereditary effects) with uniform whole-body radiation. It is a measure of the total harm that can be ascribed to the sum of the deleterious effects on individual organs. Therefore, effective dose is the sum of the equivalent dose multiplied by the tissue weighting factor (W_T) for each organ. $W_T = 0.20$ for the gonads; 0.12, for the colon, lung and stomach; 0.05 for the bladder, breast, liver, esophagus, and thyroid; 0.01 for the skin and bone surfaces; and 0.05 for the remainder (66).

The concepts of committed equivalent dose and committed effective dose are applied to internally deposited radionuclides where the total dose is obtained by integrating over a period of 50 years.

The concept of collective equivalent dose and collective effective dose is used to express the radiative dose to an exposed population. It is the average individual dose multiplied by the number of people exposed. When combined with the cancer risk per unit dose, for example, the collective dose gives the number of people who will get cancer. The collective equivalent dose is expressed in person-rads or person-Gy and the collective effective dose is expressed as person-rem or person-sievert.

The basic NCRP occupational whole body radiation standard is 1 rem/year (0.01 Sv/year). Occupational radiation exposure is not permitted under the age of 18, except for training purposes when the limit is that for the general population described later. The maximum occupational exposure in any one year, as an effective dose, is 5 rem (0.05 Sv). Extra exposure is allowed for limited areas of the skin (50 rem/year) and 15 rem/year for the lens of the eye. Emergency occupational limits up to 50 rem/year are allowed but with subsequent restrictions on exposure. Occupational exposure of the fetus after pregnancy is declared should be no more than 50 millirem/month (0.0005 Sv/month).

The limit for general population exposure is 0.1 rem/year (0.001 Sv) or 0.5 rem/year if such exposure is very infrequent. Individuals under the age of 18, if in occupational training, are allowed the general population exposure limit.

A uniform whole-body exposure to a population is estimated to produce a total detriment of 5.6×10^{-4}/rem. This is made up of the sum of 4×10^{-4}/rem for fatal cancer and equal contributions from nonfatal cancer and hereditary effects of 0.8×10^{-4}/rem each. The comparable figures for the general population are somewhat higher because of the higher sensitivity of the young, namely, 7.3×10^{-4}/rem, which is made up of 5×10^{-4}/rem for fatal cancer, 1×10^{-4}/rem for nonfatal cancer, and 1.3×10^{-4}/rem for hereditary effects (66).

A negligible individual dose is one millirem (0.01 mSv). This is the dose below which further

expenditure to improve radiative protection are unwarranted. It carries a risk of between 10^{-6} and 10^{-7} of carcinogenesis or heritable effects.

For occupational radionuclide exposures, the Annual Limit On Intake (ALI) (67) is the maximum intake in a year whose committed equivalent dose would not exceed the occupational limit.

All of the radiative standards are coupled with the ALARA principle: as low as reasonably achievable, given economic and social factors. This makes the standards upper limits of exposure. The concept is that all exposure is potentially harmful. No unnecessary exposure should be allowed. Facilities should be designed to keep exposure to a minimum and not as much as the standard. No exposure should be permitted unless risks, benefits, and alternatives are considered.

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Metallocenes

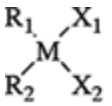
Gary P. Bond, Ph.D., DABT

1 Introduction to Metallocenes

Metallocenes are organometallic complexes with a central metal atom attached to aromatic ligands. Group II iron, which has a 2+ valence, was in one of the earliest metallocenes, but group IV metals such as titanium are currently more common. For group IV metallocenes, halides (e.g., chlorine), pseudohalides (e.g., carboxylates), or other similar molecules can also be attached to the metal. There is some debate among metallocene scientists whether one or two aromatic ligands are required for the complex to be a metallocene, but it is currently generally accepted that two aromatic ligands attached to the metal are a basic definitional criterion for metallocenes (1).

Metallocenes have been used as chemical intermediates, antiknock additives to gasoline, lubricants, and for other uses, but the main current application is as catalysts in the plastics industry. Metallocenes are also currently being actively investigated as a cancer treatment agent. Catalysts, substances that initiate or speed up desirable chemical reactions, have made possible the development of several modern plastic polymers. Metallocene catalysts are improved over the initial plastics polymerization catalysts of the 1950s of Karl Ziegler and Giulio Natta (Ziegler–Natta catalysts), which catalyzed polymerization of ethylene and propylene into polyethylene and polypropylene. Metallocenes provide better control of polymerization, making it possible to create plastics with physical properties designed for particular uses. For example, precise control over polymer growth allows making plastics that are durable for gearwheels or can withstand high temperatures for piping. The billions of pounds of plastics produced and sold every year can be light, waterproof, resistant to corrosion, and used in such items as water pipes, trash bags, hair combs, fibers for clothing and road construction, and packaging for food and medicines, just to name a few uses.

Metallocene catalysts, first synthesized in 1953 by John Birmingham, contain a metal. Unlike the Ziegler–Natta catalysts, metallocenes contain just a single atom of metal. The basic metallocene structure is



$R_{1,2}$ = cyclic group (e.g., cyclopentadiene, indene, fluorine, other)
M = metal (e.g., Ti, Vd, Hf, Mo, Zr, other)
$X_{1,2}$ = halide, carboxylate, NCS, N_3, other

The metal is frequently titanium or zirconium but can be hafnium, tin, germanium, or another group IV metal. Group II metals, chromium, cobalt, and iron, can also be the metal in the metallocene. Group IV metals are linked to two rings of carbon atoms (e.g., cyclopentadienyl or a wide variety and complexity of other cyclic molecules), which can be linked to one or more other groups. These other groups are often other carbon atoms with attached hydrogens (2). The other carbon-based groups attached to the cyclic molecules can also vary in complexity from methyl groups to longer chain carbon groups, some with unsaturated double bonds. For a more complete and thorough description of the chemistry of the metallocene catalysts refer to such technical references as the Kirk–Othmer Encyclopedia of Chemical Technology (3). Because of the widespread production of plastics via metallocene catalysts, metallocenes have become worthy of consideration for potential effects on the worker and the workplace. The antitumor effects of metallocenes underscore the importance of this consideration for protecting workers from workplace chemicals that interact with nuclear material and the cellular duplication process. Two important examples of metallocene catalysts discussed in this chapter are ferrocene and titanocene. Ferrocene, an atypical group II metallocene that has iron (Fe) as the central metal with two cyclopentadiene cyclic groups has no halide groups and is considered first because it was one of the early metallocenes. Ferrocene is the first metallocene to have the “sandwich” structure created by two cyclopentadiene rings attached to the metal. Titanocene, with group IV titanium as the metal, has two cyclopentadiene rings and two chlorine molecules attached to the metal. Little toxicological data are available at present for most metallocenes and limits the number of metallocenes covered in this chapter. If metallocenes are developed into anticancer agents for humans, the amount of available toxicological data will certainly increase. The initial chemical listed, dicyclopentadiene, although not a metallocene, is presented as a baseline for its health effects, and the intention is to compare it to dicyclopentadiene iron and the other metallocenes presented.

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2 Metallocenes as Cytostatic Anticancer Drugs
Numerous studies have compared the cancer potency and toxicity of several metallocenes (4–14). The anticancer potential of metallocenes has been investigated in cell culture and in intact animals. Metallocene dichlorides were the first organometallic complexes that exhibited both antitumor and antiviral activities. Although early studies considered that they act similarly to the cell cycle arresting agent cisplatinum, later studies suggested that the metallocene dihalides have additional cytostatic mechanisms. Metallocene dihalides form DNA adducts, and they also disrupt DNA, RNA, and protein synthesis. Because of these additional cytostatic effects on cancerous cells at doses that are relatively nontoxic and clearly less toxic than cisplatinum, metallocene dihalides are being considered for development as human cancer treatment drugs for such human cancers as ovarian cancer.

Different structural variants of metallocene dihalides have been tested. *In vitro* testing of group IV metals showed that vanadium is ~ 10- to 100-fold more potent than titanium and molybdenum which were ~ 10- to 100-fold more potent than zirconium and hafnium. Similar potency relationships were observed *in vivo*. Titanium-based metallocene exhibits increased potency compared to the vanadium metallocene.

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1.0 Dicyclopentadiene
1.0.1 CAS Number: [*77-73-6*]

1.0.2 Synonyms: 1,3-Cyclopentadiene dimer; 3A,4,7A-tetrahydro-4,7-methanoindene; biscyclopentadiene

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 132.22

1.0.5 Molecular Formula: $C_{10}H_{12}$

1.0.6 Molecular Structure:

1.1 Chemical and Physical Properties (15, 16)
1.1.1 General Dicyclopentadiene is a colorless crystalline solid.

Boiling point	172°C
Melting point	33.6°C
Solubility (at 20° C)	insoluble in water; soluble in 95% ethanol, carbon tetrachloride, acetic acid, and petroleum ether
Flash point	32°C (90°F)
Stability	stable
Density	0.93 g/mL at 35°C
Specific gravity	0.979 at 20/20°C
Vapor pressure	10 mm Hg at 47.6°C
Vapor density	4.55 g/mL
Viscosity	0.736 centipoise at 21°C
	Octanol/water partition coefficient log K_{ow} = 2.89 (estimated)

1.1.2 Odor and Warning Properties Dicyclopentadiene has a disagreeable, camphor-like odor that is not distinguishable from the odor of other hydrocarbons with closely related structures, such as terpenes. Human sensory response studies indicate that dicyclopentadiene can be detected in the range of 0.003–0.2 ppm but does not become noticeably irritating below 10 ppm. It must be inhibited and maintained under an inert atmosphere to prevent polymerization.
1.2 Production and Use
Dicyclopentadiene is produced by recovery from hydrocarbon streams from high temperature cracked petroleum fractions. It is also a by-product of the coke oven industry. Cyclopentadiene polymerizes to dicyclopentadiene on standing. It is used as a chemical intermediate for insecticides, certain (e.g., EPDM) elastomers, metallocenes, paints and varnishes, and flame retardants for plastics (15, 16).
1.3 Exposure Assessment
1.3.1 Air Although no air-specific method of exposure assessment was reported, analysis of products

and residues of dicyclopentadiene can be done by gas–liquid chromatography with a flame ionization detector (16).

1.3.2 Background Levels Dicyclopentadiene has been reported in effluent samples as a result of pesticide production.

1.3.3 Workplace Methods None reported.

1.3.4 Community Methods None reported.

1.3.5 Biomonitoring/Biomarkers None reported.
1.4 Toxic Effects
1.4.1 Experimental Studies 1.4.1.1 Acute Toxicity (15–18) Dicyclopentadiene causes mild to severe eye, skin, and respiratory tract irritation, and severe response of the eyes and skin result from 24-hour exposure. The acute toxicity varies with the route of exposure. The LD_{50}/LC_{50} in mice has been reported as 200 mg/kg (i.p.), 190 mg/kg (oral), and 145 ppm/4 hours (inhalation). The LD_{50} and LC_{50} in rats has been reported as 200 mg/kg (i.p.), 353 mg/kg (oral), and 500 ppm/4 hours (inhalation). The LD_{50} and LC_{50} in rabbits have been reported as 5080 mg/kg (dermal) and 771 ppm/4 hours (inhalation). The inhalation LC_{50} in guinea pigs is 770 ppm/4 hours and the oral LD_{50} in cattle is 1200 mg/kg. Pathological findings following acute lethal exposures were typical for large doses of irritant hydrocarbons, namely, general congestion, hyperemia, and focal hemorrhage in affected organ tissues such as the lung, kidney, and bladder.

1.4.1.2 Chronic and Subchronic Toxicity Rats were exposed to dicyclopentadiene by inhalation for 7 hours per day, 5 days per week for 10 days at levels of 72, 146, and 332 ppm (17, 18). Death, observed only in the highest dose group, included all six males and females by day 4 of dosing and was characterized by convulsions, hemorrhage in the lungs, blood in the intestines, and blood in the thymus (females only). In similarly exposed mice at 47, 72, and 146 ppm, all mice exhibited convulsive deaths on the first day of exposure. Death at 72 ppm occurred in five of six mice of each sex during the 10 days of exposure and was not associated with the convulsions or gross lesions observed in rats. No deaths occurred at 47 ppm and no other effects of treatment were observed. Male beagles (1 per group) were also exposed similarly to levels of 20, 40, and 72 ppm. Signs of toxicity included inactivity at 72 ppm, diarrhea and excessive salivation on day 2 with hind quarter spasticity on day 9 at 47 ppm, and diarrhea at 20 ppm. No treatment-related gross lesions were reported.

Groups of 12 male and female rats were exposed to dicyclopentadiene by inhalation at levels of 19.7, 35.2, and 73.8 ppm, 7 hours per day, 5 days per week for 89 days (17, 18). Some convulsions were observed only in the highest dose group. Mean body weight gains were significantly reduced for the highest dose group through only the first four days of exposure. Organ weights exhibited no clear treatment-related effects. Kidney effects, which included tubular degeneration, were observed in males and females of the two high-dose groups, and males exhibited increased frequency and severity. Three dogs per group of male beagles were exposed using the same dosing schedule of 8.9, 23.5, and 32.4 ppm. Clinical chemistry was the only biological parameter affected by treatment with dicyclopentadiene, and this occurred only at the highest dose. The microscopic pathology of 28 organs and electrocardiograms were normal.

The results of other chronic and subchronic toxicity tests were reported in the literature but could not be confirmed by obtaining the original literature. Refer to various databases in Ref. 16 for additional information.

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms (16) In general, although some dicyclopentadiene can be exhaled unchanged, most of that absorbed is hydroxylated in the liver,

undergoes glucuronide conjugation, and is excreted in the urine. When dicyclopentadiene was given by mouth to lactating cows, only trace amounts were secreted in the milk, and the majority was contained in the urine and feces.

1.4.1.4 Reproductive and Developmental (19) The National Toxicology Program (NTP) reported the completion of teratology studies in rats and rabbits at doses of 50, 200, 300, 400, and 500 mg/kg. Dicyclopentadiene was administered by oral gavage. The results of these studies were not available.

1.4.1.5 Carcinogenesis None reported.

1.4.1.6 Genetic and Related Cellular Effects Studies The NTP (19) and the EPA GENETOX (16, 20) programs reported that dicyclopentadiene was negative in the *Salmonella typhimurium* histidine reversion assay.

1.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization None reported.

1.4.2 Human Experience Human sensory responses to dicyclopentadiene were studied in three human volunteers (18). The odor threshold was reported as low as 0.003 ppm. In two of the subjects exposed to 1 and 5.5 ppm for 30 minutes, one subject experienced mild eye and throat irritation after 7 minutes at 1 ppm, and the other subject reported olfactory fatigue after 24 minutes. Eye irritation was reported after 10 minutes, but no olfactory fatigue was reported by either test subject at 5.5 ppm. The researcher interpreted these results to indicate that dicyclopentadiene does not lose its warning properties under conditions of longer exposures. During the conduct of these studies, which also included animal studies as reported in section 1.4, workers accidentally exposed to dicyclopentadiene reported headaches during only the first 2 months of the 5-month study period. No other information was found regarding human effects of exposure to dicyclopentadiene (17, 18).
1.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV for dicyclopentadiene is 5 ppm as an 8-hour TWA. The NIOSH REL is 5 ppm as a 10-hour TWA. The OSHA PEL is 5 ppm as an 8-hour TWA. The ACGIH TLV has been adopted and/or is the same value as standards in numerous other countries such as those in Europe, Australia, Colombia, Jordan, Korea, and New Zealand (15–17).
1.6 Studies on Environmental Impact
None reported.

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2.0 Ferrocene
2.0.1 CAS Number: [*102-54-5*]

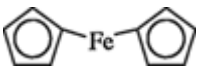
2.0.2 Synonyms: dicyclopentadienyl iron; biscyclopentadienyliron; iron bis (cyclopentadiene)

2.0.3 Trade Names: Catane, Ferrosten

2.0.4 Molecular Weight: 186.05

2.0.5 Molecular Formula: $(C_5H_5)_2Fe$

2.0.6 Molecular Structure:



2.1 Chemical and Physical Properties

2.1.1 General Ferrocene is an orange crystalline solid (16).

Boiling point	249°C
Melting point	173–174°C
Solubility	19 g/100 g benzene, 10 g/100 g catalytically cracked gasoline, 6 g/100 g jet fuel (JP-4), 5 g/100 g diesel fuel, insoluble in water, slightly soluble in petroleum ether
Flash point	unknown
Stability	stable
Sublimes	>100°C
Specific gravity	unknown
Vapor pressure	0.03 mm Hg at 40°C
Iron content	29.4–30.6%

2.1.2 Odor and Warning Properties Ferrocene has a camphor-like odor and reacts violently with ammonium perchlorate. It is classified as a flammable solid.

2.2 Production and Use

Ferrocene is produced from the reaction of cyclopentadiene with reduced iron in the presence of metal oxides. It is used as a catalyst for vulcanization acceleration and polymerization, as a chemical intermediate for polymeric compounds such as high temperature polymers, as an antiknock additive for gasoline, as a coating for missiles and satellites, and as a high-temperature lubricant (16).

2.3 Exposure Assessment

2.3.1 Air NIOSH Methods 173 (21) and 351 (20, p. v7 351-1) are available air sampling methods for iron, and the analytical laboratory methods use atomic absorption and atomic emission spectroscopy, respectively (16).

2.3.2 Background Levels None reported.

2.3.3 Workplace Methods See 2.3.1.

2.3.4 Community Methods See 2.3.1.

2.3.5 Biomonitoring/Biomarkers No information is available for ferrocene.

The use of biomonitoring/biomarkers for iron should be considered in instances of suspected ferrocene overexposure. Refer to the section on iron in this publication.

2.4 Toxic Effects

The toxicological properties of ferrocene have not been extensively investigated. Toxic effects have usually been associated with the iron in the ferrocene, but some data indicate that cyclopentadienyl may be a causative agent in liver cirrhosis (see 2.4.1.2).

2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity Ferrocene may cause eye, skin, and respiratory tract irritation. The LD_{50} in mice has been reported as 335 mg/kg (i.p.), 178 mg/kg (i.v.), 600 mg/kg (oral), and 832 mg/kg (oral). In the rat, the LD_{50} is 500 mg/kg (i.p.) and 1320 mg/kg (oral) (16, 22).

2.4.1.2 Chronic and Subchronic Toxicity Male and female rats and mice were exposed to vapors of

ferrocene for 6 hours/day for 2 weeks at target concentration levels of 2.5, 5, 10, 20, and 40 mg/m^3 (actual levels of 2.33, 5.29, 9.89, 20.02, and 36.47 mg/m^3) (23). No mortality, clinical signs of toxicity, or gross histological effects were observed. Decreased body weight gains in treated versus control animals were observed for the male rats and mice exposed to 40 mg/m^3 ferrocene and the female mice exposed to 10, 20, and 40 mg/m^3. Relative liver weights decreased in male rats (40 mg/m^3). Dose-related decreases were observed in relative liver and spleen weights (male and female mice) and relative spleen weights (female mice). The thymus weights were increased in a dose-related manner in male mice. Nasal turbinates, lungs, liver, and spleen were observed microscopically. The only effect observed was inflammation of the nasal turbinates in both species with a dose-dependent severity. Observed toxic effects from ferrocene inhalation were attributed to iron.

Male and female dogs received ferrocene in gelatin capsules at doses of 30, 100, and 300 mg/kg/day for 6 months and at 1000 mg/kg for 3 months (24). No deaths or urinalysis differences, except for an amber color of urine, were associated with ferrocene exposure. A dose-related accumulation of iron with hemosiderosis was observed (liver, spleen, bone marrow, adrenals, lungs, gastrointestinal tract, lymph nodes, testes). Blood effects (decreased hemoglobin, packed cell volume, and erythrocyte count) occurred within 4 weeks at 300 mg/kg. Liver cirrhosis, considered to be related to the cyclopentadiene, was observed in the 300- and 1000-mg/kg group. Dose-related testicular hypoplasia was observed. Treatment of other dogs with ferrous sulfate determined that only liver cirrhosis was specifically ferrocene-related because the other effects were related to iron overload. No other effects were observed during 12–26 months after treatment ended.

Male and female rats and mice were exposed to vapors of ferrocene for 6 hours/day, 5 days/week for 13 weeks at target concentration levels of 3, 10, and 30 mg/m^3 (actual levels of 3.06, 10.06, and 29.89 mg/m^3) (25). No mortality, clinical signs of toxicity, or gross histological effects were observed. Decreased body weight gains versus control animals were observed in the male rats at 3 and 30 mg/m^3 of ferrocene and in female mice at 3 and 10 mg/m^3. Increases in the lung burden of iron were dose- and time-related. Decreased thymus and testes weights in male rats and liver weights in female rats (3 and 30 mg/m^3) and decreased liver (all doses), heart, and spleen (30 mg/m^3) in female mice were observed. Increased relative liver weights (30 mg/m^3 male rats, 10- and 30-mg/m^3 female rats, and 30-mg/m^3 male mice) and kidney weights (30-mg/m^3 male rats) were observed. Decreased relative liver weights were observed in female mice (3 mg/m^3). No ferrocene-related changes were observed in respiratory function, lung biochemistry, bronchoalveolar lavage cytology, total lung collagen, clinical chemistry, and hematology. Exposure-related histopathological lesions, primarily iron accumulation, were observed in the nose, larynx, trachea, lung, and liver of both species and in the kidneys of mice. Nasal lesions were dose-related in severity and included necrotizing inflammation, metaplasia, and regeneration. Observed toxic effects from ferrocene inhalation were attributed to iron ions released from the ferrocene.

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The metabolism of ferrocene was studied in rats following a 17-minute inhalation exposure (26). Ferrocene deposition was significant in the nasopharynx and lungs. The half-life for clearance of radiolabeled iron was 200 days for the bronchopulmonary region and 70 days for the nasopharyngeal region. Within 24 hours after exposure, 75% of the radiolabeled hydrogen was cleared from the respiratory tract. For the retained radiolabeled iron, 90% was in the bronchopulmonary and nasopharyngeal regions of the lungs, 10% was in the liver, and 1% was in the spleen.

2.4.1.4 Reproductive and Developmental Dose-related testicular hypoplasia was observed in dogs that received ferrocene in gelatin capsules at doses of 30, 100, and 300 mg/kg/day for 6 months and at 1000 mg/kg for 3 months (24). Treatment of other dogs with ferrous sulfate determined that this effect was related to iron overload because administered ferrous sulfate caused similar effects.

2.4.1.5 Carcinogenesis Ferrocene was administered by intramuscular injection at a dose of 5175 mg/kg/2 years. By the criterion established by the Registry of Toxic Effects of Chemical Substances (RTECS), ferrocene was an equivocal tumorigenic agent and tumors were most evident at the site of multiple injections (16, 27).

2.4.1.6 Genetic and Related Cellular Effects Studies Ferrocene was tested for the potential to cause genetic mutations by point and frameshift mutations in bacteria (*Salmonella typhimurium*), by sister chromatid exchange in Chinese hamster ovary cells, and by heritable effects (sex chromosome loss/nondysjunction and heritable translocation test) in *Drosophila melanogaster* (28–30). Results indicate that ferrocene is not mutagenic.

2.4.2 Human Experience None reported.
2.5 Standards, Regulations, or Guidelines of Exposure (16)
The ACGIH TLV for ferrocene is 10 mg/m^3 as an 8-hour TWA. The NIOSH REL is 10 mg/m^3 as a 10-hour TWA for total dust and 5 mg/m^3 for the respirable fraction. The OSHA PEL is 15 mg/m^3 as an 8-hour TWA for total dust and 5 mg/m^3 for the respirable fraction. The ACGIH TLV has been adopted and/or is the same value as standards in numerous other countries. The U.S. EPA, Canada, and Mexico have drinking water standards for iron of 0.3 mg/L.
2.6 Studies on Environmental Impact
None reported.

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3.0 Titanocene Dichloride
3.0.1 CAS Number: [*1271-19-8*]

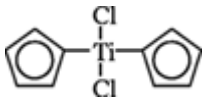
3.0.2 Synonyms: dicyclopentadiene titanium; dichlorotitanocene; bis (cyclopentadienyl) titanium dichloride

3.0.3 Trade Names: NA

3.0.4 Molecular Weight: 248.99

3.0.5 Molecular Formula: $(C_5H_5)_2TiCl_2$

3.0.6 Molecular Structure:



3.1 Chemical and Physical Properties (16)
3.1.1 General Titanocene dichloride is a reddish-orange crystalline solid.

Melting point	289°C
Solubility	moderately soluble in toluene, chloroform, alcohol, and other hydroxylic solvents; sparingly soluble in water, petroleum ether, benzene, ether, carbon disulfide, and carbon tetrachloride
Stability	stable (tetravalent titanium compounds are the most stable of the variable

	valence compounds of titanium)
Density/specific gravity	1.6

3.1.2 Odor and Warning Properties (16) Titanocene dichloride is irritating to the skin and mucous membranes.

3.2 Production and Use

Titanocene dichloride is produced by the reaction of titanium tetrachloride with cyclopentadienyl sodium. It is used as a research chemical, as a catalyst in Ziegler–Natta polymerization reactions, and as an implant material in orthopedics, oral surgery, and neurosurgery. Titanocene dichloride is being investigated as a chemotherapeutic agent (16).

3.3 Exposure Assessment

3.3.1 Air Atmospheric concentrations of titanium have been reported at an average urban concentration of 0.04 mg/m^3 with a maximum concentration of 1.10 mg/m^3 (16, 31).

3.3.1 Background Levels Titanium, an apparently nonessential metal for humans or animals, has been detected in North American rivers at levels of 2–107 mg/L with mean concentrations in U.S. drinking water of 2.1 mg/L. Titanium has been detected in food and seafood (levels unreported) (31).

3.3.2 Workplace Methods NIOSH Methods 7300 (32), 600 (33), and 500 (34) are available air sampling methods for titanium, and the analytical laboratory methods use atomic emission spectroscopy, gravimetric (respirable dust fraction), and gravimetric (airborne particulate matter) procedures, respectively (16).

3.3.3 Community Methods NIOSH method 3111 is available for determining titanium in water and wastewater by using direct aspiration atomic absorption spectrometry (35).

3.3.4 Biomonitoring/Biomarkers (16) 3.3.4.1 Blood None reported.

3.3.5.2 Urine NIOSH method 8310 is available for detecting titanium in urine by using atomic emission spectroscopy (36).

3.3.5.3 Other The estimated body burden of titanium is ~15 mg, most of which is in the lungs as a result of inhalation exposure (31).

3.4 Toxic Effects (16)

The toxicological properties of titanium dichloride have not been extensively investigated. Toxic effects have usually been associated with the titanium.

3.4.1 Experimental Studies 3.4.1.1 Acute Toxicity Titanocene dichloride may cause skin and mucous membrane irritation. The LD_{50} in mice has been reported as 60 mg/kg (i.p.), and 180 mg/kg (i.v.). In the rat, the LD_{50} is 25 mg/kg (i.p.) (16, 22).

3.4.1.2 Chronic and Subchronic Toxicity In studies conducted as part of the National Toxicology Program (NTP), titanocene dichloride was administered by gavage in corn oil to male and female rats for 14 days, 13 weeks, or 2 years (37).

In the 14-day study, titanocene dichloride was administered at doses of 0, 65, 125, 250, 500, or 1,000 mg/kg (37). All high-dose rats and four of the five males and two of the five female rats given 500 mg/kg died during the studies. A dose-related decrease in body weight gain was seen in rats at all but the 65-mg/kg dose. Treatment-related lesions included hepatocellular necrosis, tubule necrosis in the kidney, erosions and ulcers of the glandular stomach, and hyperplasia of the

forestomach epithelium.

In the 13-week study, titanocene dichloride was administered at doses of 0, 8, 16, 31, 62, or 125 mg/kg (37). One female rat in the highest dose group died due to the titanocene dichloride during the fourth week of the studies. Body weight gain was reduced compared to controls in rats given 62 or 125 mg/kg. Histopathological lesions related to treatment with titanocene dichloride were observed in the stomachs of high-dose males and all groups of females. Hyperplasia and metaplasia of the glandular stomach and hyperplasia and hyperkeratosis of the forestomach were observed.

In the 2-year study, titanocene dichloride was administered at doses of 0, 25, and 50 mg/kg (37). These doses were selected based on the stomach and body weight effects observed in the 3-week study. The principal toxic effects of administering titanocene dichloride for 2 years occurred in the stomach. Lesions observed at 15 months were similar to, but less severe than, those observed at 2 years. The lesions included focal erosions of the glandular mucosa, inflammatory responses, hyperplastic and metaplastic responses, and fibrotic changes. Effects were observed in both groups administered titanocene dichloride, but not in control animals. Macrophages with blue-gray pigment accumulated in many organs of dosed rats including the gastrointestinal tract, liver, lung, and lymph nodes. The pigment was believed to contain titanium. Inflammation of the nasal mucosa and lung was also attributed to administration of titanocene dichloride, resulting from reflux and/or regurgitation and aspiration of gavage solution due to the severe stomach lesions.

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 3.4.1.3.1 Absorption Titanium compounds are generally considered to be poorly absorbed upon ingestion and inhalation (38). However, detectable amounts of titanium can be found in the blood, brain, and parenchymatous organs of individuals in the general population; the highest concentrations are found in the hilar lymph nodes and the lung. Titanium is excreted with urine (16).

3.4.1.3.2 Distribution The subcellular distribution of titanium in the liver of mice was determined at 24 and 48 hours after administering titanocene dichloride (39). At 24 hours, titanium was accumulated mainly in the cytoplasm of endothelial and Kupffer cells lining the hepatic sinusoids. Titanium was also detected in the nucleoli and the euchromatin of liver cells. It was packaged as granules together with phosphorus and oxygen. At 48 hours, titanium was still present in cytoplasmic inclusions within endothelial and Kupffer cells, but there were only a few deposits in hepatocytic nucleoli. Titanium was found in hepatocyte cytoplasm, incorporated into cytoplasmic inclusion bodies which were considered most likely to be lysosomes. Location of these inclusions near bile canaliculi with occasional extrusion of the content into the lumen of bile capillaries suggests biliary elimination of titanium.

Titanium concentrations were not elevated in mouse embryos after injection (i.p.) of pregnant mice on day 10, 12, or 14 of gestation compared to untreated controls (40). On day 16 of gestation, after the period of organogenesis, small amounts of titanium were detectable in the fetal compartment in excess of that of controls. These results are consistent with the result of a teratology study in which there was an absence of histological lesions in developing embryonal organs and a lack of multiple teratogenic effects in newborns after application of therapeutic doses of titanocene dichloride to pregnant mice during embryonal organogenesis (see section 3.4.1.4). The teratogenic effect is considered to result from indirect effects on the maternal animal such as altered hormonal status (40–42).

3.4.1.3.3 Excretion (16) Titanium is excreted with urine, and gastrointestinal excretion via the bile is possible (38, 39).

3.4.1.4 Reproductive and Developmental The teratogenic and embryotoxic effects of titanocene dichloride were investigated after intraperitoneal injections of single therapeutic doses of titanocene dichloride (30 or 60 mg/kg) to pregnant mice on days 8, 10, 12, 14, or 16 of gestation (43). The

fetuses were removed on day 18 by caesarean section and examined for external, internal, and skeletal malformations, as well as for toxic effects of treatment. Cleft palate was observed in numerous fetuses (10% of the fetuses at 30 mg/kg; 40–50% of the fetuses at 60 mg/kg) after titanocene dichloride administration on days 10 and 12. Skeletal malformations were observed in some fetuses. No other malformations were observed. Toxic effects of treatment included a decreased number of live fetuses per litter, dose-dependent reduction of mean fetal body weight, and delayed skeletal ossification. The lack of a broad range of effects observed with other cytostatic chemicals was consistent with effects on maternal hormonal status, namely, increased cortisol release (42).

3.4.1.5 Carcinogenesis Based on the results of 2-year gavage studies, the National Toxicology Program determined that there was equivocal evidence of carcinogenic activity of titanocene dichloride in male and female rats based on a marginal increase in the incidence of forestomach squamous cell effects. Refer to study results in section 3.4.1.2 for more details (37).

3.4.1.6 Genetic and Related Cellular Effects Studies (16) Titanocene dichloride was evaluated for mutagenic potential as part of the EPA GENETOX and National Toxicology Programs. Positive and negative mutagenic effects were observed, consistent with the equivocal carcinogenic data and characterization by the National Toxicology Program. The results were as follows:

positive in *Salmonella typhimurium* strain TA100 in the absence of exogenous metabolic activation/S9 microsomal enzymes and negative in TA100 with S9 (44);

negative in all other *Salmonella typhimurium* strains with or without S9 (44);

inconclusive in bacteria *Escherichia coli* polA point mutation assay without S9 microsomal enzymes (45);

negative in yeast *Saccharomyces cerevisiae* host-mediated assay (45);

positive and dose-responsive in mouse cell transformation (45);

negative for sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells, with or without S9 (45);

positive in unscheduled DNA synthesis assay using human fibroblasts (*in vitro*) (45);

positive in SHE-clonal assay and in the transformation of rat embryo cells (45);

positive in neoplastic transformation of a cloned mouse cell line, hamster embryo cells, and virally-infected rat embryo cells (20);

3.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization None reported.

3.4.2 Human Experience The spermicidal activity of several metallocene complexes on human sperm was investigated (46). Of the metallocene complexes investigated, neither titanocene dichloride nor any other metallocenes except vanadium-based metallocenes caused immobilization of sperm.

3.5 Standards, Regulations, or Guidelines of Exposure
None reported.

3.6 Studies on Environmental Impact
None reported.

Metallocenes
Gary P. Bond, Ph.D., DABT

4.0 Vanadocene Dichloride
4.0.1 CAS Number: [*12083-48-6*]

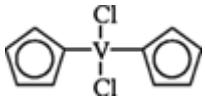
4.0.2 Synonyms: cyclopentadienylvanadiumdichloride, bis; bis (cyclopentadienyl) vanadium dichloride

4.0.3 Trade Names: NA

4.0.4 Molecular Weight: 252.04

4.0.5 Molecular Formula: $(C_5H_5)_2VCl_2$

4.0.6 Molecular Structure:



4.1 Chemical and Physical Properties
4.1.1 General Vanadocene dichloride is a pale green crystalline solid (15, 16).

Boiling point	not available
Melting point	>250°C
Solubility (at 20°C)	10–50 mg/mL in DMSO; <1 mg/mL in 95% ethanol; <1 mg/mL in acetone; soluble in chloroform, ether, benzene, and many organic solvents; insoluble in petroleum ether; slightly soluble in carbon disulfide and carbon tetrachloride
Flash point	not available
Stability	sensitive to air and moisture
Specific gravity	1.60
Density	1.60 g/mL
Vapor pressure	not available

4.1.2 Odor and Warning Properties None reported.
4.2 Production and Use
Vanadocene dichloride is used like other metallocenes as a catalyst, ultraviolet absorber, reducing agent, free radical scavenger, antiknock agent in gasoline, and as a developmental anticancer drug (15).
4.3 Exposure Assessment
None reported.
4.4 Toxic Effects (15, 16)
Little toxicity information was found. The only toxicity reported is in reference to vanadium compounds, which act chiefly as irritants to the conjunctivae of the eye and the mucous membranes of the respiratory tract. The oral LD_{50} in rats was reported at 87 mg/kg. Vanadocene dichloride was tested using the Ames bacterial mutagenicity assay, but the results of the assay were not available by press time.

4.4.1 Experimental Studies Very little data was reported other than those listed in the section on metallocenes as cytostatic anticancer drugs.

4.4.2 Human Experience The spermicidal activity of several metallocene complexes on human

sperm was investigated (46). Of the metallocene complexes investigated, only vanadium-based metallocenes caused immobilization of sperm.
4.5 Standards, Regulations, or Guidelines of Exposure
None reported.
4.6 Studies on Environmental Impact
None reported.

Metallocenes
Gary P. Bond, Ph.D., DABT

5.0 Cobaltocene
5.0.1 CAS Number: [*1277-43-6*]

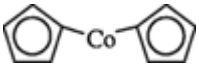
5.0.2 Synonyms: bis (cyclopentadienyl) cobalt

5.0.3 Trade Names: NA

5.0.4 Molecular Weight: 189.13

5.0.5 Molecular Formula: $(C_5H_5)_2Co$

5.0.6 Molecular Structure:



5.1 Chemical and Physical Properties
5.1.1 General Cobaltocene is a black-purple crystalline solid (15, 16).

Boiling point	not available
Melting point	173–174°C
Solubility (at 20°C)	5–10 mg/mL in DMSO; <1 mg/mL in water; <1 mg/mL in 95% ethanol; 50–100 mg/mL in acetone; soluble in other hydrocarbons
Flash point	not available
Stability	sensitive to air and moisture
Specific gravity	not available
Density	not available
Vapor pressure	not available

5.1.2 Odor and Warning Properties None reported.
5.2 Production and Use
Cobaltocene is used to catalyze the synthesis of pyridines from alkynes and nitriles, as a polymerization inhibitor of olefins up to 200°C in Diels–Alder reactions, and as a paint drier and oxygen stripping agent (15).
5.3 Exposure Assessment
None reported.
5.4 Toxic Effects
Little toxicity information was found. The intraperitoneal LD_{50} is 55 mg/kg and 80 mg/kg in the rat

and mouse, respectively. Intramuscular doses of 200 mg/kg intermittently for 60 weeks caused tumors at the dose site. Cobaltocene was classified as an equivocal tumorigenic agent. It was tested using the Ames bacterial mutagenicity assay, but the results of the assay were not available by press time (15, 16).

5.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV and NIOSH REL for cobalt is 0.02 mg/m^3 as an 8-hour TWA. The ACGIH lists an A3 designation for cobalt because it is considered an animal carcinogen. The NIOSH IDLH is 200 mg/m^3. The relevance of the cobalt standard to cobaltocene itself has not been determined (15, 16).

5.6 Studies on Environmental Impact

None reported.

Metallocenes

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Neurotoxicology and Behavior
William K. Boyes, Ph.D.

1 Importance of Considering Neurotoxicity

1.1 Neurotoxic Episodes

Neurotoxicity is important to consider as a component of occupational and environmental safety and health programs. The failure to do so has contributed to a number of tragic cases in which workers, consumers of manufactured products, and people exposed in the environment were irreparably harmed by exposure to industrial compounds that proved toxic to the nervous system (1–3). The National Institute for Occupational Safety and Health (NIOSH) has listed neurotoxic disorders as one of the ten leading occupational problems in the United States (4, 5). Many of the most severe environmental, industrial, and commercial human health disasters attributable to chemical exposure have involved neurotoxic effects (6). In Detroit, Michigan, in 1934, for example, an automotive redesign required grinding large amounts of excess lead solder from each car. Inhalation of the

resulting lead dust produced between 2,700 and 4,000 cases of lead poisoning whose symptoms ranged from mild gastrointestinal upset to severe neurological deficits, including peripheral neuropathy and encephalopathy. As many as 12 people may have died. In another case that occurred during the Prohibition Era, a single batch of the popular ethanol-based elixir "Ginger Jake" was adulterated with tri-*o*-cresylphosphate (TOCP). This batch was then distributed throughout the southeastern and midwestern United States. As many as 50,000 people suffered peripheral neuropathy caused by degeneration of the large, long axons in the peripheral nerves of the legs and spinal cord (7). In a food contamination episode, 459 people were killed and more than 6,500 became ill in Iraq from methylmercury which was applied as a fungicide to seed grain intended for planting, but which was instead ground into flour and cooked into bread (8, 9). Methylmercury was also the cause of environmental poisonings in Minamata Bay, Japan, in which industrial effluent discharged into the Bay bioconcentrated in the food chain and eventually led to exposure of thousands of inhabitants who consumed seafood from the bay (10, 11). The effects on Minamata children exposed in utero were particularly severe. Since that time methlymercury poisoning has been referred to as "Minamata disease."

Fortunately, catastrophic disasters are relatively rare occurrences that typically involve exposures to high concentrations of neurotoxic compounds. A more common concern in occupational and environmental settings is exposure to lower levels of potentially neurotoxic compounds, for long periods of time. It is important to consider neurotoxicity in long-term, low-level exposure situations. Many occupational and environmental exposure standards have been established on the basis of effects on the nervous system. There is also concern that subtle neurotoxic damage might not be evident at the time of exposure due to the plasticity and functional reserve capacity of the nervous system but may become manifest later (12–14). Damage inflicted long ago may become evident as individuals age or undergo other stresses. Alternatively, low-level exposure to neurotoxic compounds may cause a progressive accumulation of damage that becomes apparent only over an extended period of time. The possibility that there could be a latent period between exposure to neurotoxic compounds and the time at which functional impairments become evident should be considered.

Neurotoxicology and Behavior
William K. Boyes, Ph.D.

2 General Description of the Nervous System
The nervous system is diverse and complex. It contains many different types of cells, each expresses unique proteins that can act as selective targets for neurotoxic compounds. The cells of the nervous system operate using many different neurotransmitter substances and second messenger systems and interact in complex networks that perform many vital functions. A simplified view of the role of the nervous system is that it receives information through the sensory systems, processes and integrates that information in the central nervous system, and then takes actions through the motor systems. The nervous system also is responsible for regulating many vital life functions through the autonomic nervous system and helps control the neuroendocrine and neuroimmune systems as well. More extensive information on the structure and function of the nervous system can be found in a number of excellent sources such as Kandel et al. (35).
2.1 Structure of the Nervous System
2.1.1 Regions of the Nervous System The nervous system as a whole consists of the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes the brain and spinal cord, and the PNS includes the sensory and motor nerves that innervate the many peripheral organs and tissues of the body. Peripheral nerves enter and leave the CNS through the cranial nerves, connecting directly to the brain, and spinal nerves that enter the spinal cord through the dorsal spinal roots (sensory nerves) or leave the spinal cord through the ventral spinal roots (motor nerves). The spinal cord is divided into four sections including the cervical, nearest the head; the thoracic, in the upper

trunk; the lumber, in the lower trunk; and the sacral at the base of the spine. The brain includes the hindbrain that contains the brainstem (the pons and medulla) and the cerebellum, the midbrain, and the forebrain, including the diencephalon (the hypothalamus and thalamus), the cerebral hemispheres and other underlying structures, including the basal ganglia, the hippocampus, and the amygdaloid nucleus. The central nervous system is covered by meninges, a set of three protective membranes called the dura, the arachnoid, and the pia. The CNS is also protected by the blood–brain barrier, which limits diffusion of large and polar compounds from the blood into the CNS.

2.1.2 Cellular Components of the Nervous System The nervous system contains two distinct classes of cells, the nerve cells (or neurons) and the glial cells (or glia). Nerve cells are the primary information-processing cells of the nervous system. The more numerous glial cells serve a variety of roles, including physical structure and support, electrical insulation, metabolic and nutritive activity, maintenance of the extracellular ionic balance, forming part of the blood–brain barrier, and responding to injury.

2.1.2.1 Neurons Neurons come in many different shapes and sizes, but there are general characteristics that are representative for most of them. The cell body contains a nucleus and extranuclear organelles. Two types of structures extend from the cell body: dendrites and the axon. Neurons may have between one and many dendrites, which are typically long, multibranched structures. The dendrites contact other neurons to receive and integrate incoming neural signals. The other structure coming from the cell body is a single axon, which may branch many times, and transmits neural activity from the neuron to other cells. The axon of some neurons is covered intermittently by a myelin sheath, formed by specialized glial cells, that serves to increase the velocity of nerve impulse transmission. The region where one nerve cell transmits information to another is called the synapse. In the CNS, a single cell may have thousands of synaptic contacts with other neurons.

2.1.2.2 Glia There are several different types of glial cells that play complex roles in the normal structure and function of the nervous system and in the response to injury. The major types of glia in the CNS are astrocytes, oligodendrocytes, and microglia.

Astrocytes Astrocytes were named for their “starlike” appearance resulting from the abundance of processes extending from the cell body. Astrocytes are often located between neurons and blood vessels. The foot processes of astrocytes surround the capillaries and play a role in forming the blood–brain barrier. The fibrous type of astrocyte is abundant in the gray matter of the central nervous system and undergoes hypertrophy in response to neural injury.

Oligodendrocytes Oligodendrocytes are the type of glial cell that forms the myelin sheath for axons in the CNS. A different type of cell named the Schwann cell produces myelin in the PNS. One oligodendrocyte may form a myelin sheath around the axons of several different neurons. The myelin sheath is a multilayered spiral wrapping around the axon that is composed of lipid-rich material. This covering electrically insulates portions of the axon and increases the velocity of nerve conduction. The high lipid content of the brain provided by myelin is a reason that lipophilic compounds often show preferential distribution to brain tissues.

Microglia Microglia are the type of glial cells that function as macrophages in the central nervous system. The microglia respond to CNS injury by enlarging, becoming more prolific, and then by phagocytic ingestion of cellular debris. Normally, the CNS is considered “immune privileged,” meaning that the normal blood-borne immunological cells usually do not enter the CNS in response to damage or infection. The presence of immunological cells within the CNS indicates a breakdown of the normal barriers.

2.1.3 Blood–Brain Barrier The concept of a diffusional barrier between the blood and the brain developed from observations that vascular injection of dyes stain many tissues of the body, yet do not stain brain tissues. The so-called blood–brain barrier is a misnomer, however, because it is not an

absolute, but rather a selective or semipermeable diffusion barrier between the blood and the brain. The capillary endothelial cells in the brain are joined by tight junctions and lack the fenestrations and intracellular clefts found in other organs that allow relatively free exchange between the blood and the tissues. In addition, the capillaries of the brain are entirely surrounded by foot processes of astrocytic glial cells. This capillary structure limits diffusion of large and polar molecules from the blood into the brain tissue. The dyes used in the early studies of the blood–brain barrier were largely bound to proteins that could not penetrate into the brain. Smaller lipophylic dyes, however, do cross from the blood into the brain, demonstrating that the blood–brain barrier is relatively permeable to these types of compounds. The physiological role of the blood–brain barrier is the protection of the extracellular concentrations of ions, glucose, and protein, as well as the pH and osmolarity of the brain. All of these factors are critical to neuronal function. Selective uptake mechanisms in the brain capillaries are responsible for transporting specific nutrients such as particular ions, amino acids, and glucose. As a result of the blood–brain barrier, many potentially toxic compounds are effectively excluded from the brain. Compounds that have ready access to the brain include lipophilic compounds that move readily across lipid bilayers of epithelial and astrocytic cell membranes and may concentrate in brain tissues. In addition to passive diffusion, many compounds are actively transported into the brain, including compounds that resemble necessary nutrients, and are transported into the brain by the nutrient uptake pathways.

There are regions of the brain that do not have a blood–brain barrier. These include the circumventricular organs, the olfactory bulbs, and the optic nerve near the lamina cirbrosa. The circumventricular organs are regions of the brain that contain chemoreceptors that monitor blood constituents or that monitor and produce hormones. Access to plasma filtrates is necessary for the function of these areas. A list of the circumventricular organs includes the area postrema, median eminence, neurohypophysis, subcommissural organ, and choroid plexus. Areas of the brain not protected by a blood–brain barrier may be at risk of neurotoxicity from compounds that are excluded from the other areas of the brain. Further information about the role of the blood–brain barrier in neurotoxicity can be found in Jacobs (36).

2.2 Function of the Nervous System

Information is processed within neurons electrically and transmitted between neurons both electrically (gap junctions) and chemically. This combination of electrical and chemical signaling forms the basis of neuronal activity. Many neurotoxic compounds alter neuronal function by disrupting these processes.

2.2.1 Electrical Properties of Excitable Nerve Cells

Electrical informational processing by nerve cells begins with an ionic charge differential between the intracellular and extracellular sides of the cell membrane. The interior of nerve cells is usually about 60–70 mV more negative than the outside, a difference called the resting membrane potential. The resting membrane potential results from an uneven distribution of Na^+, K^+, and Cl^- ions and negatively charged organic acids and proteins. The cell membrane separates high extracellular Na^+ and intracellular K^+ concentrations. Negatively charged chloride ions in most cells align with a higher concentration outside the cell than inside so that a balance between the forces is created by the charge and ionic concentration differentials. The ionic concentration gradients are maintained through an energy-dependent process. The Na^+–K^+ pump, also known as Na^+–K^+ ATPase, transports Na^+ ions out of the cell and K^+ ions into the cell against electrical and chemical concentration gradients through an energy-dependent process. Intracellular concentrations of Ca^{2+} are typically low, allowing this ion to serve as an intracellular second messenger substance, and also protecting against toxicity associated with high intracellular Ca^{2+}.

In the area of the dendrites and axon cell body, synaptic input leads to transient depolarizing or hyperpolarizing changes in the resting membrane potential. Synaptic input may excite the cell by opening Na^+ channels, causing the membrane to become permeable to Na^+ ions. Na^+ ions then enter the cell through the opened channels along charge and concentration gradients, resulting in

depolarization of the transmembrane potential. Other synaptic contacts are linked to chloride channels. Opening of chloride channels allows Cl^- ions to flow into the cell and make the inside of the membrane more negative than the normal resting membrane potential, or "hyperpolarized". Hyperpolarization counteracts depolarizing currents and makes the cell less likely to fire. Chloride ion-based hyperpolarizing currents are called inhibitory currents. These excitatory and inhibitory currents spread in a graded fashion along the cell membrane. At any one time, the cell body trans-membrane potential reflects an integrated sum of the activity of the many incoming synaptic contacts acting upon that cell.

The region of the neuronal cell body that contacts the axon is called the axon hillock. In this region, the graded potentials of the dendrites and cell body can be transformed into an all-or-none signal called the action potential. When the transmembrane potential reaches a criterion depolarization voltage, the voltage-sensitive ion channels in the region of the axon hillock open. Opening of voltage-sensitive Na^+ channels leads to an inward flow of depolarization current carried by positively charged Na^+ ions. Shortly afterward, voltage-sensitive K^+ channels open, and Na^+ channels begin to close. Because the membrane is now permeable to K^+ and the transmembrane potential is depolarized, K^+ ions move out of the cell and create repolarizing potassium current. This rapid wave of depolarization–repolarization is called the axon potential. Unlike the graded potentials of the dendrites and cell body, the action potential occurs in an all-or-none fashion and is transmitted down the entirety of the axon.

In nonmyelinated axons, the wave of reciprocal sodium and potassium currents that constitute the action potential spreads continuously down the length of the axon. The speed with which action potentials spread, termed the "nerve conduction velocity," is relatively slow in nonmyelinated axons. In contrast, the transmembrane ion currents in myelinated axons occur only at exposed portions of the axon located between the insulated axon segments that are called the nodes of Ranvier. By restricting the current flow to the nodes of Ranvier, the wave of depolarization need not occur along the entire axon but leapfrogs rapidly from one node to the next down the length of the fiber. The nerve conduction velocity in a typical nonmyelinated axon might be a few meters per second, whereas myelinated axons can transmit nerve impulses as rapidly as 50–70 m/sec. Exposure to compounds that damage myelin, such as triethyltin or lead, reduces nerve conduction velocity (37). Electrical resistance to transmembrane currents, which is lower in larger diameter fibers, also influences nerve conduction velocity. Larger diameter axons have faster nerve conduction velocities. Myelinated axons tend to be larger in diameter than nonmyelinated axons, further adding to their advantageous conduction velocity.

2.2.2 Chemical Neurotransmission Across the Synapse When an impulse traveling down an axon reaches the region of the nerve terminal, the electrical signal of the action potential becomes converted to a chemical message for transmission across the synapse. The presynaptic region of the nerve terminal contains voltage-sensitive calcium channels that open when the action potential depolarization enters the terminal region of the nerve. Ca^{2+} ions enter the cell according to their charge and concentration gradients. The resulting rise in intracellular Ca^{2+} concentration causes small vesicles that contain neurotransmitter molecules to fuse with the presynaptic cell membrane and release the neurotransmitter substance into the synaptic cleft. Neurotransmitter molecules contact receptor proteins on the cell membrane of the postsynaptic cell. Contact of the neurotransmitter substance with the postsynaptic receptor can lead to several different events, depending upon the type of receptor involved. Postsynaptic events can involve neurotransmitter receptors linked to ion channels that can then lead to either excitatory or inhibitory postsynaptic currents as described earlier. Alternatively, postsynaptic receptors can be linked to intracellular second messenger systems that drive many different types of responses or alter the sensitivity of the cell to further stimulation.

After the neurotransmitter substance acts on the postsynaptic receptors, it is normally removed from

the synapse rapidly, which preserves the discrete nature of neural signaling. Removal of the neurotransmitter may involve passive diffusion, active reuptake into the presynaptic nerve terminal, or enzymatic degradation. The latter is particularly important for the neurotransmitter acetylcholine, which is broken down into acetate and choline by the enzyme acetylcholinesterase. Inhibition of acetylcholinesterase is the primary target of organophosphate and carbamate insecticides and several chemical weapon nerve agents such as sarin. Compounds that inhibit acetylcholinesterase cause a buildup of still active molecules of acetylcholine in the synapse, leading to repeated and prolonged stimulation of the postsynaptic cell. Acetylcholine is a neurotransmitter in the central and peripheral nervous systems, notably at neuromuscular junctions and postganglionic neurons of the autonomic nervous system. Acute overexposure to acetylcholinesterase inhibitors leads to a variety of signs and symptoms characteristic of cholinergic overexcitation, including salivation, lacrimation, urination, and defecation (the "SLUD" syndrome). In addition, cholinergic overstimulation produces pupil constriction (miosis), muscle fasciculations and tremor, headache, blurred vision, and mental confusion. Exposure to high doses can lead to respiratory paralysis and death.

In addition to acetylcholine, many substances have been identified as neurotransmitters. This list of known or suspected neurotransmitters continues to grow with new neurobiological research. A partial listing of some of the major established neurotransmitters includes acetylcholine; the catecholamines epinepherine, norepinephrine and dopamine; serotonin; the excitatory amino acids glutamate and aspartate; the inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and glycine; the family of endogeneous opioids; and a variety of peptides such as substance P. Each neurotransmitter may act on several different types of receptors. The application of molecular biological techniques to identify new neurotransmitter receptor molecules has recently led to a rapid expansion of the number and types of receptors known.

Many neurotoxic and neuroactive compounds act at voltage-sensitive and ligand-gated ion channels (38–42). Among the compounds active at Na^+ channels are tetrodotoxin from Japanese puffer fish, a variety of toxins from different species of scorpions and dinoflagellates, and pyrethroid and DDT insecticides. The pyrethroids prolong the duration of the opened state of the Na^+ channel and cause spontaneous depolarization of the resting membrane potential and repetitive action potentials to a single stimulus input (42). Type II pyrethroids keep the channel open longer than Type I pyrethroids, which may account for the differences in toxicity. Compounds that block K^+ channels include tetraethylammonium and 4-aminopyridine. Compounds active at Ca^{2+} channels include a number of divalent metallic cations such as Pb^{2+} (43), Hg^{2+} (44), and Cd^{2+} (45). In addition to elemental mercury, methylmercury also blocks Ca^{2+} channels (46, 47). Many compounds interfere with intracellular second messenger systems or intracellular calcium signaling such as Pb (48, 49), and polychlorinated biphenyls (PCBs) (50).

2.2.3 Energy Metabolism in the Nervous System The brain demands a high flow rate of metabolic energy. The brain accounts for a large proportion of the cardiac output and consumes a large amount of oxygen. Unlike other organs, the brain consumes almost all of its energy in the form of glucose used through oxidative metabolism. The more active neurons become, the more active the metabolic machinery must become in response. This high metabolic demand makes the central nervous system particularly vulnerable to interruption of the supply of blood and oxygen and to compounds that interfere with glucose metabolism or which otherwise impair oxidative respiration, such as carbon monoxide. Exposure to carbon monoxide or to other hypoxic gases causes a series of symptomatic and behavioral changes that progress with increasing dose. Feelings of headache and nausea are commonly reported during CO exposure, but systematic investigations of behavioral deficits during low level exposure have produced inconsistent results (51). Of course, exposure to high concentrations is lethal.

2.2.4 Axonal Transport The axonal processes of neurons range in length from relatively short, as in CNS interneurons, to very long for sensory and motor cells. The latter reach from the spinal cord out

to the end processes in the periphery. At the extreme are sensory neurons that innervate the toes, have cell bodies in the dorsal root ganglion at the spinal cord, and send an ascending process to the brain stem at the top of the spinal cord before synapsing. These single cells can be more than five feet long. Much of the material necessary for maintaining the structure and function of the axon and terminal regions is synthesized in the cell body and transported along the length of the axon. This axonal transport process is vulnerable to disruption by certain types of compounds, especially in the largest and longest axons. Disruption of axonal transport leads to degeneration of the axonal segment distal to the blockage site.

2.3 Response to Injury

The neurons of the central nervous system are derived from neuroblastoma cells during development. These cells divide, migrate to their positions in the mature brain, differentiate into mature cell types, and establish functional synaptic contacts as a part of normal developmental processes. Once the maturation process is completed, however, neurons in the CNS lose the ability to replace themselves. When neurons die in the CNS of mature mammals, they are not replaced. In recent years there have been interesting reports that, in some cases, neurons in the CNS can regenerate. However, in mammalian species, the vast majority of the evidence is that mature CNS neurons are not replaced. Lost neurons are lost forever.

A permanent loss of neurons does not necessarily mean that the functions performed by that neural tissue are also lost forever. The remaining neural tissue retains a great deal of plasticity. Even in the mature brain, synaptic contacts are continuously being modified through changes in structure and functional plasticity. Patients who suffer from brain injury often experience gradual recovery as remaining areas of the brain subsume lost functions. The recovery may not restore function to its original state, however, because the loss of the brain tissue can diminish the overall functional capacity of the brain. Reduced overall functional capacity may lower the ability to deal with future challenging or stressful situations and impair recovery from further injury. Conceptually, a loss of reserve capacity could also cause the functional deficits from normal aging to appear earlier (14).

Axons that are sufficiently damaged degenerate. Severing an axon from the cell body interrupts the flow of essential materials and nutrients from the cell body down the axon. The segment of the axon distal to the cut degenerates gradually over a period of weeks to months in a characteristic sequence of changes referred to as Wallerian degeneration. Cells that have synaptic contact with damaged neurons may be affected. Trophic factors associated with synaptic function are required to maintain viable contacts. When one neuron degenerates, the loss of trophic factors can cause a range of transsynaptic changes in the contacted neurons ranging from mild to so severe as to cause degeneration in the contacted neuron.

Damaged dendrites and axons can regenerate, although repair is often incomplete. This repair process is linked to the functional plasticity of the nervous system and the ability of neuronal processes to change in a use-dependent fashion. Central nervous system axons, however, typically fail to regenerate more than short processes. These abbreviated fibers do not establish restored functional connections. Improving the ability of severed nerve fibers in the CNS and PNS to regenerate and form functional contacts with lost targets is an active area of neuroscience research, particularly with regard to spinal cord injuries. At the present time, however, the ability to recover from neurotoxic or other injuries to neurons and their processes in the CNS must be considered limited at best.

The capacity for repair of nerve fiber injury and recovery of function in the PNS is better than in the CNS. If the original pathway of the nerve fiber, the nerve sheath, is intact after the injury, it is likely that the fibers can regenerate and form functional contacts again. A study of acrylamide intoxication in baboons demonstrated the gradual decline of electrophysiological function in peripheral sensory and motor nerves during the course of chronic treatment and when treatment ceased, a gradual return to normal approximately two years later (52). If the pathway is blocked or disrupted, however, then it is likely that regeneration will not be successful. In the peripheral nervous system, additional branches from remaining healthy nerves might replace lost fibers. In the case of motor neurons, this

can result in more muscle fibers being innervated by a single motor neuron. Electrophysiological studies that stimulate an individual motor nerve fiber elicit a larger muscle response than normal due to the higher number of motor units innervated. In the case of sensory neurons, such as those innervating the skin, the process is similar. If surviving neighbor neurons innervate a region of previous denervation, then the ability to discriminate between stimulation of the skin in different locations is reduced in proportion to the increased size of the receptive field surface innervated by the individual surviving neurons.

2.3.1 Glial Response Injury to the central nervous system induced by physical trauma, hypoxia, or neurotoxicant exposure elicits a stereotypical response pattern. The glial fibrillary astrocytes play a prominent role in this response. Following injury, the astrocytes surrounding the damaged region hypertrophy, support the physical structure of the remaining brain tissue, and clean up the damage. Microglial cells then invade the area and digest and remove cellular debris, as would macrophages elsewhere in the body. An astrocytic glial scar remains in the site of a lesion.

The hypertrophy of astrocytes in response to injury is associated with an increased amount of glial proteins. A protein expressed only in fibrillary astrocytes, glial fibrillary acidic protein (GFAP), has become useful as a general marker for neurotoxicant-induced injury to the CNS (53–55). This glial marker is useful in part because of the uniform nature of the astrocytic response to neural injury. Given the diverse nature of neural tissue, it is difficult to predict what neurochemical or neuroanatomical measures are sufficient to ensure that an experimental toxicity study does not miss subtle nervous system damage. An assay of GFAP utilizes the brain's own injury response system to signal neural damage and therefore can detect many types of damage.

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3 Neurotoxic Outcomes
3.1 Pathological Changes
Spencer and Schaumburg classified different types of neurotoxic damage, depending upon the region of the nervous system and cell types involved (56). Neurotoxic substances may damage neuronal cell bodies and produce a neuronopathy, they may damage the axon and produce an axonopathy, or they may damage the myelin and produce a myelinopathy. In addition, the damage may occur in the central and/or peripheral nervous system. Chang reviewed neurotoxicological aspects of neuropathology (57).

3.1.1 Neuronopathy Pathological changes in neurons can be observed as a response either to injury to the axonal processes or to the cell body (19, 56, 57). Damage to the axon can produce a reaction in the neuronal cell body called central chromatolysis. This reaction is observed microscopically as a slight distending of the cell body and dissolution of the Nissel substance (the neuronal version of rough endoplasmic reticulum) beginning around the nucleus and extending over time to involve the entire cell. Central chromatolysis has been observed in neurons of the dorsal root ganglion after methylmercury poisoning and in neurons of the brain stem after alkyl lead poisoning. Neurons may survive axonal injuries and sprout new processes.

A somewhat different reaction to injury is called peripheral chromatolysis. In this case, there is a slight reduction in neuronal size and depletion of the Nissel substance in the peripheral portions of the cytoplasm. The reaction is observed in motor neurons of the spinal cord anterior horn after degeneration or atrophy of muscles.

Atrophy and degeneration of neurons are irreversible injuries. Neurons in the process of degeneration often shrink in size and become hyperchromatic. Acute intoxication may initially

produce neuronal or axonal swelling and vacuolation, which eventually is followed by atrophy and degeneration. In some cases, an accumulation of neurofibrils is observed in the cytoplasm of neurons. This is called neurofibrillary degeneration and is commonly seen in Alzheimer's patients. A similar fibrillary condition, but not identical, has been observed in animals intoxicated with aluminum. Neuronal death (necrosis) is observed as a densely stained cell body and condensed nuclear chromatin called pyknosis.

3.1.2 Axonopathy Neurotoxic substances may cause damage to nerve axons. Axonopathies are classified by the site of damage: close to the cell body, a proximal axonopathy, or far from the cell body, a distal axonopathy. Axonopathies are typically characterized by a tangled accumulation of neurofilaments inside the axon, which blocks axonal transport and causes transported materials to accumulate. The axonal segment around the tangle swells as a result of the accumulated material. Giant axonal swellings are a hallmark of axonopathy. In some cases, the swellings resolve if treatment with the neurotoxic compound is terminated, but in other cases the portion of the axon distal to the swellings degenerates in a Wallerian fashion. Depending on the dose level and dose rate, experimental exposure to b,b'-iminodipropionitrile (IDPN) can produce proximal giant axonal swellings, whereas exposure to acrylamide, *n*-hexane, or carbon disulfide can produce distal axonal swellings (58). Primary axonal degeneration can lead to secondary degeneration of the myelin that once surrounded the now missing axons..

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4 Classes of Neurotoxic Compounds
Detailed information about the neurotoxic effects of specific chemical compounds is provided elsewhere in this series of volumes. Therefore, only a brief overview of the major classes of neurotoxic chemicals is provided here. The major classes of environmental and occupational neurotoxicants are metals, insecticides, and organic solvents. There are also many other compounds that produce neurotoxic effects but do not fall within these three categories.
4.1 Metals
Numerous metallic compounds have proven neurotoxic in humans or in experimental animals. The form of the metal compound, whether it is elemental, an inorganic salt, or contained within an organic compound, can strongly influence neurotoxicity. In general, organometallic compounds are more neurotoxic than the inorganic forms due to the greater penetration of these compounds into the brain. In addition, the route of exposure and age of the subject are critical determinants of toxicity. Inhalation exposure to mercury vapor is much more dangerous than oral exposure, for example. Developing organisms are often more sensitive to metals than adults. There is very little information regarding the sensitivity of the aged to metal toxicity, but many now suspect that the aged may be more at risk than young adults. The neurotoxicities of lead, mercury, and manganese compounds are well established in working populations. In addition, a variety of other metals produce neurotoxic effects.

4.1.1 Lead The neurotoxicity of lead has been known since ancient times. Today, lead is arguably the most widely recognized environmental pollutant. Much has been written about lead toxicity, and the interested reader can find many thorough reviews (161, 162). Lead is toxic acutely and chronically to adults and children. In the United States, regulatory actions have made a large impact in reducing sources of exposure to lead from occupational, environmental, and food and water sources. The range of toxic signs and symptoms is a function of the dose.

In worksite situations, exposure to lead has been one of the most extensively studied compounds. Anger summarized the data from 33 studies conducted in 9 or 10 countries involving a total of 3271 exposed workers and 2309 referents (6). Consistent deficits were observed across these studies in the

performance of tests designed to assess several aspects of cognitive function, including intelligence, memory, vigilance, acquisition, coding, spatial relationships, distractibility, and vocabulary. In addition, these studies consistently reported deficits in motor coordination and response speed and changes in affect. These consistent findings across a large number of studies clearly indicate the potential of occupational exposure to lead to produce adverse neurological consequences.

Currently, a major concern for lead neurotoxicity is for the cognitive function of children exposed to what was once considered an acceptable level of lead. The work of Needleman and colleagues was instrumental in demonstrating an association between the body burden of lead, measured as elevated blood and/or dentine lead levels, and deficits in performing a variety of cognitive tasks (154). A number of ongoing prospective studies around the world have confirmed and advanced the relationship between developmental lead exposure and impaired cognitive function (163, 164). Animal models of cognitive function confirm the deleterious actions of lead exposure (162, 165, 166). Recently, neurophysiological measures have shown that lead-treated animals show deficits in long-term potentiation, which is thought to reflect the cellular processes involved in learning and memory (167–169). Less appreciated are the other effects of lead on the nervous system, including toxicity to vision (170–176); and perhaps, somatosensory systems (126). The mechanisms of action through which lead produces its neurotoxic effects remain unknown despite numerous hypotheses (48, 161). Hopefully, the continued development of conceptual models and mechanistic research will lead to an eventual understanding of this most infamous of neurotoxicants.

4.1.2 Mercury Mercury in many forms can produce neurotoxic effects by inhalation of mercury vapor, ingestion of inorganic mercury salts, or by exposure to organomercurial compounds (155). Methylmercury is the most notorious of the organic forms of mercury because of its role in poisoning hundreds of individuals in Minamata Bay, Japan, (10, 11) and thousands in Iraq (8). Methylmercury is produced from industrial sources and through methylation of inorganic mercury by microbes in soils and sediments. Methylmercury is lipophilic and bioaccumulates in environmental food chains. Fish and marine mammals may have enriched methylmercury concentrations in their tissues.

Exposure to inorganic forms of mercury in the workplace has been the focus of numerous studies of neurobehavioral function. Anger (6) reviewed data from 18 studies conducted in eight or nine countries involving a total of 1002 exposed workers and 831 referents. Consistent deficits in exposed workers were observed in tests designed to assess intelligence, memory, and coding ability. In addition, exposed workers consistently performed poorly on tasks of motor coordination, response speed, and steadiness. Exposed workers also consistently showed changes in responding to personality tests. These data demonstrate that neurological function should be a concern in industrial hygiene programs for workers potentially exposed to inorganic mercury.

As with lead, exposure of children to low levels of methylmercury is currently a primary health concern. Two ongoing longitudinal studies are investigating populations that rely heavily on ocean-caught fish for their diets. One is a study of the neurobehavioral development of children who reside in the Seychelle Islands, where methylmercury-contaminated fish represent a substantial portion of the diet. No deleterious relationship between the concentration of methylmercury in hair samples and neurological development has been observed in this population (177, 178). In contrast, a study of residents of the Faroe Islands, where marine mammals contaminated with methylmercury are consumed, has observed significant deficits in the performance of cognitive tasks as a function of hair methylmercury concentration (179). Several factors might account for these apparently discrepant results, including different levels of mercury exposure, coexposure to other contaminants such as PCBs in the Faroe Islands, the older age of the children evaluated in the Faroe Islands, and more sensitive neurobehavioral evaluative procedures used in the Faroe Islands.

4.1.3 Manganese Manganese (Mn), a transitional metal and essential trace nutrient, can become neurotoxic under certain exposure conditions. The range of toxicological outcomes following exposure to Mn varies as a function of dose. Low levels of exposure cause subtle subclinical changes

in the performance of motor tasks and nonspecific subjective complaints such as fatigue, poor memory and insomnia. Workers occupationally exposed to low dose levels of Mn have changes in mood and deficits in performing cognitive and motor tasks (180–186). Continued or higher levels of exposure lead to an intermediate phase of toxicity, including psychomotor excitement, dysphoria, and abnormalities of gait and posture. This is followed by the late stage development of severe, debilitating, extrapyramidal deficits. Humans who have advanced Mn intoxication display prominent signs of basal ganglia dysfunction including bradykinesia, rigidity, fatigue, masked face, intention tremor, and disturbances of gait and balance (187, 188). The clinical, neurochemical, and pathological manifestations of Mn poisoning resemble those of Parkinson's disease but are distinct in the more global distribution of changes throughout the basal ganglia, more inclusive neurochemical changes, the spectrum of clinical manifestations, and the response to pharmacological therapy (188, 189). The motor disturbances in advanced Mn intoxication are linked to identifiable lesions in nuclei of the extrapyramidal motor system, including the globus pallidus, caudate, and the substantia nigra. The nigrostriatal pathway, which degenerates in Parkinson's disease, is evidently spared in manganese poisoning.

4.2 Solvents

Organic solvents are widely used in many industrial and commercial operations. Many solvents are highly volatile, creating an opportunity for substantial inhalation exposure. Because of their high lipid solubility, organic solvents gain ready access to neural tissues in the central and peripheral nervous system. Exposure to organic solvents can produce a variety of acute and chronic effects on the nervous system. This combination of factors makes potential neurotoxic effects a concern for workers and others exposed to organic solvents. Many different chemicals are used as organic solvents. The neurological effects of acute exposure are similar for many organic solvents, making it tempting to consider the toxic effects of these chemicals as a class. Arlien-Søborg (190) has extensively reviewed solvent neurotoxicity. Toluene, xylene, styrene, *n*-hexane, methyl *n*-butyl ketone, methyl ethyl ketone, 2,5-hexanedione, methylene chloride, methyl chloride, trichloroethylene, 1,1,1-trichloroethane, white spirits and solvent mixtures are covered in this work. Workers are often exposed to a combination of different organic solvents used either individually or as chemical mixtures. This factor can make it difficult or impossible to attribute any toxic effects observed to a particular chemical compound, and consequently the outcomes in several occupational exposure studies have been attributed to mixed solvent exposure. In some cases coexposure to multiple solvents may show greater than additive toxic effects (191).

Each organic solvent has a different chemical structure, forms a different set of metabolites and, therefore, can produce unique toxic effects (192). Despite this fact, this chapter will consider the neurotoxicity of organic solvents grouped under general categories of neurotoxic effects, rather chemical by chemical, because chemical specific information is presented elsewhere in these volumes. Four general categories of neurotoxic effects of exposure to organic solvents are of concern. These include the effects sedative/narcotic like effects of acute exposure, central/peripheral polyneuropathy produced by exposure to some organic solvents, ototoxicity that has been observed primarily in laboratory animals to date, and chronic solvent-induced dementia and toxic encephalopathy, the most controversial of the neurotoxic effects of organic solvents. The issues of ototoxicity and peripheral neuropathy produced by organic solvents were discussed previously. Therefore, this section focuses on the neurotoxic effects of acute and chronic exposure to organic solvents.

4.2.1 Neurotoxic Effects of Acute Exposure to Organic Solvents Acute exposure to many volatile organic compounds produces effects on the nervous system that resemble those of other CNS depressants, such as ethanol, barbiturates, or benzodiazapines (75, 128, 193, 194). Indeed, some commonly used industrial solvents, such as trichloroethylene, were used historically as medical anesthetics. Initial exposure produces a mild excitation or giddiness, similar to imbibing a moderate amount of an alcoholic beverage. Animal studies may show an initial increase in behavioral activity (128, 194) or an excitatory change in electrophysiological recordings (195). Continued exposure or higher concentrations produce CNS depression and deficits in cognitive function, sensory perception, and motor performance. Studies of laboratory animals or exposed human subjects show

changes in electrophysiological recordings from the brain and impaired performance of behavioral tasks (192, 196–204). Humans in such a state are prone to make errors in judgment, to have poor motor coordination, and slowed reactions. Operation of motor vehicles, industrial machinery, or other heavy equipment while exposed to organic solvent vapors can be acutely hazardous, just as is driving a car while under the influence of alcohol. Coexposure to alcohol or CNS depressant drugs and organic solvent vapors further increases the danger. The occupational exposure limits for many organic compounds have been established specifically to avoid the narcotic effects of exposure.

Many experimental laboratory studies have been published in which human volunteers were acutely exposed to organic solvents and a variety of neurobehavioral procedures were administered. Dick has extensively compiled this literature in a review article (205). Because of safety and ethical concerns, experimental studies of exposed human subjects are limited to dose levels low enough to ensure that no irreversible effects are produced. Typically, human subject protection committees will not approve deliberate exposure concentrations above the occupational exposure limits. Consequently, most of the procedures in these studies have reported negative results. However, a number of these studies have reported that solvent exposure was associated with changes in task performance. Many studies reported effects of solvents on symptom and sensory irritation questionnaires, tests of attention and vigilance, short-term memory (digit-span) tests, simple and choice reaction time, manual dexterity and motor speed, EEG and visual evoked potentials, postural sway, and various measures of visual perception (205).

The acute effects of exposure to many organic solvents have a rapid onset and rapid reversal. After inhalation, organic solvents readily cross the alveolar membranes and enter the blood where they are carried largely in the membranes and lipophilic regions of proteins in blood cells. These compounds travel from the lungs directly to the brain where favorable blood–brain partition coefficients encourage movement into brain tissues. The blood–brain barrier does not effectively restrict movement of these compounds into the brain. Once in the brain, the mechanism of action of these compounds to produce narcosis or other functional changes is not known. One hypothesis is that these compounds partially dissolve neuronal cell membranes, increasing their fluidity (206, 207). Another view is that organic solvents are attracted to the lipophilic regions of cell membrane proteins, where they alter protein function (208–211). Which proteins are critical is in question. Changes in receptors for the dopamine (190), GABA (194) and excitatory amino acid (212) neurotransmitter systems have been proposed. Following cessation of exposure, the acute neurological effects of most organic solvents rapidly dissipate as the compound is quickly eliminated. This can present a problem for the experimental study of acute solvent if the subjects must be tested after removal from the exposure chambers. The interpretation of such studies should consider that the tissue concentrations of the compound and the associated behavioral changes rapidly diminish after termination of exposure.

In expressing occupational exposure limits as a time-weighted average (TWA), it is assumed that the average amount of exposure over a workday is the critical determinant in producing an adverse outcome. Short-term excursions above the TWA may produce acute symptoms even though the average daily exposure is well within the TWA. It is important to adhere to short-term excursion limits (STELs) for volatile organic solvents because of the rapid onset of symptoms. In assessing the risk of short-term exposures, it is important to consider the relationship between exposure concentration (C) and duration (t) in producing adverse outcomes (213). If extrapolation is based on a classical linear form of Haber's Rule (i.e., $C \times t = k$, where k represents a constant toxic effect) to predict the effects of short duration exposures, it is not sufficiently protective (214, 215). A better option may be to determine the tissue concentrations of the compound associated with a toxic effect (216) and then use a physiologically based pharmacokinetic model to calculate the various exposure conditions that can achieve that critical tissue concentration (217).

4.2.2 Solvent-Induced Toxic Encephalopathy The possibility that chronic occupational exposure to organic solvents could lead to cognitive and neurological deficits was one of the most controversial issues in neurotoxicology. Concern first grew from a number of studies conducted in Scandanavian

countries (reviewed in Refs. 190, 218–220). Because many of the original cases described involved painters, the condition became known as "*painter's syndrome*," or alternatively, as solvent induced "*psycho-organic syndrome*." The later label emphasized the psychological deficits and the belief that there was organic damage to the brain as a result of solvent exposure. The cognitive deficits included global impairment of intellect, changes in personality, and loss of memory. These studies were disputed for a number of reasons; a principal reason was inadequate matching of exposed and control populations, particularly with regard to preexposure intelligence (221). The ability to use postexposure outcome measures to match groups for preexposure levels of intelligence remains controversial (222, 223). Recently, however, a growing set of studies demonstrate associations between chronic solvent exposure and neurological deficits (66, 224–229). The expression of chronic solvent neurotoxicity progresses with continued exposure from mild symptoms to severe debilitating dementia. The stages of the disorder have been categorized according to various schemes (218, 230). Milder stages feature complaints of fatigability, memory impairment, and difficulty concentrating. Intermediate phases involve sustained changes in personality and mood, emotional liability, and difficulty with impulse control and mood. As the condition progresses, there are objectively demonstrable cognitive impairments and neurological signs. The final stage of dementia features global deterioration of intellect and memory, hard neurological signs, and positive neuroradiological findings. Upon cessation of exposure, the effects of chronic solvent exposure are thought to remain stable and not degenerate further over time (231).

Worksite neurobehavioral studies of solvent exposed workers have observed a number of consistent types of deficits. For workers exposed to carbon disulfide, deficits have been reported in three or more independent studies on tests of intelligence, memory, vigilance, coding, spatial relations, motor coordination, response speed, and personality (6). For exposure to styrene, consistent deficits have been observed in tests of memory, motor coordination, and response speed (6). Consistent deficits have been reported in three or more independent studies of workers exposed to mixed solvents in tests of intelligence, memory, vigilance, acquisition, coding, concept shifting, spatial relations, categorization, motor coordination, response speed, color vision, and personality (6).

Workers with a diagnosis of solvent-induced encephalopathy after occupational exposure to solvents show ventricular and cortical atrophy by CT and MRI imaging (232). MRI was a more sensitive measure and showed changes in workers normal by CT. A case-control study of 23,000 residents in Seattle, Washington, found that a work history of potential exposure to organic solvents increased the risk of subsequent diagnosis with Alzheimer's disease (233). The risk was particularly strong for males for whom working jobs with potential solvent exposure increased the risk of being diagnosed with Alzheimer's disease sixfold over controls.

Although now there is considerable evidence that chronic exposure to solvents can lead to a degenerative neurological state, uncertainties remain as to the dose–response relationships. In most of the occupational studies to date, an objective and thorough characterization of exposure levels and exposure history is lacking. Are the effects due to current lower level exposures, or can they be attributed to past exposures when the levels were often higher? Also, the role of repeated exposure to spikes that may go well above the TWA exposure limits is unknown. One handicap in addressing these questions is the lack of good animal models that show persistent cognitive deficits following chronic solvent exposures. Answers to these questions must await further research.

4.3 Pesticides

By design, pesticides are toxic to living organisms. Ideally, they are preferentially toxic to the target pest organisms and less toxic to nontarget organisms, including humans, wildlife, and beneficial plants and insects. Many insecticides have been developed specifically for their toxicity to the nervous system. For the most part, these insecticides act on the neural tissues of humans in the same manner as they do on the target insect species. The extent to which humans are less sensitive to these agents than insects is typically due to metabolic factors. The mammalian toxicity of insecticides varies widely across agents and classes of compounds. Some compounds such as parathion or aldicarb are highly toxic, whereas others such as malathion and carbaryl have relatively low mammalian toxicity. Because insecticides typically have a known mechanism of toxicity, it is

tempting to focus toxicity studies on the known mechanisms of action. However, it is also important to consider alternative mechanisms of action and toxicity mediated through other potential actions of the compounds. The major classes of insecticides that are designed to be neurotoxic include organophosphorus, carbamate, pyrethroid, and organochlorine compounds. This section considers the mammalian neurotoxicity of organophosphorus insecticides because of the widespread use of these compounds and recent concern for their safety.

4.3.1 Organophosphorus Compounds Organophosphorus compounds are the most widely used class of pesticides. Approximately 50 compounds are currently registered for use in the United States, and more than one hundred are used worldwide. More than 50,000 organophosphorus compounds have been synthesized and screened for pesticidal activity (234). A metabolite of chloropyrifos, the most widely used organophosphorus compound, was detected in the urine of 82% of a sample of 1000 adults living in the United States (235). Exposure to organophosphorus compounds can be particularly hazardous if not used according to approved applications. For example, recently several hundred homes in the southern and midwestern United States were illegally sprayed with methyl parathion, a practice potentially lethal to residents, especially children, and had to be decontaminated at an estimated cost of over $50 million (236). A number of extensive review articles cover the toxicity of organophosphorus insecticides (234, 237–242).

Some organophosphorus compounds are active as the parent compound. Others must be metabolically activated in the liver to an oxon derivative to become active. Organophosphorus compounds produce acute toxicity through inhibition of acetylcholinesterase, the enzyme that inactivates the neurotransmitter acetylcholine in synapses and neuromuscular junctions. A discussion of the actions of acetylcholine and the consequences of acetylcholinesterase inhibition was presented earlier. The enzyme acetylcholinesterase is found in the central and peripheral nervous systems and in red blood cells. Butyrylcholinesterase, also known as nonspecific cholinesterase, pseudocholinesterase, or simply as cholinesterase is another enzyme that hydrolyzes acetylcholine and is inhibited by organophosphorus compounds and many other acetylcholinesterase inhibitors. Butyrylcholinesterase is found in myelin in the nervous system, liver, and plasma. The physiological roles of acetylcholinesterase in blood and butyrylcholinesterase in plasma are not known, but the inhibition of these enzymes is widely used as an indicator of exposure to organophosphorus compounds.

4.3.1.1 Acute toxicity Symptoms of acute overexposure to organophosphorus compounds are attributable to acetylcholinesterase inhibition and the consequent overstimulation of neurons, muscles, and glands postsynaptic to cholinergic synapses. Acute symptoms include abdominal pain, nausea, vomiting, diarrhea, dizziness, blurred vision, constriction of the pupils (miosis), increased salivation, lacrimation, and sweating. High doses lead to severe poisoning marked by dilated or nonreactive pupils, muscle twitching, pulmonary edema, tachycardia, convulsions, coma, respiratory paralysis, and death. Timely antidotal treatment, including atropine, that blocks cholinergic muscarinic receptors, and oxime compounds such as 2-PAM, that promote regeneration of active acetylcholinesterase molecules, is effective in mitigating the effects of acute organophosphate poisoning. Although the actions of organophosphorus compounds as cholinesterase inhibitors are well known, recent evidence shows that these compounds also have direct actions at cholinergic muscarinic receptors (243, 244) and, perhaps secondarily, on intracellular second messenger systems (245). Recovery of normal acetylcholinesterase activity follows the time course of new enzyme synthesis. Exposure to organophosphorus compounds also induces a down-regulation of muscarinic cholinergic receptors, that, it is thought, mediates tolerance to repeated dosing (246). Recovery of behavioral and motor functions from acute exposure can precede the return of normal levels of acetylcholinesterase and of cholinergic muscarinic receptors (247, 248).

4.3.1.2 Chronic Toxicity A number of studies have demonstrated that individuals who survive acute poisoning from organophosphorus compounds may have long-term deficits in memory, attention, mood, and changes in EEG and peripheral nerve function (249–252). Three or more worksite behavioral studies have found deficits in tests of intelligence and memory in organophoshate

exposed workers (6). Animal studies have shown persistent changes in the second messenger systems of the brain (253) and retina (254) after a single dose of an organophosphorus compound. Until recently, there was no evidence that workers exposed to organophosphorus compounds, but who were never acutely poisoned, suffered any long-term consequences (255, 256). A series of recent reports from the study of sheep dippers in Great Britain, however, show deficits in performing cognitive tests, including tests of attention and information processing speed, and peripheral nerve function, including two-point sensory discriminations, among organophosphorus workers who have not experienced acute poisoning (257–259).

4.3.1.3 Organophosphorus-Induced Delayed Neurotoxicity Exposure to some, but not all, organophosphorus compounds causes axonal degeneration in the spinal cord and peripheral nerves. This syndrome became widely recognized first during the American Prohibition Era in which the organophosphorus compound, tri-*o*-cresyl phosphate (TOCP; now called tri-*o*-tolyl phosphate) adulterated the popular drink, Jamaican ginger extract. The syndrome has since become known as organophosphorus pesticide-induced delayed neurotoxicity (OPIDN), even though many of the compounds that produce the syndrome (such as TOCP) are not actually used as pesticides. After a single or repeated dose of an active organophosphate, axons of the spinal cord and peripheral nerves degenerate in a distal, dying-back style that is distinct from that of acrylamide and the hexacarbons (260). Symptoms appear after a delay period of approximately 6–14 days. Affected individuals show weakness and sensory loss in the distal portions of the feet and legs, ataxia, and with continued dosing, progressive debilitation that can spread to the upper limbs and autonomic nervous system in severe cases. Young animals are more resistant to OPIDN than mature ages. Rats do not develop clinical signs of OPIDN such as ataxia, despite the presence of neuropathology similar to other sensitive species (261). Hens, in contrast, are quite sensitive to OPIDN and have become a standard species for screening compounds for this potential problem. The production of OPIDN does not involve inhibition of acetylcholinesterase. Johnson devised a test of enzymatic activity that does correlate well with a compound's potency to produce OPIDN, that is referred to now as neurotoxic esterase or alternatively, as neuropathy target enzyme (NTE) (262). Compounds that inhibit NTE activity by 50–70% or more are considered potential axonal pathogens. Organophosphorus pesticide products registered in the United States undergo a gait test in hens and testing for NTE inhibition to detect and eliminate compounds with this potential. More information on OPIDN can be found in review articles by Abou-Donia (234, 263), Lotti (264), and Richardson (265).

4.3.1.4 Issues Arising Recently there has been increased public concern about the susceptibility of children to exposure to organophosphorus compounds and other pesticides (266). This concern led to passage of the Food Quality Protection Act that contains provisions for assessing the safety of pesticide residues in foods. Among the novel provisions of the act are that pesticide safety evaluations should consider specifically the susceptibility of young individuals and also that cumulative and aggregate exposures to pesticides should be considered. Among adults, there is evidence that genetic differences in the enzyme human serum paraoxonase (PON1) can markedly influence susceptibility to organophosphorus agents (267). Another public concern is for the possibility for ocular toxicity resulting from exposure to organophosphorus compounds (268–270). Combining these two different concerns, recent evidence suggests that developmental exposure to organophosphates might interfere with the visual control processes necessary for proper ocular development (271). Future research on organophosphorus compounds will feature factors that influence individual susceptibility differences, understanding compound exposures, nontraditional toxicity targets such as the eye, and other, perhaps noncholinergically mediated, effects.

5 Preventing Neurotoxicity

The prevention of neurotoxic disorders should be a primary goal of occupational and environmental health programs. The National Research Council (2) outlined several facets of a program to better prevent future neurological disorders from exposure to toxic chemicals. A simplified distillation of this program might include more extensive efforts at the following:

1. screening of new and existing chemicals for potential neurotoxicity, so that neurotoxic hazards can be identified and avoided;
2. surveillance of exposures in occupational and environmental settings;
3. monitoring the neurological health of those potentially exposed, and
4. training medical and occupational health professionals to better recognized and understand neurotoxic conditions.

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Silver and Gold
Daland R. Juberg, Ph.D., F. Terry Hearne, MS

1.0 Silver
1.0.1 CAS Number: [*7440-22-4*]

1.0.2 Synonyms: argentum; collargol; C.I. 77820

1.0.3 Trade Names: NA

1.0.4 Moleculer Weight: 117.86

1.1.1 General Silver, an element of the II(B) Group, is in the second transition series of the periodic table. It is a white, lustrous, relatively soft and very malleable metal. Silver has high thermal and electrical conductivity and resists oxidation in air that is devoid of hydrogen sulfide. Silver is insoluble in water although it can exist in an aqueous environment in three cationic forms, Ag(I), Ag (II), and Ag(III), in addition to its metallic state (Ag0) (1). Most silver compounds are made from silver nitrate, which is prepared from silver metal. Although the chemical and physical properties of various silver compounds and salts may be quite variable depending on the nature of the base, some common properties of metallic silver are listed in Table 26.1.

Table 26.1. Selected Silver Compounds and Physical/Chemical Properties (REF)

Compound	Molecular Formula	CAS Number	Molecular Weight	Aqueous Solubility (g/L H_2O at 25°C)	ACGHIH TLV-TWAand MSHA Standard-air
Silver	Ag	[*7440-22-4*]	107.87	Virtually insoluble	
Silver chloride	AgCl	[*7783-90-6*]	143.32	1.9×10^{-3}	
Silver nitrate	$AgNO_3$	[*7761-88-8*]	169.87	2.2×10^{2}[a]	
Silver oxide	Ag_2O	[*20667-12-3*]	231.74	2.2×10^{-2}[b]	
Silver sulfide	Ag_2S	[*21548-73-2*]	247.74	1.4×10^{-4}	
Silver bromide	AgBr	[*7785-23-1*]	187.8	Slightly soluble	
Silver sulfadiazine	$C_{10}H_9AgN_4O_2S$	[22199-08-02]	357.1	Insoluble in H_2O and acid	0.01 mg (Ag)/m^3

4-Amino-N-(2-pyrimidinyl)benzenesulfonamide silver salt,
benzenesulfonamide, 4-amino-N-2-pyrimidinyl-, monosiliver(1+) salt,
Dermazine,
Flamazine,

Geben, Silvadene, silver sulfadiazine, silver sulphadiazone, sulfadiazone silver, sulfadiazine silver salt				
Silver acetate	$C_2H_3AgO_2$	[*563-63-3*]	166.9	Insoluble in H_2O and acid
Silver iodide	AgI	[*7783-96-2*]	234.8	Insoluble in H_2O and acid
Silver trifluoroacetate	$C_2AgF_3O_2$	[*2966-50-9*]	220.9	Insoluble in H_2O and acid
Silver fluoride	AgF	[*7775-41-9*]	126.9	Insoluble in H_2O and acid
Silver lactate	$C_3H_5AgO_3$	[*128-00-7*]	196.9	Slightly soluble in H_2O
Sodium aurothiomalate		[*12244-57-4*]		

[a] Value is per 100 g H_2O.

[b] Measured at 20°C.

Silver and Gold
Daland R. Juberg, Ph.D., F. Terry Hearne, MS

2.0 Gold
2.0.1 CAS Number: [*7440-57-5*]

2.0.2 Synonyms: Burnish gold, colloidal gold, gold powder, gold-197, gold flake

2.0.3 Trade Names: NA

2.0.4 Molecular Weight: 197
2.1 Chemical and Physical Properties
2.1.1 General Gold is a dense, yet malleable, lustrous, yellow metal widely found in nature as elemental gold or in combination with sulfides in igneous rocks and ores. Gold is very stable and nonreactive and does not burn or oxidize in air. Other than in its atomic state, the metal does not react with oxygen, sulfur, or selenium at any temperature. Gold does react with various oxidizing agents at ambient temperatures provided a good ligand is present to lower the redox potential below that of water. Therefore, gold is not attacked by most acids under ordinary conditions and is stable in

basic media. Gold does, however, dissolve readily in 3:1 hydrochloric–nitric acid to form $HAuCl_4$ [*16903-35-8*], and in alkaline cyanide solutions in the presence of air or hydrogen peroxide to form $AuCN_2$, and these chemical reactions are important to the extraction and refining of the metal. Gold reacts with halogens, particularly in the presence of moisture, and at low (≤200°C) temperatures, chlorine is adsorbed on the gold surface to form surface chlorides. Its melting and boiling points are 1064 and 2807°C, respectively. Information about common gold compounds is presented in Table 26.6.

Table 26.6. Selected Gold Compounds and Physical/Chemical Properties (REF)

Compound	Molecular Formula	CAS Number	Molecular Weight	Aqueous (H_2O) Solubility (g/L) at 25°C
Gold	Au	[*7440-57-5*]	196.97	Virtually insoluble
Gold chloride	AuCl	[*10294-29-8*]	232.42	Soluble in HCl, HBr, KCN
Gold potassium chloride	$KAuCl_4·2H_2O$	[*13682-61-6*]	414.16	618
Sodium aurothiomalate	$C_4H_6O_4S·Au·2Na$	[*42722-04-3*]	393.05	Very soluble
Aurothioglucose	$C_6H_{11}AuO_5S$	[*12192-57-3*]	392.08	Very soluble
Gold (I) sodium thiosulfate 2-water	$AuNa_3(S_2O_3)_2·2H_2O$		526.24	500
Gold trichloride	$AuCl_3$	[*13453-07-1*]	303.33	680
Gold potassium cyanide		[*554-07-4*]		
Gold (I) potassium cyanide	C_2AuKN_2	[*13967-50-5*]	288.09	

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Magnesium, Calcium, Strontium, Barium, and Radium
Mary Beth Genter, Ph.D., DABT

1.0 Magnesium
1.0.1 CAS Number:
[*7439-95-4*]
1.0.2 Synonyms:
Magnesium turnings, metal turnings
1.0.3 Trade Names:
NA
1.0.4 Molecular Weight:
24.31
1.0.5 Molecular Formula:
Mg
1.1 Chemical and Physical Properties
1.1.1 General Magnesium is one of the most common elements found in the earth's crust (2.1% by weight). There are three naturally occurring isotopes of magnesium: ^{24}Mg (78.7%), ^{25}Mg (10.13%), and ^{26}Mg (11.17%). Magnesium metal is not found as such naturally; rather, it occurs in mineral or salt form, such as magnesite, carnallite, dolomite [$CaMg(CO_3)_2$], epsomite, and many other minerals. Over 50 magnesium salts are known. Magnesium is one of the alkaline-earth elements; as such, it is insoluble but reactive in water, liberating hydrogen gas, and extremely flammable. Magnesium burns with a brilliant white flame. Melting point: 650°C; boiling point: 1107°C; flash point: 500°C; specific gravity: 1.74; vapor density: 0.84.

1.1.2 Odor and Warning Properties None attributable to magnesium, but the associated anions may be responsible for an odor characteristic of the various magnesium salts.
1.2 Production and Use
Magnesium is found in seawater and plant and animal tissues. Chlorophylls *a* and *b* are magnesium chelates of porphyrin (2, 3). Magnesium metal may be prepared industrially by reduction of MgO-containing materials (4). Magnesium is used as a constituent of light alloys, in the manufacture of precision instruments, as a deoxidizing and desulfurizing agent in metallurgy, in the production of flashbulbs and flares, for Grignard reagents, and in semiconductor research (4). Magnesium is an essential element in the diet [recommended daily allowance (RDA) is 4.5 mg/kg] and is a cofactor in over 300 enzymatic reactions (5). Magnesium is essential in the synthesis of ATP and other enzymes involved in muscle contractility and neuronal transmission. Several magnesium salts, most commonly the citrate, are used as cathartics. Magnesium nitrate is used in the production of pyrotechnics. Magnesium sulfate [*7487-88-9*] is used as an anticonvulsant in preeclampsia or eclampsia (5). Magnesium oxide and the trisilicate are used as antacids (4).
1.3 Exposure Assessment
1.3.1 Air Air samples for magnesium analysis should be collected on 0.8 mm mixed cellulose ester filters. Analysis is by inductively coupled argon plasma atomic absorption spectroscopy (6).

1.3.2 Background Levels: NA

1.3.3 Workplace Methods: NA

1.3.4 Community Methods: NA

1.3.5 Biomonitoring/Biomarkers 1.3.5.1 Blood The reference value for magnesium in blood is 1.5–2.8 mg/dL (or 1.2–2.3 meq/L) (5). Intracellular magnesium concentrations are much higher than serum magnesium concentrations, so serum measurements may not be meaningful. Ion-specific electrodes have become available for determining ionized magnesium in plasma (3). Magnesium oxide can be measured in whole blood (6). Magnesium can also be measured in blood and plasma via neutron activation analysis (7).

1.3.5.2 Urine: NA
1.4 Toxic effects
1.4.1 Experimental Studies 1.4.1.1 Acute Toxicity Magnesium chloride was administered intravenously to ICR mice, and an LD_{50} value of 14.4 mg/kg was determined (8).

1.4.1.2 Chronic and Subchronic Toxicity: NA

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Magnesium can interact with and block calcium channels (9). Parenterally administered magnesium decreases acetylchloline in motor nerve terminals and acts on myocardium by slowing rate of S-A node impulse formation and prolonging conduction time (5).

1.4.1.3.1 Absorption Magnesium absorption following oral ingestion is reported to range from 40 to 60%, with a lower percentage of absorption at higher daily intakes. The transport of magnesium into or out of cells appears to require a carrier-mediated transport system, and a Mg^{2+}/H^{+} exchanger has only recently been described in *Arabidopsis thaliana* (3, 10). Magnesium decreases the absorption of fluoride (11), and excess calcium may partially inhibit the absorption of magnesium.

1.4.1.3.2 Distribution In the plasma, magnesium is about 65% in the ionic form, with the remainder bound to plasma proteins. Of the approximately 20 g body burden of magnesium, most is stored primarily in bone and muscle following absorption (12).

1.4.1.3.3 Excretion The kidney is the primary organ involved in magnesium homeostasis, with filtration–reabsorption, but not tubular secretion, occurring. Approximately 12 mg of magnesium is excreted in the urine per day. Magnesium excretion can also occur via the sweat and breast milk. Hypermagnesiumemia has been reported in individuals with renal impairment. Severe toxicity has been reported in individuals with renal impairment who were administered magnesium-containing laxatives or antacids; cardiac and neurological symptoms can occur if serum levels reach approximately 4.8–8.4 mg/dL (3, 12, 13). Unabsorbed magnesium is excreted in the feces.

1.4.1.4 Reproductive and Developmental No teratogenicity studies were found for magnesium salts. However, magnesium deficiency (0.2 mg Mg/100 g diet during days 6–12 of gestation) has been associated with defects in rat fetuses (14). These defects occurred in 14% of the viable fetuses and reportedly included skeletal malformations, cleft lip, hydrocephalus, and heart, lung, and urogenital anomalies. A significant number of fetal resorptions was also noted. Gunther et al. (14) similarly reported a high rate of resorption in rats subjected to gestational magnesium deficiency. No significant increase in congenital defects was seen in surviving pups.

1.4.1.5 Carcinogenesis MgO is regarded as an “experimental tumorigen” (15), although the only reference in the literature that could be found relating to the carcinogenicity of MgO was an

instillation study, in which MgO dust instilled intratracheally for 30 weeks resulted in induction of histiocytic lymphomas in hamsters (16). It was also demonstrated that MgO enhanced the tumorigenesis of benzo[*a*]pyrene and was an effective carrier agent for the experimental induction of respiratory tract tumors (17).

1.4.2 Human Experience 1.4.2.1 General Information Magnesium is an essential element for human survival. The recommended intakes are 30–75 mg/day for infants; 80–130 mg/day for children; 240 mg/day (age 9–13 years), increasing with age to 420 mg/day for males >70 years of age; 240 mg/day (age 9–13 years), increasing to 320 mg/day for females >70 years of age. Normally, serum contains 2–5 mg/dL of magnesium; the total body burden is estimated at 20 g. Recommended daily allowances for pregnancy range from 360 to 400 mg/day, and 320 to 360 mg/day during lactation (3). Hypocalcemia is a prominent manifestation of magnesium deficiency in humans (3). Early clinical signs of hypermagnesiumemia include hypotension, hyporeflexia, and decreased respiration (18). Magnesium deficiency has been associated with neuromuscular irritability, pathological calcification, and damage to the heart and kidneys (19). Toxicological concerns arise from exposure to magnesium oxide [*1309-48-4*] (particulates and fumes), and, to a lesser extent, magnesite [*546-93-0*] ($MgCO_3$).

1.4.2.2 Clinical Cases 1.4.2.2.1 Acute Toxicity Large pharmacological doses of magnesium can have serious adverse effects, including metabolic alkalosis, diarrhea, dehydration, and cardiac arrest. In a number of cases, renal impairment contributed to magnesium toxicity (3). Inhalation of MgO fumes produced a febrile reaction and leukocytosis, analogous to metal fume fever induced by ZnO (12). Dermal contact with magnesium compounds, or embedded magnesium particles, can induce "chemical gas gangrene," which is slow to heal (15).

1.4.2.2.2 Chronic and Subchronic Toxicity: NA

1.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanism Oral doses of some magnesium salts, namely, the sulfate and citrate, are poorly absorbed; osmotic withdrawl of water from the gut wall causes their purgative effects.

1.4.2.2.4 Reproductive and Developmental No increase in birth defects was noted in the offspring of 141 women treated with magnesium sulfate (including six treated during the first 4 months) during pregnancy (20). Twenty-seven hypertensive women were treated with magnesium hydroxide during the third trimester of pregnancy; no effect was noted on the newborns, except a slight increase in body weight in the children born to the treated mothers vs. controls (21). Cord serum levels of magnesium were reported to be 70–100% of the maternal levels after maternal therapy. In such cases, neurological depression may occur in the neonate, characterized by respiratory depression, muscle weakness, and decreased reflexes (22). No decrease in Apgar scores was noted in infants of females treated for pregnancy-induced hypertension, although the magnesium levels in the infants reflected hypermagnesiumemia (23). Prolonged magnesium treatment during pregnancy may be associated with maternal and fetal hypocalcemia and adverse effects on fetal bone mineralization (22).

1.4.2.2.5 Carcinogenesis: NA

1.4.2.2.6 Genetic and Related Cellular Effects: NA

1.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, etc.: NA

1.4.2.3 Epidemiology Studies When ingested as a naturally occurring food source, magnesium has not been demonstrated to have adverse effects.

1.4.2.3.1 Acute Toxicity The initial sign of excessive oral magnesium intake from nonfood sources is

diarrhea; in fact, various magnesium salts are used pharmacologically for their cathartic effects.

1.4.2.3.2 Chronic and Subchronic Toxicity: NA

1.4.2.3.3 Pharmacokinetics, Metabolism, and Mechanism: NA

1.4.2.3.4 Reproductive and Developmental: NA

1.4.2.3.5 Carcinogenesis: NA

1.4.2.3.6 Genetic and Related Cellular Effects: NA

1.4.2.3.7 Other: Neurological, Pulmonary, Skin Sensitization, etc Habitual low magnesium intake or prolonged hypomagnesiumemia is associated with alterations of vascular and cardiac function, as well as with cardiovascular disease. Magnesium supplementation after a heart attack reduces the incidence of therapy-requiring arrhythmias, and individuals exposed to drinking water with high concentrations of magnesium reportedly have a reduced incidence of hypertension (3, 18). A study involving 2316 patients with acute myocardial infarction showed a 24% reduction in 28-day mortality when intravenous magnesium was used either before or at the time of thrombolytic administration (24). A subsequent study in which magnesium was administered over a different time course did not confirm these observations, so further evaluation of this issue has been undertaken (25). Magnesium supplementation may also be beneficial in the treatment of burns and migraine headaches (26, 27).
1.5 Standards, Regulation, or Guidelines of Exposure
No drinking-water standards have been established for magnesium or magnesium salts. The threshhold limit value (TLV) for magnesium oxide [*1309-48-4*] fume is 10 mg/m^3. The OSHA time-weighted-average permissible exposure limit (TWA PEL) is also 10 mg/m^3 (total particulates) and 5 mg/m^3 (respirable particles). Magnesite [*546-93-0*] ($MgCO_3$) is considered by both OSHA and ACGIH to be a dust that does not produce significant organic disease or toxic effect when exposures are kept under reasonable control. The ACGIH TLV TWA is 10 mg/m^3, measured as total particulate, and the OSHA TWA PEL is 15 mg/m^3 as total particulate, and 5 mg/m^3 for respirable fraction.

Magnesium, Calcium, Strontium, Barium, and Radium
Mary Beth Genter, Ph.D., DABT

2.0 Calcium
2.0.1 CAS Number:
[*7440-70-2*]
2.0.2 Synonyms:
NA
2.0.3 Trade Names:
NA
2.0.4 Molecular Weight:
40.08
2.0.5 Molecular Formula:
Ca
2.1 Chemical and Physical Properties
2.1.1 General Melting point: 845°C, boiling point: 1484°C, specific gravity: 1.54; vapor density: 1.4. Calcium is a silvery-white alkaline-earth metal that is seldom found as the free metal in nature. It is

an essential component of leaves, bones, teeth, and shells. It is a hard, silvery-white metal that forms a white coating of nitride in air. Calcium is found as limestone, gypsum, and fluorite, and makes up >3% of the earth's surface (fifth most abundant element). Calcium imparts a red color to flames. Calcium occurs naturally as six isotopes: ^{40}Ca (97%), ^{44}Ca (2.06%), ^{42}Ca (0.64%), ^{48}Ca (0.18%), ^{43}Ca (0.145%), and ^{46}Ca (0.003%).

2.1.2 Odor and Warning Properties No odor or warning properties are attributable to calcium itself, although calcium salts may have an odor characteristic of the associated anions.

2.2 Production and Use

The principal commercial source of calcium is limestone. Calcium metal can also be produced by electrolysis of calcium chloride. Seawater contains approximately 400 g of calcium per ton. Calcium is an essential element, required for normal physiological function of all cells. It is also a cofactor required for the function of multiple metabolic enzymes, and is required for neurotransmitter release. Calcium is used in metallurgy as a deoxidizer for copper, beryllium, and steel and to harden lead for bearings. Calcium is alloyed with cerium to make flints for cigarette and gas lighters. Calcium is used in the manufacture of electronic vacuum tubes as a “getter” to fix residual gases as oxides, nitrides, and hydrides of calcium. Calcium gluconate is used as a treatment for acute hypotension, and many calcium salts are used in the treatment of hypocalcemia. Calcium carbide is used in the production of acetylene (4). Calcium cyanamide is used medically for its Antabuse–like effect. Many calcium compounds are used as food additives for a variety of functions including calcium acetate as a texturizer and stabilizer, calcium bromate as a flour treatment, calcium carbonate as a nutritional supplement, and calcium chloride as a humectant (28). Calcium EDTA is used in the treatment of lead poisoning, as it has been shown to be effective in removing lead from soft tissues (29).

2.3 Exposure Assessment

2.3.1 Air Calcium compounds can be measured (as Ca^{2+}) using ICP-AES (NIOSH method 7300) or atomic absorption (NIOSH method 7020) (6).

2.3.2 Background Levels: NA

2.3.3 Workplace Methods: NA

2.3.4 Community Methods: NA

2.3.5 Biomonitoring/Biomarkers 2.3.5.1 Blood Measurement of serum calcium is a routine part of various clinical blood profiles. Reference values for serum calcium concentrations: up to 1 month of age: 7.0–11.5 mg/dL; 1 month of age to 1 year: 8.6–11.2 mg/dL; up to 30 years of age: 8.2–10.2 mg/dL, with a continuing slight decrease with advancing age (5). Calcium can also reportedly be measured in blood and plasma via neutron activation analysis (7).

2.3.5.2 Urine: NA

2.4 Toxic Effects

2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity Calcium chloride was administered intravenously to ICR mice, and an LD_{50} value of 42.4 mg/kg was derived from these studies (8). Severe mucous membrane irritation can result from ingestion of plant tissues containing calcium oxalate crystals (*e.g., Philodendron, Diffenbachia*), and calcium oxalate is the causative agent of the renal toxicity associated with ethylene glycol poisoning.

2.4.1.2 Chronic and Subchronic Toxicity: NA

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms In general, toxicological effects of concern related to calcium are associated with sustained increases in intracellular calcium. Although this situation can have a therapeutic benefit in certain instances, such as the increase in intracellular calcium caused secondarily to inhibition of Na^+, K^+-ATPase by such compounds as digitalis—thus causing enhanced contractility and excitability of cardiac muscle (30), sustained increases in

intracellular calcium are rarely beneficial. The intracellular concentration of cytosolic free Ca^{2+} is approximately 100 nM (31). The 10,000-fold gradient between extracellular and intracellular calcium is maintained by the impermeability of the plasma membrane to calcium and by calcium pumps that either move calcium up the concentration gradient across the plasma membrane, or sequester excess intracellular calcium in the endoplasmic reticulum or mitochondria. Because mitochondria have a low affinity transporter, they are active in calcium sequestration only when concentrations rise into the micromolar concentration range.

Sustained increases in intracellular free calcium can occur via a number of mechanisms (Table 28.1) (32, 33) and can cause cell damage in at least three ways. First, increased sequestration of calcium in mitochondria is associated with decreased ATP synthesis, with depletion of cellular energy reserves. This can potentiate a destructive cycle, as the extrusion of calcium from cells is ATP-dependent. A second means by which increased intracellular calcium can have toxic effects is via its effect on cellular cytoskeletal proteins. Increased intracellular calcium causes diassociation of actin filaments from a-actinin and fodrin; these two proteins promote anchoring of actin filaments to the plasma membrane. Without this anchoring, membrane blebbing occurs, which predisposes the membrane to rupturing (30). A third mechanism by which increased intracellular calcium can exert a toxic effect is via activation of hydrolytic enzymes that degrade protein, phospholipids, and nucleic acids. Neutral calcium-activated neutral proteases, or calpains, target integral membrane proteins and can proteolytically activate protein kinase C. Activation of phospholipases by calcium ions causes membrane degeneration directly and by the generation of detergents. Chromatin fragmentation occurs with the activation of Ca^{2+}-Mg^{2+}-dependent endonucleases. In addition, elevated intracellular Ca^{2+} can lock topoisomerase II in a form that cleaves—but does not ligate—DNA, contributing to chromatin fragmentation (30).

Table 28.1. Mechanisms and Agents Associated with Sustained Elevated Intracellular Ca^{2+}[a]

Mechanism	Agent(s)
Increased influx of Ca^{2+} into cytoplasm via	
Glutamate receptor agonists	"Excitotoxins": glutamate, domoate
Vanilloid receptor agonists	Capsaicin, resiniferatoxin
Voltage-gated Ca^{2+} channels	Maitotoxin
Newly formed membrane pores	Amphotericin B, ionomycin, A23187
Disruption of cell membranes	Detergents, hydrolytic enzymes, lipid peroxidants, cytoskeletal toxins
Release from mitochondria	Alloxan, ninhydrin
Release from sarcoplasmic reticulum	Ryanodine, also mutation in ryanodine receptor
Inhibition of Ca^{2+} export from the cytoplasm	
Inhibition of Ca^{2+}, Mg^{2+}-ATPase	DDT, cyclodiene insecticides, pyrethroid insecticides
Blockage of voltage-gated Ca^{2+} channels	Nickel, manganese, lanthanum
Inhibition of Ca^{2+}-activated K^{+} channels	Barium, apamin (bee venom), dendrotoxin

Impairment of mitochondrial ATP synthesis	
Inhibition of hydrogen delivery to the electron-transport chain	Fluoroacetate, dichlorovinylcysteine
Inhibition of electron transport	Rotenone, MPP^+, dinitroaniline, cyanide, formate
Inhibition of oxygen delivery to the electron-transport chain	CNS depressants, carbon monoxide
Inhibition of ADP phosphorylation	DDT, *N*-ethylmaleimide, dinitrophenol
Hydrolysis of $NAD(P)^+$ in mitochondria	Alloxan, *t*-butyl hydroperoxide, menadione

[a] Adapted from Refs. 9, 30, 32, 33 and 33a.

2.4.1.3.1 Absorption Calcium is absorbed from the gastrointestinal (GI) tract as a two-step process. Absorption occurs rapidly from the gut lumen into mucosal cells, and is then extruded into the interstitial fluid, with the first step faster than the second. 1,25-Dihydroxyvitamin D ($1,25(OH)_2D$, the active form of vitamin D) is required for both steps in calcium transport. Fractional calcium absorption varies inversely with dietary calcium intake. With a prolonged decrease in calcium intake, serum parathyroid hormone and $1,25(OH)_2D$ concentrations increase and the fraction of ingested calcium which is absorbed increases (3).

2.4.1.3.2 Distribution Calcium in the bloodstream is predominantly associated with albumin (33b).

2.4.1.3.3 Excretion Unabsorbed calcium is excreted in the feces. Renal calcium excretion is a function of the filtered load and the efficiency of reabsorption; the latter of these is regulated by parathyroid hormone. A high sodium diet increases the renal excretion of calcium, as both compete for reabsorption at the same sites in the renal tubules. The absorption of calcium from foods can be decreased by the presence of oxalic acid (found in spinach, sweet potatoes, rhubarb, and beans) or phytic acid (found in unleavened bread, nuts, grains, and soy isolates) (3).

2.4.1.4 Reproductive and Developmental Shackelford et al. (34) fed rats up to 1.25% dietary calcium carbonate for 6 weeks prior to mating and during gestation and found no adverse effects.

2.4.1.5 Carcinogenesis No studies on the carcinogenicity of elemental calcium were noted. The carcinogenicity of calcium chromate is attributed solely to intracellular soluble chromium (1).

2.4.1.6 Genetic and Related Cellular Effects Under normal physiological conditions, intracellular calcium concentrations are maintained approximately 10,000-fold lower than extracellular levels. Calcium cyanamide was weakly positive and inconclusive in the *Salmonella* assay, and it was negative in the mouse lymphoma assay, *Drosophila* tests, and cytogenetic tests for chromosomal aberrations and sister-chromatid exchanges (35).

2.4.2 Human Experience 2.4.2.1 General information Calcium accounts for 1–2% of adult human body weight, and the greatest proportion is found in bone and teeth. Adequate calcium ingestion is critical for proper bone and tooth development, as well as for the proper function of nerves, muscles, and other tissues. Adequate calcium ingestion is also felt to be critical in preventing osteoporosis. Recommended daily allowances (RDAs) range from 210 to 270 mg/day for infants, 500 to 800 mg/day for children, 1250 mg/day for males and females up to age 18, and 700 mg/day for

adults (3). Toxicological concern is associated with exposure to such calcium salts as calcium silicate [*1344-95-2*], calcium oxide [*1305-78-8*] (lime), calcium hydroxide [*1305-62-0*], and calcium cyanamide [*156-62-7*].

2.4.2.2 Clinical Cases 2.4.2.2.1 Acute Toxicity Calcium oxide (also known as unslaked lime) is a component of Portland cement and many commercial wall plasters. On contact with water, calcium hydroxide and heat are liberated. When calcium oxide comes into contact with the eye, both the heat and the tendency for the formation of clumps can result in ocular damage (36).

2.4.2.2.2 Chronic and Subchronic Toxicity The available data on the adverse effects of excessive calcium intake in humans primarily concerns calcium intake from nutritional supplements. The three most significant biological effects of excessive calcium intake are kidney stone formation (nephrolithiasis), the syndrome of hypercalcemia and renal insufficiency with and without alkalosis, and the interaction of calcium with the absorption of other minerals.

It is clear that other minerals, such as magnesium, are also important in kidney stone formation, but there is a clear association between high calcium intake and kidney stone formation. Hypercalcemia and renal insufficiency, also known as the *milk–alkali syndrome* (MAS), was recognized in the context of a formerly popular treatment of peptic ulcers by administering large amounts of milk and absorbable antacids. MAS was associated with progressive renal failure, which in turn led to the deposition of calcium in soft tissues, particularly the kidney. Calcium can clearly decrease the absorption of iron, although clinically, human data do not show an association between iron deficiency and high calcium intake (3).

2.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms: NA

2.4.2.2.4 Reproductive and Developmental Supplemental doses of calcium salts taken during pregnancy are regarded as unlikely to pose a teratogenic risk (37). Heinonen et al. (20) reported the results of a survey of 1007 women who took calcium compounds during the first trimester of pregnancy. In this study, 10 central nervous system (CNS) defects were observed (no specific deformity was described), and 4.7 were expected; this is likely to be a sporadic observation, as the standardized relative risk with 95% confidence interval ranged from 1.02 to 3.87. A congenital condition known as *infantile hypercalcemia* has been associated with supravalvular aortic stenosis, failure to thrive, mental retardation, and areas of dense calcification in the skull, vertebrae, and long bones. This rare condition appears to develop in children taking normal vitamin doses and whose mothers took a normal vitamin supplement during pregnancy (38).

2.4.2.2.5 Carcinogenesis Although calcium chromate is reportedly carcinogenic, the carcinogenicity is solely attributable to intracellular soluble chromium, not the calcium cation (1). The carcinogenicity of calcium cyanamide has not been evaluated.

2.4.2.3 Epidemiology Studies 2.4.2.3.1 Acute Toxicity: NA

2.4.2.3.2 Chronic and Subchronic Toxicity: NA

2.4.2.3.3 Pharmacokinetics, Metabolism and Mechanisms: NA

2.4.2.3.4 Reproductive and Developmental: NA

2.4.2.3.5 Carcinogenesis: NA

2.4.2.3.6 Genetic and Related Cellular Effects Studies Malignant hyperthermia susceptibility (MHS) is an autosomal dominant disorder of skeletal muscle and a major cause of death due to anesthesias. Malignant hyperthermia arises from stimulus-elicited release of Ca^{2+} from the sarcoplasmic

reticulum. Many individuals diagnosed with MHS have one of several known mutations in the Ca^{2+} release channel, known as the *ryanodine receptor* (39, 40). Intravenous administration of dantrolene blocks release of Ca^{2+} from the sarcoplasmic reticulum, decreasing heat production and acidosis, which characterize this condition (41).

2.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH has a TLV TWA of 0.5 mg/m^3 for calcium cyanamide. OSHA similarly has an 8-h TWA PEL of 0.5 mg/m^3 for calcium cyanamide. The ACGIH TLV TWA and the OSHA PEL for calcium hydroxide are 5 mg/m^3. Calcium silicate and calcium carbonate, regulated as nuisance dusts, have 8-h TWAs of 10 mg/m^3, and the OSHA standards are 15 mg/m^3 for the 8-h TWA, and 5 mg/m^3 limit as the respirable fraction. The TLV TWA and OSHA PEL for calcium hydroxide are both set at 5 mg/m^3. The TLV TWA and OSHA PEL for calcium oxide are 2 and 5 mg/m^3, respectively. No drinking-water standards have been established for calcium or calcium salts.

Magnesium, Calcium, Strontium, Barium, and Radium

Mary Beth Genter, Ph.D., DABT

3.0 Strontium

3.0.1 CAS Number:

[*7440-24-6*]

3.0.2 Synonyms:

NA

3.0.3 Trade Names:

NA

3.0.4 Molecular Weight:

87.62

3.0.5 Molecular Formula:

Sr

3.1 Chemical and Physical Properties

3.1.1 General Strontium is a silvery-white alkaline-earth metal that rapidly assumes an oxide film and yellow color on exposure to air. Strontium salts impart a brilliant red color to a flame. The finely divided metal ignites spontaneously in air; therefore, the metal should be stored under oxygen-free liquid. Naturally occurring isotopes include ^{88}Sr (82.56%), ^{86}Sr (9.86%), ^{87}Sr (7.02), and ^{84}Sr (0.56%) (4). In addition, at least 11 strontium isotopes are produced by fission; of these, the ^{89}Sr and ^{90}Sr isotopes are considered to be environmentally significant. ^{89}Sr emits b particles with an average energy of 583 keV (1.46 MeV maximum) and has a half-life of 50.5 days. ^{90}Sr is a long-range b-emitter (mean energy 195.8 keV; maximum 540 keV) with a half-life of 28 years (42). At least 20 strontium salts are known.

3.1.2 Odor and Warning Properties No odor or warning properties are attributable to strontium itself, although Sr salts may have an odor characteristic of the associated anions.

3.2 Production and Use

Strontium is found in small quantities associated with barium and calcium minerals. Strontium has been used in the past in the production of radioluminescent paints for use particularly on watch dials. Strontium bromide is used as a sedative; the chlorate, chloride, nitrate, and sulfate salts are used in the production of pyrotechnics. $^{89}SrCl_2$ [*14158-27-1*] (Metastron) is used therapeutically for relief of bone pain in patients with skeletal metastases (5).

3.3 Exposure Assessment

3.3.1 Air: NA

3.3.2 Background Levels Strontium is widely found, generally in association with calcium. Seawater contains 10 ppm. Celestite ($SrSO_4$) and strontianite ($SrCO_3$) are strontium-containing minerals (43). The concentration of strontium in drinking water from nine communities in Ohio and Wisconsin ranged from 0.02 to 33.9 mg/mL (44). ^{90}Sr was detected at significantly higher concentrations in soil than in food crops grown at the Los Alamos National Laboratory, New Mexico (45).

3.3.3 Workplace Methods: NA

3.3.4 Community Methods: NA

3.3.5 Biomonitoring/Biomarkers A unique body counting system (SICH-9.1) has been described for determining body burdens of ^{90}Sr via bremsstrahlung (46).

3.3.5.1 Blood A method for determination of strontium in human blood samples by ICP–AES has been described (47). Strontium can also reportedly be measured in blood and plasma via neutron activation analysis (7).

3.3.5.2 Urine A three-column system composed of a chelating concentrator column, a cation-exchange column, and an ion–exchange separator column has successfully been used to determine ^{90}Sr in water and urine samples (48).

3.3.5.3 Other Because strontium readily substitutes for calcium in many biological reactions, the content of strontium in milk is of particular interest. Several methods for determination of ^{90}Sr in milk have been described (48, 49).
3.4 Toxic Effects
3.4.1 Experimental Studies 3.4.1.1 Acute Toxicity In general, stable (nonradioactive) strontium salts are of little toxicological concern, particularly on oral ingestion, because of their limited absorption from the GI tract. Strontium chloride was administered intravenously to ICR mice, and an LD_{50} value of 147.6 mg/kg was derived (8).

3.4.1.2 Chronic and Subchronic Toxicity: NA

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 3.4.1.3.1 Absorption Strontium is highly associated with calcium throughout the food chain. However, in humans, absorption of calcium is preferred to strontium, and calcium is used preferentially over strontium in bone and milk production. The Sr:Ca ratio in bone is relatively constant for members of a species, regardless of age. Gastrointestinal absorption of strontium was reported to be approximately 20–30%. Combined nasal and gastrointestinal absorption of soluble ^{85}Sr was about 85%, with >50% directly absorbed from the nasal cavity (50).

3.4.1.3.2 Distribution Strontium is either deposited in bone or distributes into an exchangeable pool composed of plasma, cellular fluids, soft tissues, and bone surfaces. Orally administred $Sr(NO_3)_2$ accumulated in rat skeletons proportional to the administered dose, averaging 2.7% (1). $^{90}SrCl_2$ administered via inhalation (aerosol) was rapidly translocated from the lung to the skeleton, behaving similarly to intravenously administered soluble Sr on reaching the bloodstream (51). Following intravenous administration of $^{89}SrCl_2$ at two different doses (0.74 kBq/g body weight or 74 kBq/g), approximately 1.30 and 1.50%, respectively, of the administered dose was retained in the femurs 7 days after administration (52). Skeletal Sr can be mobilized during late pregnancy and lactation, migrating to the fetal skeleton and to the infant via breast milk (53). An active transplacental transfer of strontium has been demonstrated, with discrimination between strontium and calcium early in pregnancy and equal transplacental transport of the two ions later in pregnancy (54).

3.4.1.3.3 Excretion Excretion of unabsorbed Sr is predominantly via the feces, with smaller amounts in urine and sweat (1).

3.4.1.4 Reproductive and Developmental In a multigenerational miniature swine study, dams were fed ^{90}Sr at various levels, and then the offspring were exposed via lactation and feed. It was observed that levels of ^{90}Sr high enough to affect fetal or neonatal mortality would not permit the survival of the dam through gestation (51). Injection of pregnant mice with ^{90}Sr was associated with a decrease in the number of fetal oocytes (20 mCi on gestational day 11 or 16) and skeletal malformations (5–10 mCi) (14).

3.4.1.5 Carcinogenesis The carcinogenicity of stable (nonradioactive) strontium chromate was attributed solely to intracellular soluble chromium (1). ^{90}Sr has been examined in long-term studies in four species, involving beagles, mice, monkeys, and pigs. A summary of the findings of these studies can be found in Ref. 51. Following intravenous injection of ^{90}Sr at doses ranging from 0.027 to 362×10^4 Bq/kg, the most prominent ^{90}Sr-induced endpoint was bone sarcoma. Neoplasms involving the soft tissues near bone in the oronasopharynx and paranasal sinuses and bone marrow dysplasia were also significantly elevated over controls. Feeding studies in beagles extending from the *in utero* period to age 540 days resulted in the development of the same array of tumors, and, in addition, myeloproliferative disorders. Inhalation exposure to $^{90}SrCl_2$ was associated with multiple carcinogenic and non-neoplastic lesions in dogs, with an excess of bone tumors reported as the major finding. Interestingly, inhalation exposure of dogs to insoluble forms of ^{90}Sr was associated with lung tumors, but not bone tumors (51). In an additional study in which beagle dogs were injected with low levels of ^{90}Sr (21.1 kBq/kg, or 5 times the maximum permissible (retained) body burden), ^{90}Sr was not associated with a decrease in survival time (55). It has been estimated that ^{90}Sr is approximately two orders of magnitude less toxic than radium (56). Two monkey studies were also summarized by the Council on Radiation Protection and Measurements (51). One of these studies involved administration of single intravenous injections of ^{90}Sr (0.10–6.21 MBq) to rhesus monkeys. These monkeys had no symptoms or disease attributable to ^{90}Sr 20 years after exposure. In another study, administration of 1.85 or 3.7 MBq of ^{90}Sr as a single oral dose resulted in bone sarcomas (51).

3.4.1.6 Genetic and Related Cellular Effects Studies Oral administration of strontium chloride to mice resulted in dose-dependent chromosomal aberrations in bone marrow metaphase preparations (57). An increased mutation frequency was noted in the bone marrow, but not liver or spleen, in the lacZ transgenic mouse (Muta mouse) following intravenous administration of 74 MBq/kg of ^{89}Sr (58).

3.4.2 Human Experience 3.4.2.1 General Information In general, the nonradioactive salts of strontium are of little toxicological concern, particularly on oral administration, because of the low GI bioavailability of the strontium ion. However, strontium is highly dangerous in its radioactive forms. On absorption, strontium concentrates primarily in bones.

3.4.2.2 Clinical Cases 3.4.2.2.1 Acute Toxicity In patients administered $^{89}SrCl_2$ for relief of bone pain associated with metastatic bone cancer, the major side effects noted are bone marrow supression and thrombocytopenia (5).

3.4.2.2.2 Chronic and Subchronic Toxicity: NA

3.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms: NA

3.4.2.2.4 Reproductive and Developmental Leikin and Paloucek (5) list $^{89}SrCl_2$ as a pregnancy risk factor D, meaning that there is positive evidence of fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk. There are equivocal data, summarized in Shepard (14), regarding the relationship between fetal ^{90}Sr body burden and incidence of birth defects in humans.

3.4.2.3 Epidemiology Studies 3.4.2.3.1 Acute Toxicity: NA

3.4.2.3.2 Chronic and Subchronic Toxicity: NA

3.4.2.3.3 Pharmacokinetics, Metabolism and Mechanisms: NA

3.4.2.3.4 Reproductive and Developmental: NA

3.4.2.3.5 Carcinogenesis The U.S. EPA has categorized stable strontium as a cancer group D, which indicates that there is inadequate or no human or animal evidence of carcinogenicity (59). Strontium chromate is a suspected human carcinogen, an effect attributable to the chromate component.
3.5 Standards, Regulations, or Guidelines of Exposure
Strontium is listed by the U.S. EPA as a candidate for establishment of a maximum contaminant level, but none presently exists. The reference dose (RfD) for strontium has been estimated at 0.6 mg/kg per day; this corresponds to a daily level of exposure that is likely to be without appreciable risk of deleterious effects over a lifetime. The TLV TWA for strontium chromate is 0.0005 mg/m^3 as chromate, because strontium chromate is regarded as a class A2, or suspected human, carcinogen.

Magnesium, Calcium, Strontium, Barium, and Radium
Mary Beth Genter, Ph.D., DABT

4.0 Barium
4.0.1 CAS Number:
[*7440-39-3*]
4.0.2 Synonyms:
NA
4.0.3 Trade Names:
UN 1399, UN 1400, UN 1854
4.0.4 Molecular Weight:
137.33
4.0.5 Molecular Formula:
Ba
4.1 Chemical and Physical Properties
4.1.1 General Melting point: 725°C; boiling point: 1640°C; specific gravity: 3.51 at 20°C. Barium exists as multiple isotopes: 138 (71.66%); 137 (11.32%); 136 (7.81%); 135 (6.59%); 134 (2.42%); 132 (0.097%); 130 (0.101%) (4). Barium participates in chemical reactions typical of alkaline-earth metals, that is, it reacts violently with acids, water, and carbon tetrachloride. Pure barium metal exists as yellowish-white, slightly lustrous lumps that are somewhat malleable and very easily oxidized (must be kept under petroleum or other oxygen-free liquid to exclude air). Typical of other alkaline-earth metals, barium decomposes in water, evolving hydrogen gas. There are approximately 40 different barium salts. Of these barium salts, approximately half are freely soluble in water, whereas others are practically insoluble (notably barium sulfate and carbonate). Solutions of soluble barium salts give a white precipitate with sulfuric acid or soluble sulfates, and they color nonluminous flame green. Water or acid soluble barium salts should be regarded as poisonous.

4.1.2 Odor and Warning Properties Most barium salts are odorless or have an odor and characteristic of the associated anion.

4.2 Production and Use

Barium carbonate occurs in nature as the mineral witherite; barium sulfate occurs in nature as the mineral barite; also as barytes, heavy spar. Barium is used as a carrier for radium. Alloys of barium with Al or Mg are used as getters in electronic tubes. Barium carbonate is used as rodenticide (4, 60) and in paints, enamels, and marble substitutes (4). Barium sulfate (multiple trade names, including Bakontal, Esophotrast, Micropaque, Raybar) is used as an X-ray-contrast material (4) and as a weighting substance for golf balls (61). Barium nitrate is used in the manufacture of pyrotechnics and green signal lights. Barium sulfide is used as a depilatory and in luminous paints.

4.3 Exposure Assessment

4.3.1 Air Barium can be released into the air during mining and in various industrial processes.

4.3.2 Background Levels Barium's abundance in earth's crust is approximately 0.05%. The background concentration of Ba in groundwater is approximately 0.1 mg/L, although significant regional excursions from this value have been documented (62). Seawater reportedly contains approximately 13 mg/L (5). Various measurements have revealed soil concentrations to range from 15 to 3000 ppm, and the average atmospheric concentration in North America is reported to be 0.12 mg/m^3 (5). Brazil nuts are exceptionally high in barium, with a concentration of 3000–4000 ppm (5). Depending on the geographic site, daily barium intake is estimated to be 300–1700 mg/person (63, 64).

4.3.3 Workplace Methods Barium-containing fluxes used in welding can result in significant airborne barium fumes and elevated urinary barium concentrations in exposed workers (65).

4.3.4 Community Methods In addition to workplace exposures, consumer products can be a source of barium exposure. For example, about half of a sample of crayons was demonstrated to contain barium capable of migrating, thus representing a potential source of exposure for children (66). It has also been predicted that some lipsticks can represent a significant source of barium exposure (64).

4.3.5 Biomonitoring/Biomarkers No biomarkers of exposure to barium have been recognized, although methods to measure barium in various physical media have been described (67).

4.3.5.1 Blood Inductively coupled plasma–atomic absorption spectrometry (ICP-AES) has been used for measurement of barium compounds (as Ba) in biological materials, including blood. The detetion limit for Ba in blood by this method is reported to be 0.6 mg/L of blood (68). Neutron activation analysis has also been used for determining levels of Ba in human blood, with detection limits of 7 mg Ba/L of red blood cells and 66 mg Ba/L of plasma (7).

4.3.5.2 Urine Barium concentrations in urine of workers exposed to barium welding fumes reportedly increased, but the method used was not described (65). Subsequently, methods for detecting barium in urine have been published (6, 68, 69). The detection limit for Ba in urine measured by ICP-AES is reported to be 0.26 mg/L of urine (68). A proposed reference value for Ba in urine for biological monitoring purposes is <15 mg/g creatinine (70).

4.3.5.3 Other In the workplace soluble barium compounds can be monitored in air by flame atomic absorption. Samples can be collected on 0.8-mm cellulose ester membranes at a flow rate of 1 to 4 L/min (6).

4.4 Toxic Effects

4.4.1 Experimental Studies 4.4.1.1 Acute Toxicity LD_{50} values were derived following intravenous administration of soluble barium salts in two strains of mice: Swiss Webster and ICR. The Swiss Webster mice were the more sensitive strain, with LD_{50} values of 8.1, 8.5, and 11.3 mg/kg for barium chloride, nitrate, and acetate, respectively. The corresponding values for the ICR mice were 19.2, 20.1, and 23.3 mg/kg for barium chloride, nitrate, and acetate, respectively (8). In rats, the oral

LD_{50} of barium zirconate was reported to be >1.98 g/kg and the inhalation LD_{50} of barium zirconate was calculated to be 0.42 g/kg (71). A soluble form of barium, barium chloride, was considerably more acutely toxic in rats, with the LD_{50} calculated to be 220 mg/kg (as Ba) in weanling rats, and 132 mg/kg (as Ba) for adult rats (72). Elevated blood pressure, bronchoconstriction, ECG abnormalities, and myocardial hyperexcitability were demonstrated in guinea pigs administered barium-containing fume extract. These effects could be modified by nifedipine and propranolol (73). Similarly, intravenous administration of barium chloride to rabbits resulted in severe ventricular dysrhythmias, which were relieved by treatment with doxepin or verapamil (74).

4.4.1.2 Chronic and Subchronic Toxicity Barite dust inhaled by guinea pigs was reportedly associated with nodular pulmonary granulation, characteristic of human baritosis (1). A more recent study revealed no pulmonary granulomas following inhalation exposure to barium zirconate, although thickening of alveolar walls, as well as the medial layer of arteriole walls, was noted, with the general picture of a chronic interstitial pneumonitis (71).

The results of at least three subchronic barium chloride drinking-water studies have been published. In the first of these, groups of young adult Charles River rats of both sexes were exposed at concentrations of barium chloride of ≤250 mg/L (ppm) for 4, 8, or 13 weeks. No significant toxic effects were noted. A tissue distribution study revealed that barium concentration in several tissues increased with dose, but not duration of exposure, and that the highest concentrations were found in bone (72). A subsequent subchronic study in which Fischer 344/N rats and B6C3F1 mice were administered barium chloride in the drinking water at levels up to 4000 ppm revealed renal toxicity as the major toxicological finding (75). Barium-treated male and female rats exhibited higher serum phosphorous than did controls, but other electrolytes and hematological values were within normal ranges. In both species, the animals in the 4000-ppm treatment group exhibited alterations in motor activity, grip strength, and thermal sensitivity. Central nervous system effects were also reported after subchronic–chronic subcutaneous injection of barium chloride (43).

A third barium chloride drinking water study was designed to evaluate the potential *in vivo* cardiovascular effects of long–term barium exposure. Long–term administration of barium chloride (100 ppm) resulted in hypertension, hypersensitivity to barbiturate anesthesia, disturbances in myocardial energy metabolism, and depressed cardiac excitability, preferentially in the arterioventricular nodal region of the heart (76).

4.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The barium ion is a chemical antagonist to potassium, and it appears that symptoms of barium poisoning are attributable to Ba^{2+}-induced hypokalemia (77). a-Adrenergic responsiveness was found to be enhanced in barium-treated Purkinje fibers (78). Barium mimics calcium in its effects, but their kinetics in subcellular stores may be different (79). Barium also inhibits Ca^{2+}-activated K^{+} channels, which prolongs excitation and can cause potentially lethal neuroexcitatory and spasmogenic effects (30).

4.4.1.3.1 Absorption Barium, in food sources, is absorbed from the GI tract into the bloodstream at approximately 6% of the administered dose (5). Approximately 75% of inhaled barium is absorbed (5). In beagle dogs, respiratory tract absorption of inhaled particles (1.2–2.1 mm median aerodynamic diameter) contributed significantly to the absorption of $BaCl_2$. Approximately 75% of the body burden was absorbed into the circulatory system within hours of inhalation exposure; 55% was attributed to absorption deposited in the pulmonary regions of the lung and 2% to GI absorption (50).

4.4.1.3.2 Distribution Studies in rats showed that barium is cleared from the serum by deposition in bone and teeth (5, 80). Barium is also deposited in muscles, and is stored in lung, with little retention in liver, kidneys, spleen, brain, heart, or hair (81).

4.4.1.3.3 Excretion A study of the metabolism of ^{140}Ba in rats showed the urinary and fecal excretions to be 7 and 20%, respectively (1). The half life in the human body is estimated to be 3.6 days (5).

4.4.1.4 Reproductive and Developmental A subchronic study in which Fischer 344/N rats and B6C3F1 mice were administered barium chloride in the drinking water at levels of ≤4000 ppm revealed no anatomical effects in either species, but the offspring of the high dose rats exhibited a marginal reduction in pup weight. No effects were seen on reproductive indices (75). An earlier study in which $BaCl_2$ (20 mg) was injected into chick yolk sacs revealed curled toes in 50% of the surviving chicks (Ridgeway and Karnofsky, cited in Ref. 14).

4.4.1.5 Carcinogenesis A National Toxicology Program (NTP) 2-year study with male and female rats and mice, in which barium chloride hydrate was administered in drinking water, reported no evidence of carcinogenicity in either species (82). Bronchogenic carcinomas reportedly developed in rats injected intratracheally with $[^{35}S]BaSO_4$ (80).

4.4.1.6 Genetic and Related Cellular Effects Studies Barium nitrate was not positive in the Ames assay (*S. typhimurium* strains TA1535, TA1537, TA1538, TA97a, TA98, TA100, TA102c) with or without metabolic activation, with plate incorporation assay and preincubation assay methods. It was also negative in the mitotic crossing-over test, in the mitotic genic conversion test, and in the retromutation test in *Saccharomyces cerevisiae* D7 strain with or without metabolic activation (83). Genotoxicity studies with barium chloride hydrate were positive in the mouse lymphoma assay but negative in *Salmonella* assays and assays for increased frequencies of chromosomal aberrations and sister–chromatid exchanges in cultured Chinese hamster ovary cells (82).

4.4.2 Human Experience 4.4.2.1 General Information: NA

4.4.2.2 Clinical Cases Epidemic poisonings from soluble barium salts are rare. The most common poisoning occurs after ingestion of barium carbonate, which is used as a rodenticide (60). Onset of symptoms occurs within minutes to hours of ingestion and includes perioral paresthesias, vomiting, and severe diarrhea. Hypertension and cardiac dysrhythmias may follow. Profound hypokalemia and weakness progressing to flaccid paralysis are additional characteristics of barium poisoning. In one instance, a family was poisoned following accidental ingestion of barium carbonate, and one of these individuals also developed respiratory failure and rhabdomyolysis (60).

Following intentional ingestion of approximately 13 g of $BaCl_2$, a patient was hospitalized with intractable diarrhea, abdominal pain, weakness, and hiccups (84). The patient developed paralysis and profound hypokalemia, despite aggressive potassium replacement therapy. The patient also developed renal failure, possibly because he was administered intravenous magnesium sulfate. Oral magnesium sulfate is the treatment of choice to precipitate insoluble barium sulfate, thus preventing systemic absorption of barium; intravenous administration may have contributed to this patient's renal failure as a result of precipitation of barium sulfate in the bloodstream and/or kidneys (84).

4.4.2.2.1 Acute Toxicity The lethal dose of barium by ingestion is reported to be between 1 and 15 g (85), or 56 mCi/kg (5). The initial symptoms of toxicity are irritation of the gastrointestinal tract with nausea, vomiting, and diarrhea. Premature ventricular contraction and systemic hypertension often follow. The poisoned victim may progress to hiccups, convulsions, and flaccid paralysis. The paralysis often progresses centrally, and death occurs as a result of respiratory or cardiac arrest (84). Barium hydroxide and barium oxide are strongly alkaline in solution, causing severe burns of the eye and irritation of the skin (61).

4.4.2.2.2 Chronic and Subchronic Toxicity A benign pneumoconiosis, baritosis, was first described in humans in the 1930s (1). The condition occurs in individuals exposed to finely-ground $BaSO_4$ as

well as barite miners (1, 86). Because of the high radiopacity of barium, the chest radiologic picture shows discrete, dense images; however, no symptoms, abnormal physical signs, interference with lung function, or increased susceptibility to thoracic disease is believed to occur. The radiographic abnormalities disappear slowly with cessation of exposure (86). Bronchial irritation has been associated with $BaCO_3$, and BaO dust is considered a potential agent for dermal and nasal irritation (1).

4.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms The toxicity of barium is related to its direct stimulation of smooth, striated, and cardiac muscles and to severe depression of serum potassium levels. The reduced serum potassium levels are the result of increased intracellular potassium, rather than increased urinary excretion.

4.4.2.2.4 Reproductive and Developmental: NA

4.4.2.2.5 Carcinogenesis: NA

4.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

4.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, etc There is some debate as to the appropriateness of the use of insoluble $BaSO_4$ as a contrast material in patients with obstructive bowel disease. The controversy centers on the fact that, whereas $BaSO_4$ is an excellent contrast material, it causes serious peritonitis when in contact with the peritoneal cavity; such contact could potentially occur if the patient requires surgery or if there is a rupture of the bowel (87).

4.4.2.3 Epidemiology Studies 4.4.2.3.1 Acute Toxicity: NA

4.4.2.3.2 Chronic and Subchronic Toxicity There are a number of epidemiological studies which together are inconclusive concerning the health impacts of barium in drinking water. An epidemiological study released in 1979 (88) associated an elevated risk of cardiovascular mortality with barium concentrations in drinking water > 1 ppm. The area in question was a region of northern Illinois where the barium concentration in drinking water was in the range of 7–10 ppm. However, another study in the same area did not reveal an associated elevation in blood pressure in individuals consuming high barium drinking water (62). A systematic follow-up study to these reports was conducted in eleven healthy men who were monitored for cardiovascular risk factors following 4 weeks of drinking water with 0 ppm of barium, followed by 4 weeks of drinking water with 5 ppm of barium, followed by 4 weeks of drinking water with 10 ppm of barium. Diet and water volume consumption were strictly monitored. It was determined that there were no changes in blood pressure, plasma cholesterol, lipoprotein, or apolipoprotein levels, serum potassium or glucose levels, or urine catecholamine levels. There were no arrhythmias related to barium exposure. Therefore, it was concluded that barium exposure at 5 or 10 ppm in the drinking water did not appear to affect any of the known modifiable cardiovascular risk factors (89).

4.5 Standards, Regulation, or Guidelines of Exposure

The U.S. Environmental Protection Agency (U.S. EPA) has established a maximum contaminant level (MCL) of 2 ppm of barium in the drinking water. The MCL represents the maximum level of a contaminant in water that is delivered to any user of a public water-supply system. U.S. EPA also requires that discharges or environmental spills of 10 lb or more of barium cyanide be reported. The Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), and the American Conference of Governmental Hygienists (ACGIH) have set occupational exposure limits of 0.5 mg/m^3 (threshold limit value [TLV]) for an 8-h workday, 40 h/week for soluble barium compounds. The OSHA limit for barium sulfate dust in air is 10 mg/m^3 (total particulate; 5 mg/m^3 for respirable particles). NIOSH currently recommends that a level of 50 mg/m^3 be considered immediately dangerous to life and health. Australia and the United Kingdom have established exposure values of 0.5 mg/m^3 as Ba. Germany has additional exposure

values for the inhalable fraction of the aerosol: TWA short-term, 0.5 mg/m^3 1 mg/m^3; 30 min, 4 times per shift.

Magnesium, Calcium, Strontium, Barium, and Radium
Mary Beth Genter, Ph.D., DABT

5.0 Radium
5.0.1 CAS Number:
[*7440-14-4*]
5.0.2 Synonyms:
^{228}Ra (mesothorium); ^{223}Ra (actinium X); ^{224}Ra (thorium X)
5.0.3 Trade Names:
NA
5.0.4 Molecular Weight:
226.03
5.0.5 Molecular Formula:
Ra
5.1 Chemical and Physical Properties
5.1.1 General Pure metallic radium is brilliant white when freshly prepared, but blackens on exposure to air, likely because of formation of the nitride. Radium and its salts exhibit luminescence; like other alkaline-earth metals, radium decomposes on exposure to water and is more volatile than barium. Radium imparts a carmine red color to a flame. There are four naturally occurring isotopes of radium: ^{226}Ra, ^{228}Ra, ^{223}Ra, and ^{224}Ra. All isotopes of radium are radioactive, emitting a, b, and g rays. ^{226}Ra (half-life 1600 years) emits a radiation with an energy of 4.87 MeV. The endpoint of ^{226}Ra radioactive decay, emitting radioactive radon gas (^{222}Rn), is the formation of lead. ^{224}Ra has a much shorter half-life (3.62 days) and also decays via a particles (5.8 MeV). ^{222}Ra has a half-life of 11.4 days and similarly emits an a particle in its decay (5.98 MeV), whereas ^{228}Ra (half-life 5.7 years) decays by release of a b particle. Radium is over a million times more radioactive than the same mass of uranium (90). Melting point: 700°C, boiling point: 1737°C, *d*: 5.5.
5.2 Production and Use
Radium is extremely scarce but may be found in uranium ores such as pitchblende at approximately 1 g/ton. The commonly occurring salts are the chloride, bromide, carbonate, and sulfate. Radium may be made on a very small scale by the electrolysis of molten radium chloride (90). Radium was discovered in the early twentieth century, and found medicinal uses and, because of its luminescence, use in the painting of watch and clock dials, as well as military instruments. Radium therapy (^{226,228}Ra) was accepted by the American Medical Association (AMA) for treatment of rheumatism and as a general tonic, as well as for the treatment of mental disorders. ^{224}Ra was used in Europe for over 40 years in the treatment of tuberculosis and ankylosing spondylitis. The isotopes ^{223}Ra, ^{224}Ra, ^{226}Ra, and ^{228}Ra have all been used as radiation sources for treating neoplasms in humans (5).
5.3 Exposure Assessment
5.3.1 Air The combustion of coal is probably the most important mechanism of release of radium into the atmosphere. The mean concentration of ^{226}Ra in coal is on the order of 1 pCi/g. Radium combustion products may condense onto coal fly ash. The concentration of ^{226}Ra in fly ash ranges from 1 to 10 pCi/g; the ^{228}Ra content has been reported to vary from 1.8 to 3 pCi/g (91). It has been estimated that 2.2 Ci of total radium is released in this manner annually in the United States. Global release of ^{226}Ra is estimated at 150 Ci per year. ^{226}Ra concentrations in glacial ice samples have increased 100 fold since the 1920s, likely as a result of the increased combustion of fossil fuels (92).

5.3.2 Background Levels The concentration of radium in surface water is generally quite low. Shallow wells reportedly have lower ^{226}Ra concentrations than do deeper wells, and the total content in municipal water supplies is generally lower than that in untreated well water. A summary of several sampling studies reveals that ^{226}Ra generally occurs at concentrations ranging from 0.1 to 0.5 pCi/L in surface water, and the mean concentration in drinking water is 0.91 pCi/L. ^{228}Ra activity in several midwestern states in the United States ranged from 0.3 to 32 pCi/L, with typical concentrations < 1 pCi/L. The main source of radium contamination in water is believed to be from uranium mine tailings. Radium in water exists as the divalent cation and can interact significantly with sediments and dissolved solids in water.

The mean concentration of ^{226}Ra in soil in 33 states was 1.1 pCi/g, similar to levels reported for various types of rocks (91). Analysis of garden plots in Port Hope, Ontario, Canada revealed radium-contaminated plots with up to 830 pCi/g soil, compared to 1.2–2.6 pCi/g in plots uncontaminated by adjacent uranium mines (93). It has been estimated that the mean concentration of radium in the diet is approximately 0.73 pCi/kg of food (94).

5.3.3 Workplace Methods: NA

5.3.4 Community Methods: NA

5.3.5 Biomonitoring/Biomarkers Exposure to radium can be determined by the use of a whole body counter to measure the g radiation emitted by radium (95, 96).

5.3.5.1 Blood Radium can be measured in urine, feces, and other biological media by use of g-ray spectroscopy (91).

5.3.5.2 Urine Radium can be measured in urine, feces, and other biological media by use of g-ray spectroscopy (91).

5.3.5.3 Other The body burden of radium can be established by quantitation of radon in exhaled breath (94).

5.4 Toxic Effects

5.4.1 Experimental Studies 5.4.1.1 Acute Toxicity: NA

5.4.1.2 Chronic and Subchronic Toxicity For a variety of reasons, rodent studies examining the effects of a-particle emitters have been difficult to extrapolate to humans. Therefore, because of its long lifespan and the similarity of its biological properties to those of humans with regard to target organs, the beagle dog has been used as the model for study by several groups. Studies in beagle dogs indicate that a particles emitted by ^{226}Ra are bone-seeking and associated with bone tumors, whether administered as a single or repeated doses (97). Primary bone tumors (n = 155) were reported in 131 of 246 beagles injected with ^{226}Ra (5 primary bone sarcomas in 4 of 158 unexposed controls). The predominance of these (94%) were osteosarcomas (98). Mice injected with ^{224}Ra (69–550 Bq/g body weight) developed myeloid leukemia and osteosarcoma, with a dose–response correlation observed for both tumor types (99). In terms of extrapolating to human carcinogenic response to radium, these studies were interesting because a number of the mice in this study developed leukemia in the absence of osteosarcoma, and historically leukemia has not been a cancer linked to radium exposure (97, 100, 101). C57Bl/Do (black and albino) mice receiving approximately 10 mCi/kg of ^{226}Ra similarly developed bone sarcomas (102). In a beagle dog study designed to evaluate the appropriateness of permissible body burdens for humans, ^{228}Ra, administered at 16.6 times the human maximum permissible body burden (MPB), caused a shortened lifespan, whereas ^{226}Ra at 10 times the MPB was associated with neither a significant number of excess bone tumors or shortened lifespan (55).

5.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 5.4.1.3.1 Absorption In rats, oral administration results in 1–7% retention 400–500 days after administration; in contrast, 77% retention was observed 140–300 days after intradermal administration (91). In a study in which human volunteers ingested small amounts of ^{224}Ra, 20% of the ingested dose reached the bloodstream (95). Following oral administration of radium, 80% appeared in the feces 10 days following expousre, with 20% retained and distributed systemically. The fecal:urine excretion ratio was also high (30:1) following IV administration (91). Accidental human inhalation exposure was associated with sequestration of radium in the bones, suggesting absorption from the lung and distribution via the bloodstream (91).

5.4.1.3.2 Distribution Following ingestion, radium is similar to calcium in its metabolism and is incorporated on bone surfaces into the mineralized portion of bone. The long half-life of ^{226}Ra allows for distribution throughout the mineral skeleton over life.

5.4.1.3.3 Excretion The loss of radium from the body by excretion was determined to follow a relatively simple power function: $R = 0.54t^{-0.52}$, where R = total body retention and t = time in days (103). As more data became available, it became apparent that the Norris equation is relatively accurate except at very long times after exposure e.g., (106). In practical terms, one year after exposure, approximately 2% of a dose of radium is retained in the body, but after 30 years, 0.5% still remains (104).

5.4.1.4 Reproductive and Developmental An old study (14) revealed that intravenous or subcutaneous administration of 5 mCi of radium to rats late in pregnancy caused fetal death associated with hemorrhage in the head and dorsal areas.

5.4.1.5 Carcinogenesis Although the National Toxicology Program has not classified radium with regard to its carcinogenicity, multiple laboratory studies document the ability of radium isotopes to cause cancer in animals.

5.4.2 Human Experience 5.4.2.1 General Information The maximum permissible (retained) body burden for bone of ^{226}Ra for humans has been tentatively set at 1 mCi (3.7 kBq) for a 70-kg man, or 0.529 kBq/kg (55). This body burden is expected to be without radiation-induced injury.

5.4.2.2 Clinical Cases 5.4.2.2.1 Acute toxicity: NA

5.4.2.2.2 Chronic and Subchronic Toxicity Two types of cancer—sarcomas of the bone and carcinomas of the paranasal sinuses and mastoid air cells (called “head cancers”)—have been shown to be associated with radium exposure (105, 106). It is significant to note that, although all isotopes of radium are bone-seeking, and despite laboratory animal studies in which rodents exposed to radium developed both leukemia and bone sarcomas, human leukemia is not recognized as a long-term sequela of radium exposure. Raabe et al. (107) modeled bone sarcoma risk in the human, dog, and mouse and determined that there is a threshold dose and dose rate, representing a dose low enough so that bone cancer will not appear within a human lifespan; this dose is 0.04 Gy/day, or a total dose of 0.8 Gy to the skeleton. A population of 900 German patients, both juveniles and adults, who had been treated with ^{224}Ra had 54 patients who developed bone sarcomas. The average skeletal dose in this population was 4.2 Gy. In a second cohort followed by Wick et al. (91), two ankylosing spondylitis patients (mean skeletal dose = 0.65 Gy) have developed osteogenic sarcoma, with no cases in the control group.

5.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms The a-particles emitted by radium, once deposited on bone surfaces, can penetrate approximately 70 mm. The long half-life of ^{226}Ra allows distribution throughout the mineral skeleton over a lifetime. The target cells for osteogenic sarcoma reside in marrow on endosteal surfaces approximately 10 mm from the bone surface (104). With its

shorter half-life, ^{224}Ra delivers its a dose while the radium is still on bone surfaces (104).

5.4.2.2.4 Reproductive and Developmental Although many of the humans occupationally exposed to radium were women, there is little published about reproductive or developmental consequences of radium exposure. It has been reported that the adult heights of humans injected as children with ^{224}Ra for treatment of tuberculosis were markedly lower than the heights of nontreated persons (91).

5.4.2.2.5 Carcinogenesis The U.S. EPA has classified radium as a class A carcinogen, meaning that there are sufficient data to support a link between exposure to radium and the development of human cancer. The a-particle radiation associated with radium is recognized as the causative agent for sarcomas of the bone and carcinomas of the paranasal sinuses in humans (106). A study attempting to ascertain the dose–incidence relationship for induction of these tumors examined 1474 women employed in the U.S. radium dial painting industry before 1930. This population exhibited 61 known cases of bone sarcoma and 21 cases of carcinoma of the paranasal sinuses or the mastoid air cells (106). Of these individuals, the radium body burden was known for 759, among whom there were 38 cases of bone sarcoma and 17 head carcinomas.

5.4.2.2.6 Genetic and Related Cellular Effects Studies In an analysis of a number of human proto-oncogenes in persons with internal systemic exposure to radium, alterations in the c-*mos* proto-oncogene were found in many, but not all, tissues from 6 of 7 subjects (105). The changes were EcoRI restriction fragment length alterations, and these were noted in normal (*i.e.*, neoplasm-free) tissues from these individuals.

5.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, etc Leikin and Paloucek (5) report that adverse reactions associated with the use of radium in the treatment of neoplasms include leukopenia, cirrhosis, and cataracts.

5.4.2.3 Epidemiology Studies 5.4.2.3.1 Acute Toxicity: NA

5.4.2.3.2 Chronic and Subchronic Toxicity Evans (95) summarized quantitative studies of more than 450 humans who carried skeletal deposits of ^{226}Ra and ^{228}Ra for up to 50 years. For residual skeletal burdens >0.5 mCi, the occurrence of osteoporosis, dense-bone necrosis, trabecular coarsening, and spontaneous bone fractures increased with increasing skeletal burden.

5.4.2.3.3 Pharmacokinetics, metabolism, and mechanisms: NA

5.4.2.3.4 Reproductive and Developmental: NA

5.4.2.3.5 Carcinogenesis Evans (95) summarized >450 cases of humans with skeletal burdens of ^{226}Ra and/or ^{228}Ra. For residual skeletal burdens ranging from 0.5 to 60 mCi of ^{226}Ra, the fractional incidence of osteogenic sarcoma and carcinoma of the paranasal sinuses or mastoids was about 40% and appeared to be independent of residual body burden. However, in individuals with tumors, the latency period was determined to be related to the residual body burden. It has been noted that breast cancer, liver cancer, and chronic myeloid leukemia have also been associated with radium exposure (5).

5.5 Standards, Regulation, or Guidelines of Exposure

No oral reference dose or inhalation reference concentration for radium has been established. The USEPA has established a maximum contaminant level of 5 pCi/L for combined ^{226}Ra and ^{228}Ra in drinking water and has classified radium as a class A carcinogen; this represents an agent for which sufficient evidence exists to support a causal relationship between exposure and cancer.

Magnesium, Calcium, Strontium, Barium, and Radium

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Zinc and Cadmium

Marek Jakubowski, Ph.D.

1 Zinc and Zinc Compounds
1.0 Zinc
1.0.1 CAS Number: [*7440-66-6*]

1.0.2 Synonyms: Zinc dust, zinc powder

1.0.3 Trade Names: Asarcor; L15; Blue Powder; CI 77945; CI pigment Metal 6; Emanay Zinc Dust; Granular Zinc; JASAD; Merrilite; PASCO (97).

1.0.4 Molecular Weight: 97.45

1.0.5 Molecular Formula: Zn
1.1 Chemical and Physical Properties
1.1.1 General Zinc is a relatively soft, bluish-white shiny metal. It exhibits a strong tendency to react with both the inorganic compounds (*e.g.*, oxides, sulfates, and phosphates) and the organic ones. The physical and chemical properties of zinc are displayed in Table 29.1.

Table 29.1. Physical and Chemical Properties of Zinc and Zinc Compounds

Compound	CAS #	Molecular Formula	MW	Boiling Point (°C)	Melting Point (°C)	Specific Gravity	Solubility in Water (at 68°F)	Refractive Index (20°C)	
Zinc	[*7440-66-6*]	Zn	65.38	908	419.5	7.14 at 25°C	Insoluble	—	1 I 4
Zinc oxide	[*1314-13-2*]	ZnO	81.38	No data	100 (decomp.)	5.607 at 20°C	0.0016 g/L at 29°C	—	
Zinc chloride	[*7646-85-7*]	$ZnCl_2$	136.29	732	290	2.907 at 25°C	4320 g/L at 25°C	—	
Zinc sulfate	[*7733-02-0*]	$ZnSO_4$	161.44	No data	600 (decomp.)	3.54 at 25°C	1667 g/L at 25°C	—	
Zinc acetate	[*557-34-6*]	$Zn(C_2H_3O_2)_2$	183.47	—	200 (decomp.)	1.84	300 g/L at 20°C	—	
Zinc stearate	[*557-05-1*]	$Zn(C_{18}H_{35}O_2)_2$	632.23	—	130	—	Insoluble	—	
Zinc ammonium sulfate	[*7783-24-6*]	$(NH_4)_2SO_4$ ċ$ZnSO_4$ċ$6H_2O$	401.66	—	Decomp.	1.931	70 g/L at 0°C	1.489, 1.493, 1.495	

Zinc and Cadmium
Marek Jakubowski, Ph.D.

2 Cadmium and Cadmium compounds
1.0 Cadmium
1.0.1 CAS Number: [*7440-43-9*]

1.0.2 Synonyms: Cadmium dust fume, cadmium powder, colloidal cadmium

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 112.40

1.0.5 Molecular Formula: Cd
1.1 Chemical and Physical Properties
1.1.1 General Cadmium (oxidation state 2, density 8.6, melting point 320.9°C, boiling point 765°C), is a silver-white metal that belongs to the group IIb in the periodic table. Its natural isotopes are 106 (1.22%), 108 (0.88%), 110 (12.37%), 111 (12.75%), 112 (24.07%), 113 (12.26%), 112 (24.07%), 1139 (12.26%), 114 (28.86%), and 116 (7.59%). Cadmium is insoluble in water and soluble in acids. It has a relatively high vapor pressure. In ambient air cadmium vapor is oxidized rapidly to produce cadmium oxide. In the presence of reactive gases or vapors, such as carbon dioxide, water vapor, sulfur dioxide, sulfur trioxide, or hydrogen chloride, cadmium vapor reacts to produce, respectively, cadmium carbonate, hydroxide, sulfite, sulfate, or chloride. These compounds may be formed in stacks and emitted to the environment. The physical and chemical properties of major cadmium salts are summarized in Table 29.4.

Table 29.4. Physical and Chemical Properties of Cadmium and Cadmium Compounds

Compound	CAS #	Molecular Formula	MW	Boiling Point (°C)	Melting Point (°C)	Specific Gravity	Solubility in Water (at 68°F)	Refractive Index (20°C)	Vapor Pressure (mm Hg)
Cadmium	[*7440-43-9*]	Cd	112.41	765	320.9	8.642	Insoluble	—	1 at 394°C
Cadmium chloride	[*10108-64-2*]	$CdCl_2$	183.32	960	568	4.047 at 25°C	1400 g/L at 20°C	—	10 at 656°C
Cadmium oxide	[*1306-19-0*]	CdO	128.41	Sublimes at 1559	No data	8.15	Insoluble	—	1 at 1000°C
Cadmium sulfide	[*1306-23-6*]	CdS	144.47	No data	1750 at 100°C	4.82	0.0013 g/L at 18°C	2.506 2.529	No data

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Mercury
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Introduction

Mercury is a heavy metal widely distributed in nature, both as the metallic element (Hg^0) and as inorganic or organic compounds of its oxidation products, the mercurous (Hg^+) and mercuric (Hg^{2+}) ions. These mercury species are readily interchangeable in the environment and in the body, and evidence suggests that their toxicity in many cases reflects the actions of the mercuric ions formed by oxidation of mercury or by breakage of the mercury–carbon bond. To that extent, different toxicities of individual compounds can largely be attributed to differences in their toxicokinetic properties such as rates of absorption, distribution, degradation, or oxidation to Hg^{2+}, and finally excretion. Monosubstituted organic compounds of mercuric mercury may also react directly with biological molecules before degradation to Hg^{2+}.

Although all biological tissues contain traces of mercury, no essential biological function has been identified for the metal. To the contrary, because the end product of the metabolism of mercury and mercurials is usually the mercuric ion, which has high affinity for proteins and other biological molecules, many of the organic and inorganic compounds of the metal strongly inhibit biological reactions in very low concentrations. The high chemical reactivity of Hg^{2+} also helps explain the relatively nonspecific nature of mercury toxicity in the target organs. For instance, mercuric mercury accumulates primarily in the kidney, but in that organ it inhibits a large number of different enzymatic and other functions.

Natural sources of mercury include primarily deposits of the metal itself or of insoluble mercuric sulfide (HgS, cinnabar). Most of the world's production of mercury comes from mines in Algeria, China, Spain, and Kyrgyzstan. The background concentration of mercury in the environment reflects outgassing from the earth's crust and the result of volcanic activity. Large amounts of mercury are also contributed to the environment by human activities. The use of Hg by humans has been traced back thousands of years, and the high morbidity observed in mercury miners was well recognized in Roman days. Among major anthropogenic contributions to mercury pollution are the combustion of fossil fuels, the application of inorganic fertilizers and sewage sludge to agricultural lands, the amalgam process of extraction and purification of noble metals, losses incurred during the extensive use of mercury and its compounds in industry, and leaks from waste disposal. Natural and anthropogenic releases of mercury into the atmosphere in the 1980s were roughly equivalent and reached values of more than 6000 tons per year (quoted in Ref. 1).

Human exposure to mercury and mercurials also was, and in part still is, associated with their direct application for cosmetic and therapeutic purposes. Even in the twentieth century, such uses have included topical treatment with mercury-containing skin whiteners, antiseptics, and infants' teething powder. Organic mercurials have also been prescribed routinely as diuretics for treating salt and water retention. These human applications have mostly been abandoned, but the presence of the element in dental amalgams remains a significant and continuing source of human exposure.

The interchangeability of various mercury species in the environment and in the body and the overlap between the toxic effects of individual mercurials and between the biomarkers available for monitoring exposure to these mercurials make it impractical to consider the different mercurials under entirely separate headings. This chapter, therefore, discusses the occupational toxicology of mercury and selected mercury compounds under three main overlapping headings: A. Elemental Mercury, B. Inorganic Mercury Compounds (primarily the chloride salts of mercuric and mercurous mercury, although other inorganic mercury salts are also cited), and C. Organic Mercury Compounds (mostly methylmercuric chloride and phenylmercuric acetate). A very extensive literature has accumulated on all of these topics. However, no attempt will be made here to provide an exhaustive survey; a detailed listing, for instance, of all occupational uses and reported health effects of each chemical species of mercury in every animal species tested and in humans, under all exposure conditions would have to cover thousands of references and is hardly necessary to emphasize the major problems potentially associated with human occupational and general exposure to mercury and its compounds. Additional details on mercury and mercurials may be obtained from a number of informative recent publications, including the EPA document on mercury (2), a toxicological profile placed into the Federal Register by the Agency for Toxic Substances and Disease Registry (ATSDR) (3), the NIOSH Manual of Analytical Methods (4), and the authoritative review of Clarkson (5). The volume edited by Chang on the *Toxicology of Heavy Metals* (6) provides an extensive discussion of the toxic properties of mercury. Environmental health criteria for inorganic mercury were discussed by WHO (7). An earlier volume on the history of mercury contains much fascinating information on this important element (8).

Mercury
Ernest Foulkes, Ph.D.

A. Elemental Mercury
Although elemental mercury is readily oxidized to mercuric ions, the industrial applications and the toxicity of the two mercury species differ greatly. This is related to their physicochemical properties and their different distributions in the body. It is therefore appropriate to discuss the two species under separate headings.
1.0 Mercury
1.0.1 CAS Number: [*7439-97-6*]

1.0.2 Synonym: Quicksilver

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 200.61

1.0.5 Molecular Formula: Hg^0
1.1 Chemical and Physical Properties
1.1.1 General Metallic mercury at room temperature is a silvery and volatile heavy liquid (specific gravity 13.546) with a vapor pressure of 0.0012 mmHg at 20°C. The metal is slowly oxidized to mercuric oxide (HgO) near its boiling point (356.9°C) in the presence of oxygen. This reaction is reversed at higher temperatures. Similarly, the element may be reversibly oxidized to mercuric mercury in the environment and in the body. The metal reacts with halogens and sulfur and dissolves in nitric acid or concentrated sulfuric acid; it is little affected by hydrochloric acid (1). Mercury vapor is very slightly soluble in water (56 mg/L at 25°C).

Among physical and chemical properties which make the metal important for many technical

purposes are (1) the high vapor pressure of Hg^0, which permits purification of the metal by distillation. Vaporization also provides a convenient tool for spectroscopic analysis of mercury (see section 1.3). The volatility of mercury makes inhalation exposure an important potential risk. (2) The high surface tension of Hg^0 reduces wetting of glass and other surfaces. This property, together with its uniform thermal expansion, makes the metal ideal for use in thermometry. (3) The high electrical conductance of Hg^0 is important in thermostats, electrical switches, electrodes, etc. (4) The high specific gravity of Hg^0 is important in manometers, barometers, and other control devices. (5) Hg^0 forms amalgams with gold and other metals that are used extensively in extracting and purifying of noble metals and in dental fillings.

1.1.2 Odor and Warning Properties The metal is odorless, but its presence can readily be detected by UV spectroscopy or cold-vapor atomic fluorescence measurements, as proposed by the EPA (9). These techniques have also proven useful for analyzing biological and other samples for trace amounts of inorganic mercury compounds following their reduction to the element by reagents such as stannous chloride (see section 2.1.2). Listing of other techniques for estimating total mercury content may be found in Ref. 1.

1.2 Production and Use

Mercury is mined primarily in underground mines as the metal or as the red sulfide cinnabar (HgS). Like HgO, the sulfide decomposes at higher temperatures. Heating of the ore and condensation of the mercury vapor constitute a convenient procedure for reducing, extracting, and purifying mercury from its ore. Total world production fell from 8698 metric tons in 1975 to 1760 in 1994, reflecting in part increasingly prohibitive environmental, health, and safety regulations. In the United States, mercury is produced primarily from secondary sources; this involves recycling a variety of industrial waste products. Total consumption of the element in the United States in 1995 amounted to 463 metric tons (3). More than 150,000 workers are believed to have been potentially exposed to mercury and its compounds in the United States in 1990 (10); the majority of these exposures involved mercury vapor.

Some of the many uses of the metal have been described in section 1.1.1. Others include, for instance, mercury vapor lamps, and as a heavy liquid in fluid bearings and clutches. A major application is as a cathode in chloralkali plants that produce NaOH and chlorine by electrolyzing NaCl. The significance of the exposure from this process can be illustrated by the work of Langworth et al. (11) who found fourfold increases in blood Hg levels and 13-fold increases in normalized urinary levels in workers engaged in this process. The toxicity of mercury and the cost of its safe disposal have led to the search for alternative, Hg-free processes. Thus, total U.S. consumption of mercury fell from 1503 tons in 1988 to 621 in 1992. By way of illustration, about 50% of chloralkali plants used Hg-free processes in 1994 (2). Although as much as 16% of mercury consumed by industry has been recovered and recycled (3), the remaining major portion represents a very significant addition to the environment.

1.3 Exposure Assessment

Exposure to elemental mercury, as well as to most of its compounds, can best be monitored by the total levels of mercury in blood and urine. A difficulty in relying on the level of blood mercury for quantitatively evaluating an earlier exposure to mercury vapor is posed by the peak in the blood concentration that occurs 2–4 days after exposure; blood analyses after longer periods are therefore generally less informative. Another problem in evaluating mercury exposure especially from blood mercury levels arises from the likelihood of mercury release from tissues. Peaks of mercury concentration in urine after exposure appear and decline more slowly than in blood. Total mercury concentrations in urine following exposure to mercury vapor are of interest especially because of the oxidation of Hg^0 to Hg^{2+}; the latter accumulates primarily in the kidney, from which it may directly enter the urine (see section 2.4). The significance of exhaled Hg^0 following acute exposure may be confounded by the output from dental amalgam and by the possibility of the reduction of Hg^{2+} in the body.

Hair analysis has also proven useful, and reasonably good correlations have been observed between hair and blood mercury contents. Segmental analysis of scalp hair, growing at a rate of around 3 mm/week, can provide some indication of the history of exposure over relatively long periods. Hair analysis is particularly useful in providing evidence of exposure to methylmercury because this compound is incorporated into hair as such (see section 4). The estimation of mercury and its compounds is discussed in greater detail in section 2.3. In environmental or biological samples, as emphasized before, the interchangeability of the various chemical species of Hg makes total mercury levels more significant than those of elemental Hg.

Mercury vapor can pose health problems in occupational settings and also following, for instance, accidental breakage of such instruments as thermometers and barometers in the home or the use of mercury and mercurials for cosmetic, therapeutic, and other purposes. A major contribution of mercury from such sources at present results from the application of Hg amalgams in dental fillings. Urinary levels of mercury, ultimately derived from dental amalgams, have attained or even exceeded occupational health limits. To quote just one of many papers, urine collected from individuals carrying more than 36 dental amalgam restorations contained on the average 30 nmol Hg/L, compared to 6 nmol/L in the urine of control subjects without amalgams (12). According to WHO reports (7), occupational exposure to 50 mg Hg vapor/m^3 air increases the rate of urinary Hg excretion to more than 30 nmol/mmol creatinine. The potential internal Hg exposure due to dental amalgams may also be judged by the report that mean levels of Hg^0 in the breath of subjects who carry amalgam restorations was 8.2 ng/L (or mg/m^3), more than 100 times higher than in the breath of subjects without amalgam fillings (3). Individuals who have many amalgam restorations may absorb 10–12 mg of mercury per day (12). Exposure of dental health professionals also results from present practice, and one report describes an increased frequency of reproductive failures in female dentists and dental assistants (13). Overall, however, no clear-cut health effects of amalgam exposure have been described (14), and its toxicological significance remains under discussion.

1.3.1 Biomonitoring/Biomarkers Blood and urine levels of Hg are commonly assayed and provide at least a qualitative measure for evaluating exposure to mercury. This topic has already been considered earlier in section 1.2 Exposure Assessment. Because elemental mercury is fairly rapidly oxidized to Hg^{2+} in body fluids, exposure to Hg^0 is generally evaluated by blood and urine analysis for elemental plus inorganic mercury. This commonly involves reducing the inorganic mercury to the element and using UV spectroscopy for Hg vapor. Analysis specifically for Hg^0 in the presence of Hg^{2+} omits the reduction step. Further details will be given under the heading of mercuric chloride (section 2.3).

1.4 Toxic Effects

Because the element is relatively inert, it exerts little direct toxic action. On the other hand, it is readily oxidized to mercuric ions. One biological mechanism for this oxidation involves the enzyme catalase in presence of hydrogen peroxide; the reverse reaction, the reduction of Hg^{2+} to Hg^0, has also been observed in animals. In any case, all evidence points to Hg^{2+} as the ultimate toxicant during exposure to mercury vapor, salts of mercurous mercury, and in part also to organic mercurials. Many aspects of the toxicity of elemental mercury will therefore be included in section 2.4 under the heading of Toxic Effects of Hg^{2+}. The fact that Hg^0 to some extent like methylmercury (see section C on Organic Mercury Compounds), but in contrast to Hg^{2+}, acts primarily on the central nervous system can be explained by its lipid solubility and consequent ability to cross cell membranes such as those in the blood–brain barrier. After moving across this barrier, elemental mercury is likely to be extensively oxidized to Hg^{2+} and consequently to become trapped in the central nervous system.

1.4.1 Experimental Studies Liquid (metallic) mercury is very poorly absorbed from the gastrointestinal tract. Release of mercury vapor in the intestine may be retarded by a coating of insoluble HgS formed in the intestine. This may help explain the survival of patients treated in

former centuries for constipation by ingestion of the metal. Inhalation is the most important route of exposure to Hg^0: as much as 80% of inhaled vapor is retained in the lungs (15). As pointed out by Clarkson (5), this high value represents essentially complete absorption across the alveolar membranes. Dermal absorption of elemental mercury has also been described but, though not insignificant, is much smaller. Thus, for every mg of Hg/liter of air, the vapor is taken up by the skin at an average rate of 0.24 $mg/cm^2 \cdot min$. The calculated amount of mercury thus retained amounted only to about 2% of simultaneous pulmonary absorption. Moreover, only half of the Hg^0 taken up in the skin could be recovered as systemic mercury (16); the remaining portion presumably is retained and accumulates in dermal cells and is subsequently lost upon their desquamation.

Mercury vapor is rapidly distributed throughout the body, readily penetrates cellular barriers such as the placenta and the blood–brain barrier, and appears in milk and other secreted body fluids. Once it has crossed the placenta and the blood–brain barrier, elemental mercury is oxidized and becomes largely trapped as Hg^{2+} in the central nervous system. Inhalation of the vapor by rats and mice, leads to mercury accumulation primarily in the gray area of the central nervous system. The highest levels are in certain neurons of the cerebellum, the spinal cord, the medulla, the pons, and the midbrain (17). Such inhalation is, therefore, associated primarily with neurotoxic effects. Similar lesions are produced by methylmercury, also reflecting the trapping of mercury in the brain (see section 4). Toxic effects of Hg^0 on the developing central nervous system have been described in rat fetuses and pups. Limited evidence only has been found for carcinogenic actions of elemental mercury (see the genotoxicity of Hg^{2+} in section 2.4), and it is not classified as carcinogenic by the USEPA. Sarcomas have been reported in rats following intraperitoneal injection (18).

In general, many of the cytotoxic actions of the metal resemble those of its oxidation product, the mercuric ion (see section 2.4). Differences in their overall toxicity are mostly related to their usual portals of entry and to their different distributions in the body. Thus, the first pass of Hg^0 through the lungs during inhalation exposes these organs to much higher concentrations of mercury than the kidneys; the inverse is true for Hg^{2+} following ingestion. Similarly, the ready passage of mercury vapor across the blood–brain barrier, in contrast to the essential impermeability of that barrier to Hg^{2+}, helps to explain the primarily neurotoxic effects of the vapor.

1.4.2 Human Experience Hursh et al. (15) studied the clearance of radioactive mercury vapor inhaled by human subjects. Seven percent of inhaled mercury in their study was exhaled again, with a half-time of 18 h. The half-life of total mercury in the kidney region was as long as 64 days, consonant with oxidation to Hg^{2+} and preferential renal uptake. Acute inhalation of mercury vapor at a concentration in excess of 1 mg/m^3 may cause damage to the lungs; renal malfunction has also been observed. The major functional lesions, however, are found in the central nervous system. They are manifested by behavioral and other deficits. Erethism, a peculiar form of emotional instability, has long been recognized as a symptom of mercury intoxication. Other symptoms include tremor, weight loss, gingivitis, headache, and drowsiness. Acute exposure can also cause pneumonitis and contact dermatitis. Overt toxicity may be expected in populations exposed to time-averaged air concentrations of Hg^0 that exceed 0.1 mg/m^3.

There are conflicting reports in the literature on reproductive effects of human exposure to metallic mercury. The potential problems encountered by workers exposed to dental amalgam have already been discussed in section 1.3 Exposure Assessment. Reproductive toxicity in males was studied by Cordier et al. (19) whose results indicate that paternal exposure prior to conception might increase the subsequent risk of spontaneous abortion.

Elemental mercury does not react with chelators (see section 2.4). Their successful therapeutic use following exposure to Hg^0 therefore indicates, as already mentioned, that the element is oxidized to Hg^{2+} in the body. Indeed, about 80% of Hg^0 taken in by humans is subsequently excreted as

mercuric mercury.

1.5 Standards, Regulations or Guidelines of Exposure

OSHA, NIOSH, and the American Conference of Government Industrial Hygienists (ACGIH) have selected a permissible exposure level (PEL) (time-weighted average) of 50 mg Hg^0/m^3 of air. The USEPA Integrated Risk Information System (see Ref. 52) quotes a reference concentration in air of 0.3 mg/m^3; no NOAEL was determined for chronic inhalation exposure, but a LOAEL, adjusted for occupational inhalation and workweek was calculated as 9 mg/m^3 (2).

1.6 Studies on Environmental Impact

Because of the ready interchangeability of elemental, inorganic, and organic mercury, the problem of general environmental impact of mercury will be considered here under a common heading for the element and its compounds. Additional information is provided in section 4.6 for methylmercury, a frequent and potentially very toxic contaminant of the human food chain. This compound is formed by bacterial methylation of inorganic mercury, a further reason for minimizing levels of total mercury in the environment.

Mercury is added to the environment from two main sources: “natural” mercury, and mercury arising from human activities (anthropogenic mercury). Natural sources include degassing of mercury from the earth's crust and from volcanic eruptions. The presence of mercury in fish (mostly in the form of methylmercury, see section 4.6) such as sword fish, which is at the top of the marine food chain and is harvested far from likely industrial sources of mercury, has thus been attributed ultimately to mercury from volcanic activity. The anthropogenic origin of mercury is associated with mining, coal combustion and incinerators, agricultural and industrial applications, surface waste disposal and other activities; these anthropogenic sources contribute a major fraction of the Hg added to the atmosphere each year (20). Atmospheric Hg^0 becomes oxidized to Hg^{2+}, and as such may be deposited on land or water. Deposited Hg, in turn, tends to be reduced to the volatile metal. Because of this volatility, elemental mercury is continuously cycled through various environmental compartments and becomes widely distributed throughout the environment. However, it is only in proximity to specific point sources that environmental damage is likely to become significant.

The total mercury content of unpolluted waters usually falls below 1 ng/L. The average daily intake of total mercury from air by the general population in the United States has been estimated at 0.04 mg/day; a similar value was found for drinking water (0.05 mg/day). The total intake in non-fish food was calculated as 3.6 mg/day; normal fish consumption raised this value to 6.6 mg/day. Note that intake of Hg^0 from dental amalgams can rise as high as 21 mg/day.

Section 1.2 already referred to the considerable scope for minimizing the anthropogenic input of mercury into the environment, especially by substituting Hg-free processes for those that depend on mercury. It was noted, for instance, that washing of coal reduces its mercury content by an average of 21% (2). Further reductions are probably achievable with the development of new procedures. Of course, washing of coal only transfers the metal to waste slurries and thereby does not automatically reduce the concentration in the environment.

The magnitude of the human contribution to environmental pollution is reflected in the two to fivefold increase in atmospheric Hg since the beginning of the Industrial Revolution. The persistent problem of such contributions is dramatically emphasized by the report that during a period of 33 years, about 213 metric tons of mercury and mercuric nitrate were spilled into creeks at the Oak Ridge National Laboratory (3). Mercury remaining at that site is present now primarily as insoluble HgS; bacterial oxidation to the more soluble sulfate, however, will continue to make the metal slowly available for reactions in the biosphere.

Mercury
Ernest Foulkes, Ph.D.

B. Inorganic Mercury Compounds

Occupational exposure to inorganic mercury compounds occurs during mining for the major mercury ore, cinnabar (mercuric sulfide, HgS), and as a result of their extensive industrial applications. Among these compounds, for instance, is mercuric oxide (HgO), once a common constituent of many types of batteries, including Zn–carbon cells, Zn–silver oxide cells, and others. Mercuric sulfate has also been used in paints and is a catalyst in the chemical industry (see section 4.2). Mercuric nitrate was formerly applied in the felting process for beaver furs in the hat industry (thence the suggested origin of the term "a mad hatter," believed to have been originally applied to an affected victim of occupational exposure in the hatting industry). Mercuric fulminate is a common constituent of percussion caps of firearm ammunitions. Mercuric acetate and bromide are common laboratory reagents. Several mercuric mercury salts have, in the past, also been extensively used as antibacterial compounds.

Among important mercurous salts are mercurous chloride (calomel), employed as the standard calomel electrode, and mercurous sulfate, also found in batteries. Mercurous acetate, iodide, phosphate, and tannate salts have all been used at one time to treat syphilitic lesions. Mercurous chromate has served as green colorant for chinaware.

The various salts of mercurous (Hg^{+}) and mercuric (Hg^{2+}) ions are all more or less toxic; the toxic entity is usually the mercury ion. The actual toxicity of the compounds also depends, of course, on their water solubility and thence their availability for absorption. The actions of mercurous ions in the body have been attributed to their oxidation to the mercuric form; this, in turn, readily reacts with biological molecules. Mercurous mercury $(Hg–Hg)^{++}$ in aqueous solution decomposes into mercuric and elemental mercury according to the equation

$$(Hg–Hg)^{2+} = Hg^{0} + Hg^{2+}$$

Mercuric ions in solution readily form a variety of coordination complexes. For instance, in the presence of high chloride concentrations such as in physiological saline, Hg^{2+} exists mostly as polychloride anions like $HgCl_3^{-}$; such anions are involved in the intestinal absorption of mercuric mercury (21). Iodide complexes such as K_2HgI_4 are freely available. Complexes are also produced with ammonia or amino groups, as in $Hg(NH_3)_2Cl_2$. Mercuric ions also form relatively stable covalent mercury–carbon bonds to produce the organic mercurials; these are used for many purposes and will be discussed further under heading C. Organic Compounds of Mercury. Some organic mercury compounds are relatively nontoxic, whereas others, especially the short-chain alkyl derivatives, are potent neurotoxins.

Although mercury vapor is absorbed primarily through the lungs, uptake of inorganic mercury compounds mostly follows ingestion. Table 30.1, based on Ref. 22, summarizes the daily retention of mercury and mercurials by adults in the general environment.

Table 30.1. Daily Retention of Mercury and Mercurials by Adults in the General Environment[a]

Source	Hg vapor	Inorganic mercury	Methylmercury
Air	0.024	0.001	0.0064
Food: fish	0	0.042	2.3

Non-fish	0	0.250	0
Water	0	0.003	0
Dental amalgams	>3.0	0	0
Total	>3.0	0.3	2.3

[a] Values represent individual retention (in mg/day) of different species of mercury taken in from air, food, and water, or from dental amalgam. Calculations are based on 80% fractional retention of inhaled Hg vapor and 7% and 96% fractional intestinal absorption of ingested inorganic and methylmercury, respectively.

Several points in this table deserve special emphasis. Note in particular that dental amalgam represents the major source of total mercury uptake and retention, significantly higher than that from background levels in food, water, and air. Mercury as mercuric chloride and similar salts is not well absorbed; the same is even truer of essentially insoluble mercurous salts. In contrast, methylmercury, derived mostly from fish in the diet, is strongly retained in the body (see section 4.4.1). It represents the major source of body mercury in populations that consume larger than average amounts of fish in their diet. These observations were made in studies of several isolated populations, and their toxicological significance is further reviewed in section 4.4. In an unpolluted environment, the FDA Total Diet Study (23) on populations not primarily dependent on fish consumption reported for the period 1982–1984 an average daily Hg intake in the general environment of approximately 50 ng/kg body weight; this applied to all age groups except young children. To this daily dose must be added any mercury taken in as a result of cosmetic and therapeutic uses of mercury and its compounds. The percutaneous toxicity of inorganic heavy metal compounds, including those of mercury, is generally relatively low (24).

The two representative inorganic salts selected for more detailed discussion are mercuric and mercurous chloride.

Mercury
Ernest Foulkes, Ph.D.

C. Organic Compounds of Mercury
As mentioned in the introduction to section B, the mercuric ion readily forms covalent bonds with carbon; some organic mercurials contain Hg–N bonds, as in mercuric succinimide. A large number of carbon–mercury compounds have been synthesized, and some are extensively used in agriculture and industry, for instance, for seed dressing and as antifungal compounds in paints and other materials.

Some organic mercurials have also been employed for therapeutic purposes, although especially systemic administration is rare now. Mercurials such as mercurochrome (dibromohydroxymercurifluorescein) and merthiolate (ethylmercurithiosalycilate) have been applied as topical antiseptics. Among widely used systemic mercurial drugs were the diuretic isopropyl alcohol derivatives whose general structure is $R \cdot CH_2 \cdot CH(OY) \cdot CH_2 \cdot HgX$, where X stands for chloride, thioacetate, or other residues, and Y is commonly a methyl group. The $Hg \cdot X$ bond is ionic, leaving one mercury valence free to react with tissue components. The same important property is found in the monoaryl or monoalkyl derivatives of mercuric mercury. Thus, parachloromercuribenzoate is a common sulfhydryl reagent, extensively used in biochemical laboratories, and monomethylmercury forms biologically active complexes with L-cysteine or glutathione (see section 4.1).

Although monosubstituted organic mercurials may react directly in this manner with, and thereby inhibit the function of, critical sulfhydryl groups, much of their toxic potential is associated with the likelihood of degradation to free mercuric ions. The highly neurotoxic dimethylmercury, which is very lipid-soluble and rapidly absorbed through the skin and taken up across the blood–brain barrier into the brain, is presumably demethylated at least to the monomethyl compound before exerting any effects. Risks of exposure to dimethylmercury are exacerbated by the ability of the compound to pass through latex gloves; this apparently permitted the fatal poisoning of a laboratory worker, as reported recently in the news media.

The mercurial diuretics and many of the other organic mercurials are relatively nontoxic and possess little occupational relevance; they will therefore not be discussed in detail here. However, exceptions to the generally low toxicity of many organic mercurials are the extremely toxic short-chain alkylmercurials. Of primary interest from the environmental and toxicological points of view are monomethylmercury salts, as further discussed in section 4.0. The dimethyl compound is a volatile and extremely potent neurotoxin; it is very easily absorbed through the skin or by inhalation, but poses little threat outside the laboratory. As already mentioned in section 1.4, the high neurotoxicity of methylmercury compounds, in contrast to the primarily nephrotoxic action of inorganic mercury, can be explained by their respective abilities rapidly to cross the blood–brain barrier. The alkylmercurial selected here for more detailed discussion is the chloride salt of monomethylmercury (see section 4). Other salts, like the nitrate, are biologically indistinguishable from the chloride. Ethyl mercury, another short-chain monosubstituted alkylmercury compound, has also been used as a biocide and exhibits toxic effects similar to those of the methyl derivative.

A large number of aryl and alkoxyalkyl mercury compounds are known. The aryl compounds especially are used in occupational settings. A well-known example is the application of phenylmercury as a biocide in paints and agricultural products. Parachloromercuribenzoate (PCMB) is an aryl compound frequently employed in biochemical laboratories as a sulfhydryl reagent. The arylmercurial selected here for more detailed consideration is the acetate salt of phenylmercury (see section 5). The nature of the alkyl or aryl residue in organic mercury compounds largely determines their ability to reach especially intracellular target sites in selected organs and the stability of the mercury–carbon bond. Generally, long-chain alkyl mercurials are more readily dealkylated than short-chain compounds.

4.0 Methylmercuric Chloride

4.0.1 CAS Number: [*115-09-3*]

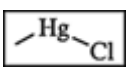
4.0.2 Synonyms: Chloromethylmercury; MMC; methylmercury chloride; monomethyl mercury chloride; caspan; methylmercury (II) chloride

4.0.3 Trade Name: Caspan

4.0.4 Molecular Weight: 251.10

4.0.5 Molecular Formula: $CH_3 \cdot HgCl$

4.0.6 Molecular Structure:



4.1 Chemical and Physical Properties

4.1.1 General Monomethylmercuric mercury is a univalent cation. Despite its ionic nature, however, it is significantly more lipid-soluble than inorganic mercury compounds. The chloride salt is a white crystalline solid at room temperature and has a melting point of 170°C. Its specific gravity is 4.06,

and its vapor pressure at 25°C is 0.0085 mmHg. At higher temperatures, it volatilizes with a disagreeable odor. It is slightly soluble in water (<0.1 mg/mL at 21°C). The free mercury valence bond in monomethylmercury reacts with sulfhydryl groups in biological molecules. Thus, biliary secretion of methylmercury involves a complex with glutathione, the most common endogenous and low molecular weight thiol compound in cells (37). An L-cysteine complex of methylmercury is transported across membranes by the neutral amino acid carrier system (38). The direct binding of methylmercury, for example, to protein sulfhydryl groups through the free valence bond of mercury may, in part, explain the toxicity of methylmercury. At the same time, demethylation to the mercuric ion in the body also contributes to the toxic effects observed.

4.1.2 Odor and Warning Properties In spite of its disagreeable odor, methylmercury is not readily recognized at low concentrations. In biological matrices the compound is set free from sulfhydryl complexes at pH 1 and can then be measured by gas chromatography and other convenient techniques (see section 2.1.2). The procedure of Magos (25) for determining methylmercury in the presence of inorganic mercury was referred to in section 2.1.2. It avoids the need for separating inorganic from organic mercurials before chemical reduction, based on the fact that stannous chloride does not reduce mercury bound covalently to carbon. Another sensitive method (lower detection limit 15 ng/g) for estimating methylmercury takes advantage of its enzymatic conversion to methane (39).

4.2 Production and Use

Alkylmercury compounds, like methylmercury, are generally prepared by a Grignard reaction in ethyl ether:

$$RMgX + HgY_2 = RHgY + MgXY$$

The compounds served in the past for seed dressing, but by 1970 this application was abandoned after a disastrous episode of methylmercury poisoning in Iraq (5). Although no longer widely used, the compound may enter the environment as a by-product of mercury-catalyzed reactions, as in the case of the production of acetaldehyde in the presence of mercuric sulfate: Minamata disease in Japan resulted from the contamination of marine food supplies by methylmercury, produced either in the catalytic reaction or by the microbial methylation of inorganic mercury. Both drained in industrial wastes into Minamata Bay. Methylmercury becomes widely spread through the aquatic food chain, where it accumulates, especially in organisms like swordfish in the ocean or pike in fresh water. Such organisms at the top of the food chain are then likely to be consumed by humans.

Because of its high toxicity, industrial and agricultural use of the compound and therefore its industrial production have generally been abandoned. Methylmercury remains of considerable concern, however, because of its continuous synthesis in nature by bacterial methylation of inorganic mercury. Minimization of environmental mercury contamination therefore remains imperative.

4.3 Exposure Assessment

The odor of methylmercury at low concentrations is not sufficient to detect it. Current assessment of exposures therefore requires chemical determination of the compound in air, food, or water. Detection of past exposures can be based on an analysis of blood or hair. The compound becomes incorporated into hair at a concentration much higher than its level in blood. It remains stable in hair, so that a longitudinal history of its blood levels may be obtained.

In spite of its fairly long half-life in blood (see section 4.4), methylmercury is slowly degraded in the body to inorganic mercury. After longer periods following exposure to methylmercury, total mercury levels in blood and urine may prove informative. Analytical techniques for estimating methylmercury were briefly reviewed in sections 2.1.2 and 4.1.2.

4.4 Toxic Effects

4.4.1 Experimental Studies Methylmercury is one of the most toxic common mercurials. ATSDR has described the NOAEL and LOAEL values for different organ systems in various species (3). Lethal doses vary with the duration and rate of administration, the strain and developmental stage of the animal, the gender, and presumably other factors such as diet. An acute oral dose equivalent to

16 mg Hg/kg resulted in the death of 4 of 6 male mice, but no increased mortality was seen in females that received less than 40 mg Hg/kg.

The compound is readily absorbed into the body by inhalation or ingestion. Pulmonary uptake was measured in rats (40); net intestinal absorption of 95% of the compound present in a fish diet has been seen in human volunteers (41). Some absorption may also occur through the skin.

As described later, methylmercury is readily distributed throughout the body. The central nervous system is not well protected against the toxicant by the blood–brain barrier and is highly sensitive to its actions, especially in immature organisms. Indeed, methylmercury acts primarily as a general neurotoxin that affects cortical function, neuromuscular coordination, and other activities. Such neurotoxic effects characterize the so-called Minamata disease (see section 4.4.2). The mechanism of the neurotoxic action reportedly involves a variety of effects (42). For instance, methylmercury decreases the evoked release of neurotransmitters, perhaps through changes in Ca^{2+} metabolism; it inhibits several mitochondrial enzymes and depolarizes the mitochondrial membrane, thereby decreasing production of ATP; protein synthesis is also inhibited. Like the nonspecific cytotoxicity of Hg^{2+}, the early cellular effects of methylmercury are diverse, and damage can be attributed to more than one mechanism. One such mechanism involves damage to the microtubules involved in intracellular solute distribution and other functions (5).

The toxicant also crosses the placenta, and the fetal LD_{50} in rats was reached at maternal doses of approximately 20 mg/kg body weight. Reproductive effects of methylmercury have frequently been reported following oral exposure of various animal species, including rats, mice, hamsters, and monkeys (3).

The relatively free passage of methylmercury across cell membranes is further illustrated by its secretion into maternal milk; it appears in bile as sulfhydryl complexes (37). Enterohepatic recirculation, as well as renal tubular reabsorption, contribute to the relatively long biological half-life of the mercurial. The compound may also be demethylated in the intestine and excreted in feces as Hg^{2+}.

4.4.2 Human Experience The absorption of methylmercury in humans and its wide distribution in the body are partly explained by the appreciable lipid solubility of the compound; this facilitates its passage across cell membranes. Attention must be drawn, however, to the fact that the lipid solubility of methylmercury is limited by its ionic nature. Transfer across some cellular barriers like the blood–brain barrier is further catalyzed by membrane transporters for neutral L-amino acids; these react with and transport the L-cysteine complex of methylmercury into cells (38).

Large numbers of humans have been accidentally exposed to methylmercury, mostly by ingestion of contaminated fish or grain. In some isolated populations that depend primarily on fish as a source of dietary protein, levels of methylmercury in hair or blood may exceed estimated safe levels (5). Acutely fatal oral doses estimated from tissue concentrations range from 10 to 60 mg/kg (43).

The half-life in human blood reportedly varies from 5 to 23 weeks; such a long residence time may reflect extensive enterohepatic recirculation, as well as renal tubular reabsorption. In blood, the concentration ratio of methylmercury in red cells and plasma is generally elevated; values as high as 20/1 have been observed. This is in strong contrast to the distribution ratio of about 1 for Hg^{2+}, a fact potentially useful in distinguishing between exposures to the two toxicants.

Methylmercury is secreted into maternal milk and may constitute a serious risk to nursing infants. The risk of exposure in utero is enhanced by the ready passage of the compound through the placenta. Methylmercury is one of the most important developmental neurotoxins. The great sensitivity of the developing central nervous system to the compound has been dramatically demonstrated in several major episodes of accidental exposure, as in Minamata Bay in Japan. Unlike

the extensive information on developmental toxicity of methylmercury, there is little documentation of reproductive effects in humans.

Another catastrophic episode was caused in Iraq by consumption of seed grains treated with methylmercury as a fungicide. The estimated exposure in this case ranged from 0.71 to 5.7 mg/kg · day for a period of 43–68 days; there was a high mortality (459 deaths out of 6350 hospital admissions) (44). The symptoms of the so-called Minamata disease, typical of severe nervous system toxicity, have included paresthesia of the extremities and/or the perioral area, ataxia, visual disturbances, speech and hearing difficulties, tremors, and other neuromuscular deficiencies.

The high affinity of methylmercury for—SH groups has encouraged the development of treatments aimed at reducing its absorption from the intestine and at stimulating its excretion. Thus, Clarkson et al. showed that a synthetic polythiol resin (45) inhibits intestinal absorption of the mercurial by 50%. Keratin, in the form of reduced hair powder, had been previously used for this purpose by Takahashi and Hirayama (46).

Evidence for human carcinogenicity is limited. A number of authors have reported carcinogenic effects in rats and mice exposed orally to methylmercury; other investigators observed no increase in tumor incidence. The EPA has classified the compound as a possible human carcinogen (2).

4.5 Standards, Regulations, or Guidelines of Exposure

A benchmark dose was established by the EPA for ingestion of methylmercury (2) not to exceed 1.1 mg/kg body weight per day. It was derived from observations on neurological changes in Iraqi children and represents the intake of the compound associated with the lower limit on a 95% confidence interval for a dose that produces a 10% increase in adverse effects. This dose maintains a blood concentration in adults of about 44 mg/L or a hair concentration of 11 mg Hg/g. As pointed out by the EPA (2), fetuses of mothers whose hair concentrations are less than 1 mg Hg/g, a level associated with the present RfD (Reference Dose, defined as the daily permissible intake over a lifetime) of 0.1 mg/kg body weight per day, are not likely to suffer ill effects. The World Health Organization (22) concluded that exposure leading to hair levels in adults of up to 50 mg Hg/g and a blood concentration not exceeding 200 mg Hg/L has minimal risks.

An action level of 1 mg Hg/g was chosen by the FDA for human consumption of fish, which contain almost all of their body burden of mercury as methylmercury. This compares to an average level in tuna fish, for instance, of 0.2 mg/g. A minimal risk level for neurodevelopmental lesions of 0.5 mg Hg/kg · day was derived for methylmercury uptake for periods of 1 year or longer (47); the same value was proposed by ATSDR. Application of different safety factors to the results of epidemiological studies carried out on the fish-eating population of the Seychelle Islands led the EPA to a maximum permissible methylmercury intake equivalent to 0.1 mg Hg/kg · day (95% of this intake consists of methylmercury). The American Conference of Government Industrial Hygienists (ACGIH) chose a concentration of 10 mg/m^3 for the maximum permissible and time-weighted concentration of methylmercury in air. No standards have been set by the Occupational Health and Safety Administration (OSHA). There is currently no OSHA PEL for this compound.

4.6 Studies on Environmental Impact

Methylmercury may be added to the environment as such or may be formed by biological methylation of soluble inorganic mercury, especially in lake and marine sediments. Therefore, control of methylmercury levels in the environment requires minimizing the concentration of total mercury. Significant bioaccumulation of methylmercury has been observed in both marine and fresh water fish, especially those at the top of the food chain; in albacore tuna, the average body concentration of Hg was reported as 264 ng/g (2). In Minamata, fish-eating animals such as sea gulls and cats exhibited symptoms of neurotoxicity. Generally, wildlife is likely to be strongly affected by methylmercury in their food chain.

5.0 Phenylmercuric Acetate

A number of phenylmercuric salts are commonly available, including the acetate, bromide, chloride, cyanide, and iodide. The acetate salt, $[(C_6H_5) \cdot Hg]^+[OOC \cdot CH_3]^-$, (PMA), has been selected here

for more consideration. It must be emphasized, however, that the toxic properties of water-soluble phenylmercury salts, as of other salts of mercury and of its derivatives, are generally independent of their anion.

5.0.1 CAS Number: [*62-38-4*]

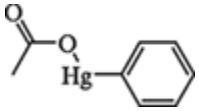
5.0.2 Synonyms: Phenylmercury acetate; PMA; (acetato-O)phenylmercury; (acetato)phenyl mercury; phenylmercury (II) Acetate; acetoxyphenylmercury; (aceto)phenylmercury; PMAC; PMAS; Gallotox; Liquiphene; Phix; Mersolite; Tag HL-331; Nylmerate; Scutl; Riogen; Advacide PMA 18; Cosan PMA; Mergal A25; Metasol 30; Nildew AC 30; Nuodex PMA 18; Agrosan; Cekusil; Celmer; Hong Nien; Pamisan; Seedtox; Shimmer-ex; Unisan; acetic acid, phenylmercury deriv.; (acetoxymercuri)benzene; agrosan gn 5; algimycin; antimucin wdr; benzene, (acetoxymercurio)-; Bufen; ceresan universal; contra creme; dyanacide; Femma; FMA; fungitox or; HL-331; hostaquik; kwiksan; leytosan; mersolite 8; norforms; phenmad; phenomercuric acetate; phenylmercuriacetate; pmacetate; PMAL; purasan-sc-10; puraturf 10; quicksan; quicksan 20; sanitized spg; SC-110; spor-kil; TAG; tag 331; trigosan; ziarnik; Anticon; Fungicide R; Fungitox; Meracen; Mercuron; Neantina

5.0.3 Trade Names: PMA, PMAS, liquiphene, mersolite, and numerous others

5.0.4 Molecular Weight: 336.75

5.0.5 Molecular Formula: $C_8H_8HgO_2$

5.0.6 Molecular Structure:



5.1 Chemical and Physical Properties
5.1.1 General The salt crystallizes in small, white, rhombic crystals, whose melting point is 153°C. It is only slightly soluble in water but dissolves in glacial acetic acid and in various organic solvents. It is readily degraded *in vivo* to mercuric ions.

5.1.2 Odor and Warning Properties The salt possesses no significant odor or other physical properties that would reveal its presence in low concentrations. Therefore, evaluating its presence requires a chemical assay (see section 5.3).
5.2 Production and Use
Phenylmercury compounds are used as catalysts in manufacturing certain polyurethanes. They were also formerly employed for seed dressing (see methylmercury in section 4); as slimicides; as fungicides in paper, pulp and both latex and waterborne paints; and as topical disinfectants and spermicides. The use of PMA in interior latex paints was banned by the EPA in 1992. The compound is synthesized by refluxing a mixture of mercuric acetate and acetic acid in a large excess of benzene; the excess benzene prevents the formation of polymercurated benzene derivatives.
5.3 Exposure Assessment
Assessment of exposure requires chemical analysis. Because of the instability of the Hg–C bond, especially in the body, it is usually most convenient to determine total mercury. The NIOSH Manual of Analytical Methods (4) lists no specific analytical procedure for phenylmercury.
5.4 Toxic Effects
There is relatively little information on the toxic effects of PMA in humans and animals. However, because of the relative ease with which the C–Hg bond can be split, it is not surprising to find a number of adverse effects described in the literature. In general, the toxicity of PMA resembles that of inorganic mercury.

5.4.1 Experimental Studies PMA is absorbed from the intestine in rats, dogs and chicks, and can cause a variety of lesions (48); the compound circulates in the blood. NIOSH lists more recent references to gastrointestinal effects (3). Daily intake of PMA in feed at a level equivalent to 1.7 mg Hg/kg body weight produced no observed gastrointestinal effects in rats over a period of 2 years. Solecki et al. (49) observed nephrosis in rats at a lower chronic dose in drinking water, equivalent to 0.4 mg Hg/kg/day. A daily dose of 4.2 mg led to increased incidence of renal cell adenomas. Takeda et al. (50) compared the distribution and excretion of various mercury compounds injected subcutaneously into rats. Mercury administered as phenylmercury distributed in the body and was excreted in urine similarly to mercury given as $HgCl_2$; this confirms the conclusion that the aryl compound rapidly breaks down to inorganic mercury. Urinary excretion of Hg from both compounds peaked 2 days after injection.

5.4.2 Human Experience There is very little information on the toxicity of PMA in humans. Use of phenylmercury as a disinfectant by a diaper service in Argentina (51) led to acrodynia in infants.

5.5 Standards, Regulations, or Guidelines of Exposure

An oral reference dose for PMA equivalent to 0.08 mg Hg/kg · day was calculated for human consumption by the EPA (52). This was based on a LOAEL in rats equivalent to 50 mg Hg/kg · day. The ACGHI has chosen 100mg as the time-averaged maximum concentration of arylmercury per liter of air. No standards have been set by OSHA.

5.6 Studies on Environmental Impact

No information was located on the possible environmental impact of PMA. In general, as with any other mercurial, contamination of the environment should, of course, be avoided. This is especially desirable because degradation and metabolism of mercurials may lead to formation of more toxic compounds in the human food chain, such as methylmercury in fish.

Mercury

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Aluminum

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A. Introduction

Because of this element's electrochemical properties, its positvely charged ions form very tight chemical bonds with other anions such that dissociation is minimal in neutral or near-neutral-pH environments. Since most living organizations operate at or about such pH levels, by implication most naturally occurring aluminum compounds would display minimal potentials for cellular or subcellular interactions. Its binding forces, in addition to making this element available only recently (at the time of writing), has also meant that aluminum was relatively unavailable to the milieu intériur. However, since progressively more of the metal and its compounds came into common human use and commerce, ultimately its wide usage could be expected to eventually result in the possibility intimate human contact and finally, human health and hazard concerns.

These events have indeed occurred so that aluminum and its possible association with neurological disorders became a prominent health issue of the late twentieth century. Because of the foregoing electrochemical physical realities, concerns have focused on the *element's* health effects per se, with little or attention directed at effects of aluminum compounds, such as chloride, phosphate, and sulfates. This should also not be unexpected, given their *relative* biological inavailability. Obviously, some aluminum compounds do ionize sufficient to lower pH in aqueous environments (e.g., aluminum chloride or phosphate) and act as simple irritants. However, most other aluminum compounds, as expected have had very little *apparent* biologic availability or effects, and thus are accorded little scientific attention as compounds per se.

These facts are reflected in the content of contemporary biomedical literature. Although multiple aluminum compounds have been studied, few, if any, are studied except as they serve to “transport” aluminum into the body. The overwhelming majority represent interest in aluminum's effects alone rather than an individual compound's possible bioimpact.

For these reasons, this chapter deals mainly with aluminum as an element and the most common prevalent form: the oxides. Since its other compounds as such are the subject of so little current investigation, these other compounds are considered separately later in this chapter.

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B. Aluminum and its Oxides

Aluminum is the third most common element—after oxygen and silicon—of the lithosphere, representing 8.13%. Paradoxically, despite its ubiquity in the environment, because of its high affinity for oxygen it is never found in its free, elemental state. In the *pH-neutral, aqueous environments* characteristic of most biological systems the common, naturally occurring aluminum oxides, oxy- and hydroxides, silicates, alkali and alkaline-earth metal, and phosphate compounds are extremely insoluble and thus relatively inaccessible to biological interaction. Other compounds of aluminum that *do not commonly occur in nature*, such as aluminum sulfate or aluminum citrate, are more soluble and thus have been used by experimentalists. Unfortunately, information so derived often bears questionable relevance to aluminum's relative biological inactivity resulting from real-world encounters with this element. In addition, its amphotericity and ability to form double salts contributes toward serious analytical problems in defining its various chemical and physical species in natural systems. Inadequate understanding of the physicochemical behavior and chemical species of aluminum occuring in living systems have accentuated inconsistencies in biomedical research outcomes. Confusion among aluminum physicochemical nomenclature (1) has further obscured understanding of inconsistent toxicological research results (2). Thus, although aluminum has been present at microgram levels in most biotic systems over evolutionary timescales, its effect on such

systems remains controversial and poorly defined.

Indeed, relative physicochemical inaccessibility caused it to be the last of the common metals to be commercially produced. The Romans referred to any astringent substance as *alum*, but in the Middle Ages it was recognized as an independent substance manufactured from *alum stone*. A few drops of the metal were chemically isolated in 1825 by Hans C. Oersted, but its importance in commerce dates from the almost simultaneous appearance of patents in 1886. Charles Martin Hall via a backdated, refiling claimed to have discovered the electrolytic reduction process in the United States on February 23; in France Paul-Louis-Toussaint Héroult filed his patent application on April 23. (Ironically, Hall and Héroult subsequently both died at age 51 in 1914 of the same cause: typhoid fever.) After both legal and commercial developmental problems, the inventors finally succeeded in developing the new industry so that the price of the metal dropped from $75 a pound in 1890 to 29–30 ¢ /lb by the end of the nineteenth century.

Regardless of problems regarding the physicochemical behavior of this element and its compounds, toxicologists have paid considerable attention to this element and its compounds. As early as 1897, Doelkin (3) applied aluminum to the cortex of experimental animals with locally damaging results. (Such interest undoubtedly reflects the simultaneous ready availability of the metal and the development of modern toxicology.) However, this and subsequent other experiments should also consider issues such as the biological relevance of those chemical species studied, the dose-dependent effect of the doses employed, or to the appropriateness of portals of entry. The direct application of various chemical species to organs or tissue sites of interest implicitly reflects the particular difficulty of delivering these biologically nonreactive compounds of the element to a target organ or cellular site via the usual natural routes of transfer. Although positive experimental outcomes could be assured by such design strategies, their relevance to biological reality may be tenuous.

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C. Aluminum Chloride, Sulfate, Phosphide, and Fluoride and Sodium Aluminate
As has been noted in the foregoing, the electrophysical forces strongly binding aluminum to the anion(s) results in compounds possessing little—if any—aqueous solubility, which, in turn, favors neither their absorption nor biological accessibility at physiologic pH ranges. This is clearly the case for essentially all of the oxides that are insoluble in water at normal pH. By contrast, several of the double salts display a range of slight solubilities, whereas, in turn, the simple salts show a higher range. (These statements represent generalizations, since within this classification of salts there is a small range; e.g., the simple salt AlF_3 is relatively insoluble in water). As would be expected, these simpler salts, such as aluminum chloride or the simple sulfate, are capable of evoking irritant effects at biological interfaces. Even here, such effects usually require relatively large dosing or protracted skin contact; when they are inhaled, irritation can also be seen at higher doses, particularly with respirable particulate sizes (see Ref. 148 and Section 3.4.2.2).

Biomedical research periodically focuses on the health effects of aluminum; however, which chemical species is active and significant in biological systems has yet to be defined. Despite this lacuna, biomedical researchers generally have not been reluctant to administer a wide variety of aluminum compounds via variably relevant or pertinent portals of entry. Under these circumstances such research focuses on the effects of *aluminum atom or ion*, rather than on the aluminum *compound* itself. These aluminum compounds are regarded as simply carriers of the element into the milieu intériur; thus, there is very little health and biomedical literature concerned with effect(s) of the compounds per se, beyond any exceptions to be noted. Accordingly, it is such biological

misperceptions that help account for the relative paucity of recent literature on aluminum compounds that follow.

2.0 Aluminum Chloride

2.0.1 CAS Number: [*7446-70-0*]

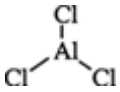
2.0.2 Synonyms: Aluminum trichloride; trichloroaluminum; aluminum chloride, anhydrous

2.0.3 Trade Names: NA

2.0.4 Molecular Weight: 1233.34

2.0.5 Molecular Formula: $AlCl_3$

2.0.6 Molecular Structure:



2.1 Chemical and Physical Properties

2.1.1 General

Melting point	194°C
Density (at 20°C)	2.44 g/L
Boiling point	262°C, decomposes
Appearance	granular crystals, white to colorless; when impure, gray or yellow to greenish
Vapor pressure	1 mm Hg at 100°C
Vapor density	4.5
Solubility	69.9 g/L water; dissolves freely in benzene, ether, many organic solvents
	Very deliquescent, readily forms HCl fumes in atmospheric water or air
	When heated in small quantities, volatilizes without melting

2.1.2 Odor and Warning Properties Strong odor of hydrogen chloride

2.2 Production and Use

This compound can be synthesized by a number of methods, including the heating of aluminum in a current of chlorine, followed by dissolving the product in water and crystalization. The synthesis can also be accomplished by reacting purified gaseous HCl with molten aluminum.

This compound has many uses; the major use is in cosmetics (aluminum chloride hexahydrate antiperspirants) and the pharmaceutical industry. It has wide application in chemical synthesis as a catalyst, especially in Friedel–Crafts reactions, for instance, in cracking of petroleum, for ethylbenzene, dyestuff intermediates, and detergent alkylate and as a chemical intermediate for numerous aluminum compounds. It also finds major uses in manufacture of specialty papers and in photography.

2.3 Exposure Assessment

Either NIOSH method 7300 (10) or NIOSH method 7013 (9), in which the analyte is aluminum, can be used. Although methods for analysis of aluminum in blood or urine are also applicable, the meaning of any findings in terms of aluminum chloride body exposure or body burdens would be only speculative.

2.4 Toxic Effects

2.4.1 Experimental Studies The acute oral LD_{50} (rat) was reported to be relatively high, 370 mg/kg (31); similarly, the LD_{50} for the rabbit was 400 mg/kg rabbit (169).

2.4.2 Human Experience Because of this compound's ready tendency to volatilize hydrochloric acid in the presence of moisture, it may produce an unpleasant, irritant environment. If it is applied as a dry material on the skin or mucous membranes, an astringent as well as inflammatory response may occur. Splashes or other exposures to the eye produce marked irritation and possible conjunctival inflammation and ulceration. Although respiratory tract inflammation might be expected, there are no reliable reports that this has occurred.

2.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV TWA is 2.0 mg/m^3 soluble salts, as aluminum. This TLV is based on the amount of hydrolyzed acid and the corresponding TLV. On the basis that 3 mol of HCl, with a TLV of 5 ppm, hydrolyze from 1 mol of $AlCl_3$, a TLV TWA of 2 mg/m^3, as aluminum, is recommended to yield a comparable degree of freedom from irritation as provided by the TLV for HCl.

The (OSHA) PEL is 2.0 mg/m^3.

3.0 Aluminum Sulfate

3.0.1 CAS Number: [*10043-01-3*]

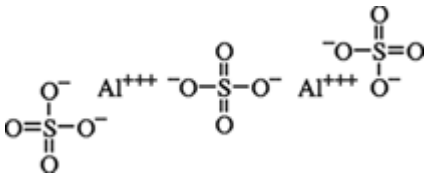
3.0.2 Synonyms Although "alums" were used by the ancient Greeks and Romans as medicinal astringents, knowledge of their exact chemical nature long postdated this use. Currently, it is clear that "alum" consisted of a group of crystalline double salts composed primarily of aluminum and sulfate plus a monovalent cation, namely, potassium, ammonium, or sodium, with the general formula $M^+Al^{3+}(SO_4)_2{}^* 12\ H_2O$. Accordingly, although these three compounds, specifically (*1*) aluminum potassium sulfate ($AlKO_8S_2$), (*2*) aluminum sodium sulfate ($AlNaO_8S_2$), and (*3*) aluminum ammonium sulfate [$AlNH_4\ (SO_4)_2$]—may be referred to and used as an "alum", such usage is imprecise. To further complicate the issue, $Al_2(SO_4)_3 \cdot 18\ H_2O$—most properly referred to as "aluminum sulfate"—in common usage equally inappropriately is called and used as an "alum." Given these common usages, it is not unexpected that a large number of synonyms are in common use, such as aluminum trisulfate alum, kaolinite, cake alum, exsiccated alum, pearl alum, potassium alum, alum flour, alum meal, and filter alum.

3.0.3 Trade Names: NA

3.0.4 Molecular Weight: 342.14

3.0.5 Molecular Formula: $Al_2O_{12}S_3$

3.0.6 Molecular Structure:



3.1 Chemical and Physical Properties

3.1.1 General

Physical appearance	odorless white or colorless powder or crystals
Specific gravity	2.71
Melting point (decomposes)	770°C, becomes anhydrous at 250°C

Solubility	freely in water, glycerine; solution in water is medium strong acid, pH insoluble in alcohol

3.1.2 Odor and Warning Properties Odorless; when heated or burning, produces irritant sulfur oxides fumes.
3.2 Production and Use
Aluminum sulfate is used mostly for clarification as a particulate flocculant in raw water, clarifying sugar and in baking powders. Other major applications are in pulp/papermaking, in fabric dying, in dye manufacture, in lakes, and as a catalyst.
3.3 Exposure Assessment
See Section 2.3.
3.4 Toxic Effects
3.4.1 Experimental Studies Presently there is very scanty modern data; a 1966 study indicated very low acute toxicity in rats at an oral LD_{50} of 6.1 g/kg (170).

3.4.2 Human Experience 3.4.2.1 General Information: NA

3.4.2.2 Clinical Cases 3.4.2.2.1 Acute Toxicity No human experience has been reported. On the basis of its potential irritant behavior, one might expect its mild to moderate irritant capacity to cause skin redness and mild inflammation on moderate to heavy skin contact with particulate dusts or powdered forms, especially if not removed. Similarly, it could be expected to produce mild pulmonary irritation and cough with heavy exposure to dusts. With pyrolysis, sulfur oxide fumes can be generated, and could produce upper and possibly midrespiratory tract lung irritation cough, and other disorders.

3.4.2.2.1.1 The Camelford Episode Acute oral ingestion of aluminum sulfate occurred in a population accidentally exposed for several days to 20 tons distributed through the water distribution system of Camelford, Cornwall in 1988. Acute symptomatology seen in this episode is nondescript, numerous and varied; questionable, involving the digestive, (sore throat, gastric upsets), skin rashes, backache, and musculoskeletal problems; and with general neuropsychological (anxiety, depression, cognitive problems such as partial loss of memory and concentration ability) complaints and generalized fatigue (171). Because of nonuniform distribution, dose estimations of this large, short-term loading could not be determined, although elevated levels of aluminum as well as other metals persisted for the next several days.

Two years after the episode Rowland et al. (172) compared a 480-person cohort from the Camelford area with 532 persons from an uninvolved district. The exposed cohort more readily reported the occurrence of *all* 18 symptoms in a questionnaire than covered the control cohort. The exposed cohort had a statistically significantly higher relative risk of joint pains complaints, although this complaint occurred in less than 25% of all respondents. The minimal 45% overall response rate among the exposed cohort confounded this study's positive findings.

Further complicating this investigation, neuropsychological evaluation of 10 individuals was performed serially between 8 and 26 months after the episode; the adequacy of information processing and memory was assessed. While showing “consistent impairment of these functions,” the investigators qualified these findings, as they were unable to differentiate between acute brain damage and the imposed psychological stress of the episode (173). By contrast, the same investigator led a study of the psychological performance of children from Camelford and outside the area and could find no differences (175).

Seven years after the Camelford episode, public health authorities (176) reported a 5-year retrospective study of two similar-sized cohorts as previously. Over this 5-year period, serial determinations of standardized hospital discharge ratios were compared and analyzed. They reported

standardized discharge ratios for the Camelford cohort higher than those of the control groups but offered no explanation for this phenomenon.

McMillan et al. (173) also reported that 6 and 7 months after the Camelford exposure the aluminum present in the bones of two of those exposed had disappeared. Similarly, no stainable aluminum was present in bone biopsies of eight exposed persons 12–17 months after the episode. Although this might generally be expected, whether this test (i.e., biopsy and bone stain) of the continued presence of Al in bone is sufficiently sensitive to truly indicate its presence in bone could be questioned, given Priest's (49) indications of a more prolonged bone residence time.

3.4.2.2.2 Chronic and Subchronic Toxicity 3.4.2.2.2.1 Occupationally Exposed Populations Simonsson et al. (148) reported on the exposures of workers engaged in the synthesis of the simple aluminum sulfate salt; three other workers in another plant producing aluminum fluoride were reported incidentally. Exposures were poorly controlled as a result of start-up problems, and atmospheric exposure concentrations ranged from 0 to 53 mg/m^3 as dusts with 25–30% in the respirable range. The employees manifested nocturnal wheezing and breathlessness characteristic of occupational asthma. This reversible airway obstruction persisted despite 2–5 years of nonexposure (mean = 41 months) in 11 of the 19 workers initially affected. The similarity of these cases of reversible obstructive airway disease or occupational asthma cases to those seen in aluminum smelters is noteworthy. However, the occupational asthma syndrome is not uncommon, as it has been been reported consequent to other irritant metal salt exposures, such as from chromates, platinum, nickel, and vanadium. The onset of this condition following production upsets has been seen elsewhere, suggesting a similarity to the reactive airway dysfunction syndrome (RADS). In the cases reported here, the potential irritant capacities of large doses of the simple aluminum sulfate salt would not be not unexpected. It is not reasonable to suggest that many of these cases represented RADS.

3.5 Standards, Regulations, or Guidelines of Exposure

ACGIH: TLV TWA as soluble Al salt; ACGIH = 2.0 mg/m^3 (For discussion of rationale, see Section 2.5)

OSHA: PEL = 2.0 mg/m^3

4.0 Aluminum Phosphide

4.0.1 CAS Number: [*20859-73-8*]

4.0.2 Synonyms: Aluminum monophosphide, phostoxin, aluminum phosphide, celphos, celphide, celphine

4.0.3 Trade Names: Alutal, Celphide, Delicia, Gas-Ex-T, Phosfume, Phostek, Zedesa, AlP; Fumitoxin; Detia; Phos-Kill; L-Fume; Quik-Phos; Gastoxin; Quik-Fume; AL-PHOS; Celphine; Aluminum Phosphide, Tech

4.0.4 Molecular Weight: 58

4.0.5 Molecular Formula: AlP

4.0.6 Molecular Structure: Al≡P

4.1 Chemical and Physical Properties

4.1.1 General Dark gray to yellow crystals; density $2.9_{(water = 1)}$ melting point > 1000; hydrolyzes in water, acids

4.1.2 Odor and Warning Properties None if dry; reacts if contacts water or acids, hydrolyzing to

highly irritant products and garlic odor.
4.2 Production and Use
Because aluminum phosphide hydrolyzes to phosphine in the presence of moisture, it is used to sterilize grain against insect infestation and as a rodenticide in grain storage.
4.3 Exposure Assessment
NIOSH methods 7300 (10) and 7013 (9) can be used to analyze air.
4.4 Toxic Effects
4.4.1 Experimental Studies This compound exhibits toxicity as a consequence of its hydrolysis in water to phosphine (see Chapter covering "Phosphorus and Its Hydride Phosphine, sec —). Rats fed aluminum phosphide exhibited an LD_{50} of 11.5 mg/kg; inhalation exposures have previously indicated an LD_{50} of 15.5 mg/m^3 after 4 h of exposure (176); subsequent studies (177) suggested that these results may be overstated.

4.4.1.1 Acute Toxicity: NA

4.4.1.2 Chronic and Subchronic Toxicity: NA

4.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Aluminum phosphide is not apparently absorbed transcutaneously. Experimentally, its hydrolysis product has consistently produced severe systemic intoxications as a consequence of phosphine formation subsequent to hydrolysis to phosphine in gastric acid and/or respiratory moisture. From those junctures toxicity is due to phosphine.

4.4.2 Human Experience As with the animal data, toxicity stems from phosphine intoxication (see Chapter, sec —).
4.5 Standards, Regulations, or Guidelines of Exposure
See chapter,"phosphine".
5.0 Aluminum Fluoride
5.0.1 CAS Number: [*7784-18-1*]

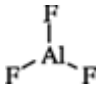
5.0.2 Synonyms: Aluminum trifluoride

5.0.3 Trade Names: NA

5.0.4 Molecular Weight: 83.98

5.0.5 Molecular Formula: AlF_3

5.0.6 Molecular Structure:



5.1 Chemical and Physical Properties
5.1.1 General

Hexagonal crystals, slightly soluble in water 0.6 g/100 mL
Melting point 250°C
Sublimes at 1272°C; sparingly soluble in acids and alkalis, even in hot H_2SO_4

5.2 Production and Use
Inhibitor in fermentation, in ceramics, as catalyst in organic reactions.

5.3 Exposure Assessment
NIOSH methods 7300 (10) and 7013 (9) can used to analyze air.
5.4 Toxic Effects
5.4.1 Experimental Studies No relatively recent animal experimentation data appear to be available. Aluminum fluoride has been considered to have low oral toxicity because of its low aqueous solubility. Evidence is contradictory regarding cutaneous and mucous membrane irritant properties, given this behavior.

5.4.2 Human Experience The report by Simonsson et al. (148) (see Section 3.4.2.2.2.1) included three individual workers who worked in a separate aluminum fluoride production facility. As was the case with the larger group of 19 employees at the other plant, these three individual developed asthma-like symptoms characteristic of reversible airway obstructive disease. Relatively few details of the conditions of exposure or the clinical course among these AlF_3 exposed individuals were reported, as was the clinical course of these few cases. Given the nature of these exposures, their responses, and the relative paucity of human exposure cases, this report remains only suggestive and requires confirmation.
5.5 Standards, Regulations, or Guidelines of Exposure
Both the ACGIH TLV and the OSHA PEL limit exposure to AlF_3, as a"soluble salt of aluminum," at a maximum concentration of 2.0 mg/m^3. It is open to question whether the same standard should apply to aluminum fluoride in view of its relatively minimal solubility compared to aluminum chloride or sulfate.
6.0 Sodium Aluminate
6.0.1 CAS Number: [*1302-42-7*]

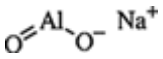
6.0.2 Synonyms: Aluminum sodium oxide, aluminum sodium dioxide, sodium aluminum hydride

6.0.3 Trade Names: NA

6.0.4 Molecular Weight: 81.97

6.0.5 Molecular Formula: $AlNaO_2$

6.0.6 Molecular Structure:



6.1 Chemical and Physical Properties
6.1.1 General

White hygroscopic powder
Melting point 1650°C
Insoluble in alcohol
Solubility in water = very high, strongly alkaline
Density $_{(water = 1)}$ > 1.5
Reacts violently with acid
Corrosive with aluminum, zinc

6.2 Production and use
Printing on fabrics, sizing paper, water softners.
6.3 Exposure Assessment
NIOSH methods 7300 (10) and 7013 (9) can be used to analyze air.

6.4 Toxic Effects
Because of the highly alkaline nature of this compound in solution, it should be treated as a corrosive.
6.5 Standards, Regulations, or Guidelines of Exposure
ACGIH: TLV TWA—in view of its relatively high aqueous solubility, it would clearly be considered under the category of "soluble salt of aluminum." The ACGIH assigns a maximum concentration value of 2.0 mg/m^3.

Aluminum
Bertram D. Dinman, MD, Sc.D

D. Alkyl Aluminum Compounds
This class of chemicals represents a large and continuously expanding group of organometallic compounds with varied uses in industry. They have the following general structures: R_2AlH, R_3Al, R_2AlR', R_2AlX, $RAlX_2$, and $R_2AlR'X$, where R and R' are straight-or branched-chain, saturated or unsaturated or mixed alkyls, and X is a halogen. These are treated as a class of aluminum compounds having similar chemical properties that determine their physical behavior and consequently their potential health impacts. They are extremely reactive in air and especially in the presence of water, where they may decompose explosively. Such rapid decomposition is accompanied by rigorous rearrangements of their carbon skeletons with the formations of flammable and/or explosive concentrations of ethylene, propylene, and butylene.
7.0 Diisobutyl Aluminum
7.0.1 CAS Number: [*1191-15-7*]

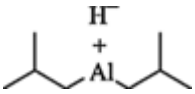
7.0.2 Synonyms: Aluminum, hydrobis (2-methylpropyl)-aluminum diisobutyl; diisobutyl alane

7.0.3 Trade Name: DIBAL-H

7.0.4 Molecular Weight: 142.22

7.0.5 Molecular Formula: $C_8H_{19}Al$

7.0.6 Molecular Structure:



7.1 Chemical and Physical Properties
7.1.1 General

Colorless liquid
Melting point –70°C
Boiling point 105°C at 2 mm Hg
Specific gravity 0.701 g/ml
Pyrophoric in air at concentrations > 25% by weight
Soluble with hydrocarbon solvents

7.2 Production and Use

Major uses as polymerization catalyst; intermediates in silicones, certain polymers and organic acid synthesis.

7.3 Exposure Assessment

NIOSH methods 7300 (10) and 7013 (9) can be used to analyze air.

7.4 Toxic Effects

Essentially no toxicity data have been reported, although the known corrosive properties of the family of compounds is well established. It has been reported that contact with solutions of < 20% concentration (172) may be without hazard. Corrosive action can be expected on eye contact (173).

Atmospheric exposures to fumes of Al_2O_3 will result following pyrophoric and/or explosive reactions as a consequence of oxidation of the aluminum of this compound. Although numerous investigators have suggested that metal-fume fever might result from the aluminum oxide fume so formed, no primary source can be found for that assertion.

7.5 Standards, Regulations, or Guidelines of Exposure

A TLV has been set by the ACGIH for the alkyl aluminum compounds as a class, recognizing the paucity of experimental and/or human exposure data. Although they recognize that their major thermal decomposition product of these metalloalkyls would be Al_2O_3, they also note that many species in this class are halogenated. (see introductory paragraph preceding Section 7.0). Consequently, it could be assumed that pyrolysis would also be accompanied by the formation of halogen acid gases. Given the (possible) presence of such acid gases, ACGIH recommended a blanket guideline lower than that set for aluminum welding fume, specifically 2 mg/m^3 for those alkyl aluminum compounds not otherwise classified (NOC).

8.0 Triisobutylaluminum

8.0.1 CAS Number: [*100-99-2*]

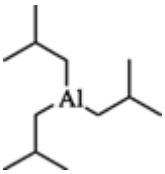
8.0.2 Synonyms: Aluminum triisobutyl; aluminum, tris (2-methylpropyl)-; Tibal; aluminum triisobutamide; triisobutylalane

8.0.3 Trade Names: NA

8.0.4 Molecular Weight: 198.33

8.0.5 Molecular Formula: $C_{12}H_{27}Al$

8.0.6 Molecular Structure:



8.1 Chemical and Physical Properties

8.1.1 General

Clear, colorless liquid
Melting point 6°C
Boiling point 86°C (at 10 mm Hg)
Vapor pressure 1 mm Hg (at 47°C)
Pyophoric or explosive in water
Explosive reactions with alcohols, benzene

8.1.2 Odor or Warning Properties White fumes with musty odor.
8.2 Production and Use
Major use is as a polymerization catalyst in synthesis of polybutadiene, polyisoprene, primary alcohols, and olefins; also as an intermediate in synthesis of phosphate insecticides, and as a reductant.
8.3 Exposure Assessment
NIOSH methods 7300 (10) and 7013 (9) can be used to analyze air.
8.4 Toxic Effects
See Section 7.4.
8.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH guideline TLV is 2.0 mg/m^3. (For discussion of rationale, see Section 7.5.)

Aluminum

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Gallium, Indium, and Thallium
Guillermo Repetto, MD, Ana del Peso

A. Gallium and Gallium Compounds
1.0 Gallium
1.0.1 CAS Number: [*7440-55-3*]

1.0.2 Synonyms: Gallium, gallium metal

1.0.3 Trade Names: UN2803

1.0.4 Molecular Weight: 69.72

1.0.5 Molecular Formula: Ga
1.1 Chemical and Physical Properties
1.1.1 General The chemical element gallium (Ga), of atomic number 31, is a bluish metal of group IIIA in the periodic table. Gallium is a relatively rare metal that is becoming increasingly important in the manufacture of semiconductor electronic devices. Gallium was isolated for the first time from zinc sulfide ore in 1875 by the French chemist Lecoq de Boisbaudran, who named it after Gallia, the Latin name for France. Later the same year Dmitry Mendeleyev showed that gallium was the missing group IIIA element predicted in his theory of chemical periodicity, below aluminum and above indium.

Gallium is present in the earth's crust in a concentration of 5–15 ppm. It often occurs in small amounts in the sulfide ores of its neighbors in the periodic table, zinc and germanium; because of its chemical similarity to aluminum, it is a minor component of all aluminum ores. It is not present in significant concentrations in the ocean. The richest source, which is located primarily in southwestern Africa, is the mineral germanite, a sulfide. Germanite may contain 0.5–0.7% of gallium, but gallium is widely distributed in small amounts in zinc blends, aluminum clays, feldspars, and coal, and in the ores of iron, manganese, and chromium. Bauxite, the clay-like ore from which aluminum is obtained, contains 0.0002–0.008% gallium, whereas some tin ores contain 0.01–0.05% of gallium.

Gallium is a lustrous, silvery liquid or bluish metal or a gray solid. It is the only metal, except for mercury, caesium, and rubidium, that can be liquid near room temperatures; this makes possible its use in high-temperature thermometers. It has one of the longest liquid ranges of any metal and has a low vapour pressure even at high temperatures. Ultrapure gallium has a beautiful, silvery appearance, and the solid metal exhibits a conchoidal fracture similar to that of glass (1).

Molten gallium expands by as much as 3.2% on solidifying; therefore, it should not be stored in glass or metal containers, as they may break while the metal solidifies. Bismuth is the only other metal having this property. High purity gallium is attacked only slowly by mineral acids. Gallium arsenide is capable of converting electricity directly into coherent light, as it is a key component of LEDs (light-emitting diodes).

Gallium, Indium, and Thallium
Guillermo Repetto, MD, Ana del Peso

B. Indium and Indium Compounds
8.0 Indium
8.0.1 CAS Number: [*7440-74-6*]

8.0.2 Synonyms: Indium metal

8.0.3 Trade Names: NA

8.0.4 Molecular Weight: 114.82

8.0.5 Molecular Formula: In
8.1 Chemical and Physical Properties
8.1.1 General Indium is a rare, lustrous silver-white metal with atomic number 49 and In as its atomic symbol. It is widely distributed in the earth's crust in minute quantities (0.1 ppm) and is also found in the hydrosphere. Indium belongs to group IIIA in the periodic table. It was found and spectroscopically identified as a minor component in zinc ores and isolated in 1863 by Ferdinand Reich and Theodore Richter. Indium is so named for the indigo blue color that its salts lend to flames. Indium resembles tin in its physical and chemical properties and to some extent in its toxicological properties. It is extremely soft and malleable, with a Brinell test hardness of less than 1 and a Mohs scale hardness of 1.2. In the electromotive series it appears between iron and tin, and does not decompose in water at boiling temperature. It is stable in air, but when heated, it burns with a nonluminous, blue-red flame yielding indium oxide. The surface of indium remains bright up to its melting point; above this, it forms an oxide film.

Indium has a density of 7.3 g/mL (at 20°C), a melting point of 156.61°C, a boiling point of 2000°C, and a specific heat of 0.0568 cal g^{-1} $°C^{-1}$. Indium is insoluble in hot or cold water, soluble in acids,

and very slightly soluble in sodium hydroxide (163). There are two natural isotopes: 115 (95.77%) and 113 (4.23%). Indium-115 is a b-emitter, with a half-life of 6×10^{14} years. The artificial radioactive isotopes are 107–112, 114, and 116–124 (1–5). Indium forms mono-, di-, and trivalent compounds, of which the last is the most common. The trichloride is deliquescent; the sulfate is hygroscopic. Intermetallic semiconductors are formed from group III and group V elements. Most used are InSb, InAs, and InP. All require very high element purity (0.1 ppm). InSb is employed in infrared detectors and magnetoresistors. It wets glass, as does gallium. It is useful for making low melting alloys. An alloy of 24% indium and 76% gallium is liquid at room temperature.

8.1.2 Odor and Warning Properties Indium is flammable in the form of dust, yielding indium oxide when exposed to heat or flame. Mixtures of indium with sulfur ignite when heated. Indium reacts explosively with dinitrogen tetraoxide plus acetonitrile. Indium exhibits a violent reaction with mercury(II) bromide at 350°C. Indium is unaffected by water, is attacked by mineral acids and is very resistant to alkalies (7).

Gallium, Indium, and Thallium
Guillermo Repetto, MD, Ana del Peso

C. Thallium and Thallium Compounds
14.0 Thallium
14.0.1 CAS Number: [*7440-28-0*]

14.0.2 Synonyms: Thallium, rod; thallium metal, ramor

14.0.3 Trade Names: NA

14.0.4 Molecular Weight: 204.383

14.0.5 Molecular Formula: Th
14.1 Chemical and Physical Properties
14.1.1 General Thallium is a soft, gray-white metal. It is a member of group IIIA in the periodic table. The name derives from the Greek root *thallos*, meaning green or young twig. Thallium metal was isolated in 1861 by William Crookes and, independently, by the French chemist Claude-Auguste Lamy. Thallium's innate toxicity was recognized shortly after its discovery, when Crookes suffered from its effects. Thallium does not occur in nature in the elemental state but is present as a trace compound in many minerals, mainly associated with potassium and rubidium. Although thallium is widely distributed in the earth in an estimated abundance of 0.3 ppm, its wide distribution belies its availability, for it occurs chiefly as a minor constituent in iron, copper, sulfide and selenide ores, crooksite $(TlCuAg)_2Se$, orabite $(TlAs_2SbS_5)$, and lorandite $(TlAsS_3)$, mainly in Texas and Brazil. One exception is the occurrence of lorandite in gold ore in Nevada, which contains an average of 60% thallium. The deposits of thallium minerals are so small as to have no commercial significance at present.

Thallium metal is somewhat softer and more malleable than lead and, when freshly melted, resembles tin in whiteness. Thallium, however, oxidizes rapidly, turning gray, then brownish black from an oxide coating. For this reason thallium rods are often paraffin-coated. The metallurgical properties of thallium are unknown because of limited use of the metal. The most interesting properties include boiling point 1457°C, melting point 303.5°C, commencement of volatilization at 174°C, density 11.85, vapor pressure 1 mm Hg at 825°C and 20 mm Hg at 1040°C, specific heat at 20°C 0.13 J/g, first ionization energy 590 kJ/mol, fusion heat 21.1 J/g, atomic volume $5.15 \times 10^{+30}$ W/(C.m), thermal conductance 0.39 W/(cm·K), covalent radius 0.148 nm, electronegativity 1.8

according to Pauling's scale, linear coefficient of expansion 28×10^{-6}, electrical resistivity 18 mW/cm, tensile strength 9.0 MPa, bond strength <22 kcal/mol, heat of formation (gaseous) 43.55 kcal/mol. Easily fusible, thallium leaves a streak on paper; below 230°C it forms close-packed hexagonal crystals and above 230°C, body-centered cubic crystals. It may be distilled in a stream of hydrogen. Two natural isotopes of thallium have been found: 203 (29.50%) and 205 (70.50%) (1–5).

Gallium, Indium, and Thallium

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Germanium, Tin, and Copper
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1.0 Germanium
1.0.1 CAS Number:
[*7440-56-4*]
1.0.2 Synonyms:
NA
1.0.3 Trade Names:
NA
1.0.4 Molecular Weight:
72.59
1.0.5 Molecular Formula:

Ge
1.1 Chemical and Physical Properties
Germanium is a semiconducting metal from Group IVA of the periodic table.

The physical and chemical properties of germanium and some of its compounds are listed in Table 33.1.

Table 33.1. Physical and Chemical Characteristics of Germanium and Some of Its Compounds

Form	Germanium (Ge)	Germanium Dioxide (GeO_2)	Germanium Tetrachloride ($GeCl_4$)	Germane[a] (GeH_4)
Atomic or mol. wt.	72.60	104.6	214.4	76.63
Specific gravity	5.35 (20°C)	4.228 (25°C)	1.879 (20°)	—
Melting pt. (°C)	937.4	1115	–49.5	–165
Boiling pt. (°C)	2830	—	84.0	–90
Solubility	Insol. water, alkalis; sol. hot H_2SO_4	Sl. sol. water; sol. acids, alkalies	Dec. water; sol. dil. HCl, alcohol, ether	Insol. water; sol. NaClO

[a] Germanium tetrahydride.

In 1886 Clemens A. Winkler, a German chemist, isolated germanium from the mineral argyrodite, a mixed sulfide of silver and germanium. It was named after the country of the discoverer. In recent years various germanium compounds, for example, carboxyethyl germanium sesquoxide (Ge-132) and lactate–citrate–germanate, have been sold as nutritional supplements, thereby increasing exposure above predicted levels.

Germanium metal has the most unusual property of being highly transparent to infrared light. This characteristic, coupled with a high index of refraction, is used to advantage in making unique optical elements. Crystalline germanium is a true semiconductor; traces of impurities of 0.1 ppm such as antimony, tin, and lead will lower its electric resistivity from 50 to 0.1–10 ohm/cm. Germanium forms alloys with many metals, producing solid solutions or intermetallic compounds that expand on solidification. Germanium is not attacked by O_2 in air or by HF (aq.) or HCl (aq.), but reacts slowly with concentrated nitric and sulfuric acids. Alkaline H_2O_2 or aqueous NaClO rapidly oxidizes germanium. Germanium forms two series of salts, divalent and tetravalent, which chemically resemble stannous and stannic compounds. The tetravalent is the most common, stable form. Germanium does not form salts with the common inorganic oxy acids. In its tetravalent compounds germanium is in coordinate valence with neighboring atoms. Germanium forms a series of hydrides, germanes, by the reaction of HCl and Mg_2Ge. They possess pungent odors, are combustible, and are often explosive. Germanium tetrahydride, GeH_4, does not react with O_2 below 230°C or explode below 330°C; digermane (Ge_2H_6) is more explosive. A series of halogenated germanes are known that are colorless gases or liquids. Although germanium does not form a carbide, it forms strong bonds with carbon atoms to form a variety of organo compounds such as tetraalkyl- and

tetraarylgermanes. They are volatile, stable, colorless substances, insoluble in water, but soluble in organic solvents.

Germanium forms a series of hydrides that correspond chemically to the methane series of hydrocarbons and to silanes (silicon series of hydrides). The germanes are insoluble in hot and cold water, soluble in sodium hypochlorite (aq.), and slightly soluble in hot HCl (aq.).

There are numerous organogermanium compounds. Interest in the organogermanium compounds has centered around their antimicrobial activity and the fact that their mammalian toxicity is considerably lower than the corresponding derivatives of tin or lead.

1.2 Production and Use

Although it looks like metal, in the pure form it is fragile like glass. The concentration in the earth's crust is 1.5 to 7 ppm. Germanium is not found in the free state, but in combination with other elements as a mineral, such as in the principal minerals argyrodite (Ag_8GeS_6, 5–7% Ge) and germanite ($7CuS–FeS_2–GeS_2$, 8.7% Ge). Enargite, a Cu–As sulfide, is found in the western United States and contains as much as 0.03% Ge; but none of these minerals is utilized for recovery of germanium because of the small quantities available. Germanium is commonly distributed within the structure of other minerals, most abundantly in sphalerite (ZnS) in quantities of less than 1%. Some silver and tin ores contain germanium, as do some coals; the germanium content of coals in West Virginia, Illinois, and Kansas has been reported, but no commercial recovery has been made. A germaniferous lignite in the Unites States has been reported. Oak and beech humus in one locality in Germany contains 70 ppm Ge. Germanium is taken up by cereals, especially oats, from germanium-bearing soils. The principal domestic source of germanium is from the residues of cadmium derived from zinc ores. Commercial recovery of germanium has been chiefly from zinc and Zn–Cu–Pb ores, germanite, and flue dusts from coals.

Ores from the tristate area of Missouri, Oklahoma, and Kansas are concentrated and roasted to a crude zinc oxide by conventional means. Roasted ores mixed with salt and coal are sintered at a high temperature; germanium, cadmium, and some other impurities are vaporized. The vapors are then condensed and collected in an electrostatic precipitator. This by-product fume is chemically treated to obtain crude fractions of germanium, cadmium, and the other impurities.

The germanium concentrate is reacted with strong hydrochloric acid, and the resultant $GeCl_4$ (bp 86° C) is distilled off. The crude tetrachloride is purified further and finally distilled with chlorine (to hold back arsenic). The purified, redistilled $GeCl_4$ is then hydrolyzed in water to form GeO_2, which is reduced to a powdered metal by heating to 650°C in an atmosphere of hydrogen. The powdered metal is melted at 1100°C in an inert atmosphere to form ingots. When extreme metal purity is desired, multiple-zone melting and fractional crystallization are used, which make the impurities concentrate at one end of the bar.

The modern field of semiconductors owes much of its development to the early use of germanium. In 1948, William Shockley used germanium to make the first transistor. Many of the uses for which germanium is noted arise from its property as a semiconductor: in transistors, diodes, and rectifiers, replacing and exceeding the functions of vacuum tubes. Their development during World War II was responsible to a large extent for the “revolution in electronics.” Diodes are used in various types of electronic circuits, including ratio, television, telegraphy and telephony, multiposition switching, and in voltage-multiplier circuits. Small diodes are made by the millions; large ones for power generation are also produced. Transistors are utilized in radio and television as amplifiers and oscillators. Because germanium is only one of several substances with semiconductor properties, other substances such as silicon are competing with germanium as transistor diode material. Various combinations, such as arsenic and antimony alloyed with aliminum, gallium, and indium, also are being developed for these purposes.

In 1998 the largest use was in fiber optic systems (40%) followed by polymerization catalysts (20%), infrared optics (10%), electrical/solar operations (20%), with the remaining 10% used in metallurgy, chemotherapy or formation of phosphors (1).

Lenses of germanium have been made for industrial infrared work. $MgGeO_3$ is used as a phosphor. Glass in which germanium replaces silicon possesses a high refractive index and is used in wide-angle camera lenses and in microscope objectives.

Germanium is used as a catalyst in the hydrogenation of coal, and particularly as an extremely low-temperature catalyst. More recent uses are for gamma-ray detection, principally in nuclear research, activation analysis, and medical applications. It is used in gold alloys when precision casting is needed. Germanium catalysts are used in some petroleum refining operations and processes for the production of polyester fibers.

1.3 Exposure Assessment

Industrial exposures are to the dusts and fumes of the metal and its oxide during the separation and purification from the ore concentrate. Exposure to cadmium, lead, and zinc occur concomitantly during this process. In the electronics industry, exposures are confined to dopant application, diode production, and substrate production. No reports of hazardous industrial exposures have yet appeared in the literature.

Exposure assessment methods have been developed for measuring air levels of germanium tetrahydride and germanium dioxide. NIOSH does not have a method for either compound or any other germanium compounds (1a). The suggested sampling methods are given in Table 33.2.

Table 33.2. Chemical Sampling Methods and Related Data for Common Germanium Compounds

Name	Germanium Tetrahydride	Germanium Dioxide
CAS Number	[*7782-65-2*]	[*20619-16-3*]
Physical state	Gas	Solid
Monitoring media	Charcoal tube (100/50 mg sections, 20/40 mesh)	Mixed cellulose ester filter (MCEF) 0.8 mm pore size
Maximum volume	48 L	960 L
Minimum volume	24 L	480 L
Analytical method	Atomic absorption spectroscopy	Atomic absorption spectroscopy

1.3.5 Biomonitoring/Biomarkers Urine samples have been recommended as an effective medium for biological monitoring. The “tentative maximum persmissible concentration” in the urine is 40 mg/g creatinine with a reference value of 1 mg/100 g creatinine.

A molybdenum blue method has been used by Rosenfield (2) for the determination of microgram amounts of germanium in biologic samples. Although the procedure has not been reported in detail, a critical examination of the optimal conditions for analysis of microgram quantities with an error of 5% is given by Shaw and Corwin (3). A spectrographic procedure, adapted for the analysis of

germanium in silicon alloys over a concentration range of 1 to 98 mol.% Si, with a standard deviation of 8%, has been reported (4). Atomic absorption spectroscopy has not been reported for determining small quantities of germanium, but electron probe X-ray microanalysis has been employed to determine tissue concentrations (5).

1.4 Toxic Effects

There is no know biologic requirement for germanium, germanates, or any organogermanium compound. Germanium deficiency has not been demonstrated in any animal. The estimated average dietary intake of germanium in humans is 1.5 mg/d. Germanium is widely distributed in edible foods, such as baked beans (5 ppm), canned tomato juice (5 ppm), and canned tuna (3 ppm).

Neutron-activated, commercially cast germanium metal dust (Ge) with a mean particle size of 1.7 mm proved innocuous to rats exposed by inhalation for 1 h at an unspecified concentration, as did GeO_2 of particle size 0.45 mm (6). Harrold et al. (7) had previously reported that GeO_2 is innocuous, based on their results of intraperitoneal injection at large doses (100 mg) in guinea pigs and intrapleural or intravenous injections in rabbits. Dermal application of either pure or buffered solutions of GeO_2 in humans and animals are also not harmful. Later work by Rosenfeld and Wallace (8) found that the maximal tolerated single intraperitoneal dose of neutralized (pH 7.3) GeO_2 approximated 600 mg/kg for the rat; the corresponding minimal lethal and "absolute" lethal doses were 700 and 1200 mg/kg, respectively. The estimated intraperitoneal LD_{50} was 750 mg/kg. Similarly administered germanium–annitol and germanium–glycerin were tolerated at 140 mg/kg. Most of the deaths from GeO_2 were rapid, occurring within 12 h; the remaining deaths occurred within 24 h. Gross tissue changes consisted of edematous, hemorrhagic lungs, multiple petechiae in the walls of the small intestine, and peritoneal effusion. The peritoneal fluid was voluminous and rich in protein. Death was usually preceded by hypothermic shock (rectal temperatures sometimes below 80°F) and almost complete respiratory depression. No effects on the nervous system or on the blood were found. Loss of retroperitoneal fat was due to the alkalinity of Na_2GeO_3, and not to germanium per se, confirming the results of Harrold et al. (7).

Inhalation of GeH_4 in minimally effective concentrations (70 mg/m^3 for GeH_4) for 2–15 d resulted in nonspecific and nonpersistent changes in the nervous system and kidneys and in the blood composition. When adequate physiological loads were applied, a strain on the compensatory mechanisms was discernible after two to four inhalation periods. Under analogous conditions, $GeCl_4$ at 4 mg/m^3 caused changes in the respiratory system that persisted (9).

Acute (4-h) and subacute (4-wk) inhalation toxicity studies of germanium metal powder (purity 99.8%, mean particle size 2.0–2.4 mm) were carried out in young adult Wister rats. The 4-h LC_{50} value of germanium metal powder in rats is greater than 5.34 g/m^3. Rats were exposed to 0, 9.9, 65.1, or 251.4 mg/m^3 for 6 h/d, 5 d/w, for 30 d. At the end of the exposure period, fasting blood glucose was decreased in males exposed to the high concentration. In females of this group, blood creatinine and urea levels and urine volumes were increased, but urine density was decreased. Increased blood creatinine levels and urine volume and decreased urine density were also observed in females exposed to 65.1 mg/m^3. The absolute and relative lung weights were increased in rats in the mid- and high-concentration groups. Histopathological evaluation revealed accumulation of particulate material in the lungs of all treated groups, accumulation of alveolar macrophages in the mid- and high-concentration groups, and alveolitis, mainly in the high-concentration group. After a 4-w recovery period, urine volume was increased in males that had been exposed to germanium. In exposed rats of both sexes, lung weights were still increased and histopathological changes were present, but to a lesser extent than at the end of the exposure period. The no-adverse-effect level in the 4-w study was 9.9 mg/m^3 air (10).

Additional acute and subacute studies were performed on wistar-rats to assess the effects of exposure

to amorphous or hexagonal germanium dioxide. Exposures were for 4 h or 4 wk. A variety of biochemical and histopathological variables were examined at various times following exposures. At the end of the study, changes were identified consisting of gray spotted lungs with macrophage accumulation. In the subacute study, alterations included decreases in body weights, hematocrits, thrombocyte counts, fasting glucose levels, total protein concentrations, and urine density and pH, and increases in neutrophil and white blood cell counts, plasma alanine aminotransferase and aspartate aminotransferase activities, plasma urea nitrogen, plasma bilirubin, urinary volume, and kidney, spleen, heart, and lung relative weights. These changes occurred primarily in rats exposed to the highest germanium dioxide levels. Histological evaluation of the kidney revealed changes in the renal tubular epithelium. In the acute study, the LD_{50} for amorphous germanium dioxide was calculated to be 3.10 g/m^3 and 1.42 g/m^3 for hexagonal germanium dioxide, while the NOAEL (no observed adverse effect level) in the subacute study using hexagonal germanium dioxide was 72 mg/m^3 (10a).

Ohinishi (1989) used rats and monkeys to assess the neurotoxicity of germanium dioxide. Rats were administered orally and intraperitoneally doses of 100 mg/kg/d of germanium dioxide 3 days a week for 8 weeks and 400 mg/kg/d once a week for 8 weeks. No degeneration of the peripheral nerves was observed. In addition to the rats, two monkeys were also exposed via the oral route to 30–40 mg/mg/day, 5 days a week for 8 months. As with the rats, no degeneration of peripheral nervous system was observed. However, proteinuria and elevated blood urea nitrogen were observed (10b).

The effects of exposure to germanium dioxide and germanium tetrachloride were studied in chickens to assess whether germanium affected weight gain (10c). In one experiment there were 9 groups of birds. They were fed a basic diet supplemented with 0, 1, 10, 100 or 1000 ppm germanium (as germanium dioxide) and 1, 10, 100, 1000 ppm germanium (as germanium tetrachloride). Germanium dioxide at 10 ppm improved growth and feed conversion by 12% and 7.5% ($p < 0.05$), respectively. The fattening effect was not observed for any of the germanium tetrachloride exposed chickens. In the highest exposure group (1000 ppm germanium from either germanium dioxide or germanium tetrachloride) all the birds died in 17 and 28 d, respectively. In the second experiment, there were 8 groups of birds. They were also fed a basic diet and 0, 2, 5, 10, 20, 50, 100, and 200 ppm germanium as germanium dioxide. The 5 ppm group showed a slight growth-promoting effect (3.3%) over the controls. No adverse effects were observed in any of the groups in experiment 2.

A study on the suppressive effects of Ge-132 (carboxyethyl germanium sesquioxide) on protein glycation was undertaken to test the hypothesis that reduced protein glycation would result in reduced cataract formation. Sprague–Dawley rats were fed a 50% galactose diet, a diet that historically leads to development of cataracts in these rats. One group of rats received topical saline; the other group received Ge-132 in saline four times per day. The lenses were examined for cataract development starting on day 3 and continuing through day 21. The study found that the abnormalities associated with cataract formation were present in both groups but that the treated group experienced delayed cataract development (10d).

1.4.1.2 Chronic and Subchronic Toxicity Germanium dioxide (GeO_2) behaves as a potent antimutagen on frameshift-type reverse mutations induced by Trp-P-2 (3-amino-1-methyl-55H-pyrido[4,3-blindole]) in strains of *Salmonella typhimurium* TA98 and TA1538 (11). This observation has led to the investigation of the chronic nephrotoxicity in rats orally administered GeO_2 for 24 wk. Increased blood urea nitrogen (BUN) and serum phosphate, as well as decreased creatinine clearance, weight loss, anemia, and liver dysfunction, were apparent at week 24 only in the GeO_2-treated rats. Vacuolar degeneration and granular depositings were observed by light microscopy in the degenerated renal distal tubules of the rats. Electron microscopy revealed electron-dense inclusions in the swollen mitochondrial matrix of the distal tubular epithelium among the GeO_2-treated rats. Although systemic toxicities were reduced after GeO_2 was discontinued at week 24,

renal tubulointerstitial fibrosis became prominent even at week 40. A Ge-K alpha X-ray spectrum was clearly demonstrated in the mitochondrial matrix of the distal tubular epithelium in the GeO_2 rats by electron probe X-ray microanalysis. The renal tissue content of germanium was high at weeks 24 and 40 in the GeO_2-treated rats. It appears that residual GeO_2 remains for a long time, even after the cessation of intake (5).

Chronic nephrotoxicity was investigated in rats administered germanium dioxide and carboxyethyl germanium sesquioxide for 24 wk. The germanium dioxide group experienced increased blood urea nitrogen, increased serum phosphate, as well as decreased creatinine clearance, weight loss, anemia, and liver dysfunction. Degeneration of the renal distal tubules was observed. There was also observable granular deposition in the degenerated tubules. These effects were only observed in the germanium dioxide exposed group. It was concluded that germanium dioxide causes this characteristic nephropathy while carboxyethyl germanium sesquioxide does not (11a).

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Inorganic germanium as neutralized GeO_2 is readily absorbed following small (a few milligrams) oral, subcutaneous, intramuscular, or intraperitoneal doses in the rat (2). Blood concentrations somewhat less than 10 mg/g are attained within a few hours after administration. Following a single small dose, germanium leaves the bloodstream within a few hours. Germanium is transported via the blood unbound to protein. Germanium is widely distributed throughout the body and is not selectively retained in any tissue. After 1 wk following a moderate intraperitoneal dose (40 mg Na_2GeO_3/kg) all germanium that had gone to the tissues had disappeared. Germanium is excreted by both the kidneys and the gastrointestinal tract, but the kidney is the chief excretory organ (80 versus 13%).

Excretion studies of elemental Ge and GeO_2 in the rabbit and rat showed elimination chiefly via the urine (12). Essentially the same type of kinetic activity occurred with neutron-activated Ge and GeO_2 dusts by inhalation (13). Rats exposed to (unmeasured) atmospheres of Ge for 1 h at respiratory particle sizes (1.7 and 0.45 mm mean diameter, respectively) showed moderately fast elimination of the Ge from the lungs; 52% disappeared in 1 d and 82% in 7 d, the longest period of observation. The kidneys and liver contained only trace amounts at 7 d. Germanium dioxide-Ge was cleared somewhat more rapidly from the lungs, kidneys, and liver (79% in 1 d); and only trace amounts remained in these organs at 4 and 7 d.

Spirogermanium is a new metallic investigational anticancer drug. The metal germanium is substituted for a one-carbon moiety in the ring structure to form spirogermanium. This drug inhibits DNA and RNA synthesis in HeLa cells. The mode of action has not been fully elucidated; however, spirogermanium is not a phase- or cell-cycle-specific drug and inhibits DNA, RNA and protein synthesis, and protein synthesis being the most susceptible to this agent. Spirogermanium has revealed activity *in vivo* against intraperitoneally implanted Walker 256 sarcoma, 13762 mammary adenocarcinoma, and 11095 prostatic carcinoma in rats, but no antitumor activity *in vivo* was found in the murine tumors used in L 1210 and P 388 leukemia, B 16 melanoma, or Lewis lung carcinoma. In addition, spirogermanium has shown cytotoxic activity *in vitro* against several human tumor cell lines at concentrations (1 mg/mL) that were toxic to the cultured rat neurons. Although spirogermanium has no effect on normal bone marrow colony-forming cells in mice, dogs, or humans, it has shown cytotoxic activity *in vitro* against human myeloid leukemia cell line K 562 at clinically acceptable concentrations. These *in vitro* findings indicating selective cytotoxic activity against leukemia cells suggest this agent as a candidate for clinical studies in acute and chronic leukemias. Spirogermanium lacks bone marrow toxicity, unlike many other anticancer drugs. This has been confirmed in preclinical toxicology and clinical studies. However, moderate, predictable, and reversible CNS toxicity is dose limiting. Activity in malignant lymphoma, ovarian cancer, breast cancer, larger bowel cancer, and prostatic cancer was also reported in the clinical studies. A dose of 80–120 mg/m^2 (body surface) given by 60-min infusion three times a week was used in the clinical studies (14).

1.4.1.6 Genetic and Related Cellular Effects Studies Benzo(a)pyrene (BaP) is a known carcinogen and mutagen found in tobacco smoke and a number of other environmental sources. Olson et al. (1995) conducted a study to assess the ability of germanium dioxide to reduce the mutagenic potential of BaP in the Ames assay. In general, germanium dioxide was found to be relatively ineffective in reducing the mutagenic potential of BaP. In three out of four strains tested germanium showed some effect, and then only at highest concentrations, for example, 400–600 mg/plate (14a).

1.4.2 Human Experience There have been 18 reported cases of acute renal dysfunction or failure, including two deaths linked to oral intake of germanium elixirs containing GeO_2 or Ge. In these cases, biopsies show vacuolar degeneration of the renal tubular epithelial cells in the absence of glomercular changes, without proteinuria or hematuria. Serum creatinine levels have been well above 400 mmol/L in such patients. In 17 of 18 cases, accumulated elemental germanium intakes reportedly ranged between 16 and 328 g over a 4–36 mo period, or between 100 and 2000 times the average estimated dietary intake for humans. In surviving patients, renal function improved after discontinuation of germanium suplementation. However, in no case was recovery complete (15).

In a typical case a 55-year-old woman was admitted to a hospital, complaining of general malaise, muscular weakness, anorexia, and weight loss. She had a history of ingesting a germanium compound for the preceding 19 months, with a total dose of 47 g as Ge. The patient had renal failure (BUN, 44 mg/dL; serum creatinine, 2.6 mg/dL) without abnormal findings in urinalysis, and muscular and nervous damage. Polymyositis was diagnosed and prednisolone given. She did not improve. The neuromuscular signs continued to develop until she died. In the histopathological evaluation of the kidney, lipofuscin granules increased in the cells of the thick ascending limb of Henle's loop to the distal convoluted tubule accompanying mild tubular atrophy. Some of the tubules of these segments had vacuolar degeneration or desquamation. No glomercular and vascular changes were observed. Germanium was found in serum, urine, and various tissues, including the spleen, liver, kidney, adrenal gland, and myocardium, whereas in normal individuals germanium cannot be detected in serum, urine, or tissues (16). The principal clinical toxic effects observed were neurological, manifested as lethargy, dizziness, and ataxia; and a grand mal seizure was produced after an accidental overdose. A partial response was achieved in a patient with lymphocytic leukemia (17).

In another clinic, five patients were evaluated who had taken inorganic germanium preparations over a prolonged period. In each patient, renal function had deteriorated with no proteinuria or hematuria. Through histological examination the kidneys were found to have widespread tubular degeneration and interstitial fibrosis with minor glomercular abnormalities. The most common symptomatolgy included gastrointestinal symptoms such as vomiting, anorexia, and weight loss; however, one patient had peripheral neuropathy and myopathy. Germanium was detected in the hair or nails of the patients (17a).

Another case involved a 4-year-old female who had orally received 225–450 mg/kg/day of germanium dioxide for the previous 28 months. The child had suffered from gait disturbances and muscle weakness for the past 22 months. Findings were made of chronic renal failure, anemia, diffuse muscle atrophy, tongue fasciculation, and reductions in median and ulnar nerve conduction velocities. On the seventeenth day of hospitalization the child died of renal failure. Autopsy showed damage to the renal tubular cells, widespread nerve fiber loss, and axonal degeneration (17b).

No recent studies of the toxicity of the germanes appear to have reached the open literature, but early, limited toxicity tests (30 and 60 min) of GeH_4 indicated 610 mg/m^3 for 30 min was ultimately lethal to a mouse, whereas 480 mg/m^3 for 60 min was lethal to a mouse but not a guinea pig, and in a rabbit 310 mg/m^3 for 60 min produced only dyspnea, not death (18). Hemoglobinuria was noted in the animals, thus resembling AsH_3 in this respect. Thus the order of increasing toxicity would appear

to be GeH_4, AsH_3, and SnH_4, but comparisons on such limited data are very uncertain. The higher hydrides of Ge are noted (6) to be less toxic than GeH_4, but no supporting evidence is given.

1.5 Standards, Regulations, or Guidelines of Exposure

Germanium tetrahydride is the only germanium compound for which air standards have been established (19). The NIOSH REL and the ACGIH TLV are 0.2 ppm (approximately 0.63 mg/m^3). In Australia and the United Kingdom the permissible level is also 0.2 ppm. The toxicity, hemolysis, is similar to that of stibine, but GeH_4 is believed to be about half as toxic as stibine (20). No IDLH (immediately dangerous to life and health) level has been established for any of the germanium compounds, including germanium tetrahydride. The TLV for germanium tetrahydride was based on acute toxicity. There are currently no TLV, RELs, etc. for other germanium compounds.

Germanium, Tin, and Copper
James H. Stewart, Ph.D., CIH, Donald V. Lassiter, Ph.D.

2.0 Tin

2.0.1 CAS Number:

[*7440-31-5*]

2.0.2 Synonyms:

Tin, metal, metallic tin, tin element, tin powder, tin paste

2.0.3 Trade Names:

C.I. Pigment Metals 5, Silver Matt Powder, Wang

2.0.4 Molecular Weight:

118.69

2.0.5 Molecular Formula:

Sn

2.1 Chemical and Physical Properties

Tin is a solid, rather unreactive metal in Group IVA of the periodic table. Its chemical symbol, Sn, is derived from stannum, the Latin word for tin. Tin is known as Etain in French and Zinn in German. Tin has 10 naturally occurring stable isotopes, the largest number of stable isotopes of any element. The most abundant stable isotope is one having a mass of 120 (32.85%). Tin has a large number of unstable isotopes with half-lives ranging from 2.2 min to 10^5 years.

Tin has played a major role in the development of civilization. The Bronze Age began approximately 3500 B.C. with the discovery that easily smelted soft copper could be made harder and stronger by alloying with tin. The first inclusion of tin in bronze was probably an accidental result of tin ore being found in copper ore; pure tin was most likely obtained at a later date.

The physical and chemical properties of tin and some of its compounds are listed in Table 33.3.

Germanium, Tin, and Copper
James H. Stewart, Ph.D., CIH, Donald V. Lassiter, Ph.D.

3.0 Copper

3.0.1 CAS Number:

[*7440-50-8*]

3.0.2 Synonyms:

NA

3.0.3 Trade Names:
NA
3.0.4 Moleculer Weight:
63.5
3.0.5 Molecular Formula:
Cu
3.1 Chemical and Physical Properties
Copper is located in Group IB of the of the periodic table and was one of the first metals used by humans and is second only to iron in industrial importance.

The electrical conductivity and malleability of copper are its most importance properties. The boiling point of copper is 2567°C, the melting point is 1083.4°C, and the density is 8.92. Other properties of copper compounds are shown in Table 33.5. Copper is slowly attacked by dilute hydrochloric acid or dilute sulfuric acid and is slowly soluble in ammonia water (56).

Table 33.5. Physical and Chemical Properties of Selected Cu Compounds

Form	At. or Mol. Wt.	Sp. Gr.	MP (°C)	BP (°C)	Solubility
Copper, Cu	63.57	8.92	1083	2567	Insol. water; sol. HNO_3, hot H_2SO_4; v. sl. sol. HCl, NH_4OH
Copper oxide, CuO	79.54	6.4	Dec. 1226	—	Insol. water; sol. NH_4Cl, KCN
Copper acetate, $Cu(C_2H_3O_2)_2 \cdot 6H_2O$	199.65	1.88	115	Dec. 240	72 g/L cold water; sl. sol. alcohol
Copper carbonate, $CuCO_3 \cdot Cu(OH)_2$	221.11	4.0	Dec. 200	—	Insol. cold water; dec. hot water
Copper chloride, $CuCl_2$	134.44	3.386 (25°C)	620	(93 dec. to CuCl	706 g/L (0°C); sl. sol. alcohol
Copper cyanide, $Cu(CN)_2$	115.58	—	Dec.	—	Insol. cold water, sol. acids, alkalies, KCN

3.2 Production and Use (128)
Copper, like silver and gold, the other members of the noble metals, is found free in nature. Because it was found free in nature, was malleable, and could be utilized in making tools copper was in use before 5000 B.C. A naturally forming “patina” of copper carbonate that covers exposed copper prevents further oxidation. The name *copper* is derived from the Latin word *cuprum*, which, in turn, is derived from an earlier word, *cyprium* or “Cyprium metal.” The Romans obtained much of their copper from Cyprus, as the name implies.

Copper is found at a concentration of 50 ppm in the earth's crust, and its concentration in seawater is 0.001 to 0.02 ppm. Although copper can also be obtained in an almost pure state in nature, about 85% of the copper mined today is derived from low-grade ores containing 2% or less of the metal. The major ore is chalcopyrite ($CuFeS_2$). Ores are removed by open-pit mining as well as underground mining. Ores containing as little as 0.4% Cu can be profitably recovered in open-pit mining. The sulfide ores such as chalcopyrite and chalcocite must be enriched before smelting

begins. In this ore-flotation procedure, the ore is crushed, powdered, and agitated with water containing a foaming agent and an agent to make the copper-bearing particulates water repellent. The particles are then accumulated on the foam, which is removed and heated to about 800°C to remove water, arsenic, antimony, and sulfur. The residue is mixed with silica and melted in a furnace at 1500°C. Of the two liquid layers produced, the upper layer of silicate slag is removed. The lower layer (matte) consists of copper sulfides and oxides. Silica or siliceous copper ore is added to the matte, and the liquid is aerated. The iron slag is removed, and the remaining copper sulfide is reduced to copper by heating in limited air. The remaining molten copper is about 98% pure. This material can be further purified by electrolytic refining. The impure copper is the anode in this process, and pure copper strips are the cathode. Aqueous copper serves as an electrolyte. The copper is transferred from the anode to the cathode. The anode sludge may contain silver and gold, making the process more economically feasible. Oxidized copper ores such as cuprite and tenorite can be directly reduced by heating with carbon in a furnace.

In the United States the major use (about 50%) for copper is an an electrical conductor, and copper piping is widely used in private and commercial plumbing.

Bronze, which is composed of copper and as much as 10% tin, was one of the first alloys used by humans. The brasses are also a most useful group of alloys. Copper and zinc are the main components of brass. Brasses having less than 58% copper are of limited application. Medicinally, copper sulfate has been used as an emetic, and copper is a component of several intrauterine devices, responsible for their contraceptive effects.

Copper, particularly copper sulfate, has many uses in agriculture. Copper sulfate is used as a fungicide, an algicide, a source for copper in animal nutrition, and in some fertilizers.

3.3 Exposure Assessment

U.S. Environmental Protection Agency (EPA) identified copper contamination at 210 of the 1177 total sites on the National Priorities List (NPL) (129). Workplace exposure to copper dust and fumes may be determined using NIOSH method 7029 (132).

Copper dusts and mists may be collected on a particulate filter (0.8 mm); the filter is digested with acid and analyzed. Atomic absorption spectrometry is the preferred method of analysis (132).

Copper is one of the metals to which workers have a great deal of occupational exposure. It is estimated that 46,481 workers are exposed to copper on a full-time basis. Of 12,035 combined federal and state OSHA samples, 7.8% were above the PEL, and 15% were above half of the PEL (130). The adverse health effects associated with copper production may be due to the large amounts of sulfur oxides generated or because of the impurities, such as arsenic and antimony, which are associated with the copper ores.

The Agency for Toxic Substances and Disease Research (129) estimated that the concentration of copper in air ranges from 1 to 200 ng/m^3. The average concentration in drinking water ranges from 20 to 75 ppb, although morning concentrations may reach 1 ppm due to water standing overnight in copper pipes and brass faucets. Uncontaminated soil may contain between 2 and 250 ppm of copper, although soil concentrations may reach nearly 7000 ppm in the vicinity of copper production facilities. The average daily dietary intake (water and food) is approximately 1 mg/d. Copper is essential to health and longevity in humans (131).

3.4 Toxic Effects

As with many essential metals, biochemical mechanisms have evolved that control the oral absorption and excretion of copper in order to maintain an appropriate balance. Copper is found in more than a dozen proteins, including cytochrome C oxidase. Relative to metabolic requirements, all human diets have sufficient copper. The daily requirement is 2–3 mg (133).

Clinically significant copper deficiency is rare and limited to instances of marked gastrointestinal

malabsorption, drastically reduced dietary intake, or to the presence of an X-linked disorder of copper absorption and transport known as Menkes's steely- or “kinky-hair disease”. Menkes's disease in males is characterized by physical and mental retardation, with widespread degeneration of the brain, hypothermia, and death occurring in the first few years of life (131).

The homeostatic mechanisms controlling oral absorption also make copper toxicosis rare. In humans, about half of the dietary copper is not absorbed, but is excreted in the feces. Urinary exretion accounts for approximately 3% of the absorbed dose. The fraction of the intake that is absorbed decreases as the dose increases. Thirty percent is absorbed at 100 mg, whereas about 56% is absorbed at doses of 0.4–4.5 mg.

After absorption, copper is transported via the plasma bound to albumin or amino acids. Almost all the copper is deposited in the liver. Free copper ions are not normally found in the body fluids. Eighty percent of absorbed copper is found in the cytosol bound to hepatocuprein, copper-chelatin, or metallothionein. Incorporation of copper into metallothionein apparently requires prior binding of the copper to glutathione, thus defining a requirement for intracellular availability of glutathione. Metallothionein, a cysteine-rich metal-binding protein, serves as a temporary, intracellular binding site for copper, which, as a free ionic metal, is a strong oxidizing agent, capable of generating hydroxyl radicals. The remaining 20% of absorbed copper is bound to other copper proteins, such as cytochrome C oxidase, or is sequestered by the lysosome. Despite absorption, the body burden of copper does not increase with age. The secretion of some copper into the blood and incorporation into ceruloplasmin, a copper-containing globulin of blood plasma, plays an important role in hematopoiesis and oxygen reduction. Copper excretion from the lysosome maintains a balance of about 150–300 mg of ceruloplasmin containing 0.5–1 mg of copper. Ceruloplasmin is broken down in the liver, and 0.1 mg is excreted into the intestine. Biliary copper may not be reabsorbed because it is bound to protein.

The body content of copper in animals on an average diet is about 2 ppm in fat-free tissue. The highest concentrations are in the liver and the brain, with lesser amounts in the heart, spleen, and kidneys. The concentration in the brain doubles from birth to maturity (131).

Copper toxicity in humans as a result of oral intake occurs only in cases of attempted suicide or when there is a genetic defect in copper metabolism, as in Wilson's disease. However, ingestion of large amounts of copper salts, most often copper sulfate, can result in death. Vomiting, sometimes with a blue-green color of the vomitus, hematemesis, hypotension, melena, coma, and jaundice are symptoms. Centrilobular hepatic necrosis may be an autopsy finding (134). The therapeutic emetic dose of copper sulfate is 300 mg in water.

In Wilson's disease, an autosomal recessive hereditary disease, the copper steadily accumulates first in the liver, and then in other tissues. Wilson's disease has been found in every racial group. The illness is inherited as an autosomal recessive trait, with a general prevalence of about 1 in 200,000. Approximately, there is a single “Wilson's disease gene” in every 200 people. The heterozygotes remain free of pathological manifestations of Wilson's disease. Relatives, particularly siblings of patients with Wilson's disease, must be examined, even if they appear perfectly healthy because of the autosomal recessive transmission of the illness. Fortunately, biochemical findings in patients with the manifest disease have made it possible to confirm the diagnosis in an asymptomatic individual when there are less than 20 mg ceruloplasmin/100 mL serum and more than 250 mg Cu/g dry liver (131). Decreased serum concentrations also have been found in about 20% of the healthy heterozygous carriers of the one abnormal “Wilson's disease gene” and in all newborns during the first 6 months of life. Ceruloplasmin is generally less than 20 mg/100 mL in those individuals with Wilson's disease, whereas it normally ranges from 20 to 50 mg/100 mL. Damage to the liver and central nervous system is usually fatal. Chelation with D-penicillamine is most often a successful treatment (131).

Almost all patients with Wilson's disease exhibit a lifelong deficiency of the plasma copper protien

ceruloplasmin and an excess of hepatic copper. This excess copper in the liver may be caused, in part, by impairment of lysosomal excretion of hepatic copper into bile, and is associated with diminished or absent hepatic synthesis of ceruloplasmin. It is remarkable that retaining only 1% of the dietary intake of copper (10–20 mg/year) is sufficient to cause Wilson's disease. During the early stages of Wilson's disease, the liver is capable of binding as much as 30 to 50 times its normal concentration of copper with little, if any, overt clinical disorder. Hepatic copper is released into the bloodstream, and in the face of massive necrosis of hepatic parenchyma, that action may suddenly infuse large amounts of copper into the plasma, inducing severe hemolysis and jaundice. In most patients, however, the metal diffuses into the circulation gradually, causing the plasma concentration of free copper to rise 5–10 times, to about 25–50 mg/100 mL. Characteristic ultrastructural changes, fatty degeneration of hepatocytes, necrosis, collapse of parenchyma, and postnecrotic cirrhosis occur in the liver. Later, the excess hepatocellular copper is sequestered by lysosomes, a process that seems to render the metal innocuous for other cytoplasmic organelles. Unless the patient with Wilson's disease succumbs to hepatic necrosis, the toxic effects of copper ultimately are manifested primarily in the central nervous system and kidneys. In the corneas, copper deposits are visible as Kayser–Fleischer rings, blue crescents. In about half of all patients, the first clinical evidence of Wilson's disease is dysfunction of the liver. Ascites, esophageal variceal hemorrhage, a syndrome mimicking toxic or infectious hepatitis, hemolysis caused by sudden release of sequestered copper, deficiency of clotting components, hypersplenism, or gonadal dysfunction may occur. In almost all other patients, neurological or psychiatric disorders are the initial clinical manifestation. The neurological picture may resemble Parkinsonism, multiple sclerosis, chorea, dystonia, or any combination of these diseases. The usual onset is insidious. Dysarthria is a frequent sign in children; and often subtle incoordination, resting or intentional tremors, athetoid movements, rigidity, or dystonic posturing, and distortion can occur at all ages. Epileptiform seizures have been reported but are unusual. Psychiatric disorders may accompany the neurological symptoms or may precede any other evidence of disease. In young adults the spectrum ranges from mild behavioral disturbance, through marked deterioration of schoolwork and neurosis, to a manic–depressive or schizophrenia like psychosis, which may appear in all age groups. The emotional disturbance may be partly a reaction to the somatic dysfunction (131).

Reports from India have indicated infants and children can develop a condition termed Indian Childhood Cirrhosis (ICC) from drinking milk boiled and stored in brass vessels. This condition has largely disappeared from India following preventive measures. Reports from the United States show children developing severe liver disorders from ingestion of 10 mg Cu in contaminated milk. It is possible that the homeostatic mechanisms controlling copper absorption are not developed early in life (135).

Copper is an important component of the human metalloezyme copper/zinc superoxide dismutase (cu/znSOD). This enzyme protects oxygen-metabolizing cells from the oxidizing actions of superoxide free radicals. It catalyzes the following reaction:

$$2O_2^- + 2H^+ \rightarrow O_2 + H_2O_2$$

The damaging superoxide ion (O^{2-}) is formed *in vivo* via reduction of O_2 during various enzymatic reactions, or by ionizing radiation. This ion has been implicated in aging, lipid peroxidation and such neurologic diseases as amyotrophic lateral sclerosis (ALS) and Alzheimer's Disease. Also, there is some evidence from animal studies that copper deficiency promotes oxidative damage. Hence, while free copper ions can be cytotoxic oxidizing agents, copper is important as an active component of the antioxidant enzyme, cu/znSOD.

Contact dermatitis associated with copper has been reported, but few cases of dermatitis caused by copper metal or its compounds occur in industry. A green coloration, noted more than a century ago among copper workers, is mentioned. A similar localized coloration is caused today from wearing jewelry made of copper or high-copper alloys. There have been occasional reports of allergic contact

dermatitis following patch testing with copper pennies or copper sulfate (136, 137). Eye irritation has been reported among sheet metal workers (138).

Copper's usefulness in contraception is based on its spermatocidal activity. For this application, copper concentrations must range from 8 to 60 mg/mL in human uterine fluid (139). *In vitro*, copper spermatocidal activity has been found to be potentiated by washing the spermatozoa free of seminal plasma. Once immobilized, spermatozoa do not regain motility, even after extensive washing, prolonged dialysis, or treatment with copper-specific chelating agents. Apparently, copper induces a change in the properties of the spermatozoa, which results in irreversible immobilization (140).

Occupational exposure to copper fume at 0.1 mg/m^3 causes nausea and metal fume fever, with reversible flulike symptoms (141). Metal fume fever (also called brass founder's ague) is a transient condition and is characterized by fever, chills, muscle pain, and vomiting. Recovery normally occurs within 24 to 48 h. Tolerance may develop, but is generally lost over the weekend. Metal fume fever has also been observed among workers exposed to freshly formed zinc fume.

Metal fume fever occurred among workers involved in cutting brass pipes with electric torches in an enclosed, poorly ventilated steam condenser. Symptoms most commonly reported among the 26 workers were fever (21), dyspnea (23), chills (21), headache (21), and nausea (19). Fourteen of the workers experienced the symptom of an unusual sweet or metallic taste in the mouth. Clinical signs were limited to wheezing or rales in eight patients; leukocytosis (21) and an elevation of band cell forms (20) were seen in a total of 24 workers. The average time between exposure and onset of symptoms was 5 h. None of three workers who spent less than 1 h in the condenser became ill, whereas 25 of the 26 who spent more than 1 h became ill. Five of 12 workers had urine copper levels in excess of 0.05 mg/L (142).

Reports of granulomatous and fibrotic changes among vineyard workers using a Bordeaux mixture containing 1–2% copper sulfate and hydrated lime have been made (143, 144). This mixture is no longer used in the United States.

Among hamsters, 3.3 mg/m^3 of copper sulfate decreased cilia activity and caused alveolar thickening. This effect was not present in mice (145).

Although an increase in lung cancer has been reported among workers in copper smelters, this is generally accepted as the result of exposure to arsenic trioxide and, perhaps, sulfur dioxide (146). The animal bioassays on copper and copper compounds do not provide any support for the classification of copper as an occupational carcinogen. The carcinogenicity of a copper-containing compound, copper hydroxyquinoline, was studied in two strains of mice ($B6C3F_1$ and $B6AKF_1$). Groups of 18 male and 18 female 7-day-old mice were administered 1000 mg copper hydroxyquinoline/kg (180.6 mg Cu/kg) suspended in 0.5% gelatin, daily until they were 28 days old, after which they were administered 2800 ppm (505.6 ppm Cu) in the feed for 50 additional weeks. No statistically significant increases in tumor incidence were observed in the treated 78-week-old animals. In the same study, a single subcutaneous injection of gelatin (control) or 1000 mg/kg of copper hydroxyquinoline (180.6 mg Cu/kg) suspended in 0.5% gelatin to groups of 28-day-old mice of both strains produced, after 50 days of observation, an increased incidence of reticulum cell sarcomas in the male $B6C3F_1$ mice, compared with controls. No tumors were observed in the treated male $B6AKF_1$ mice, and a low incidence of reticulum cell sarcomas was observed in the treated female mice of both strains (147). Intramuscular injections containing 20 mg of cupric oxide (16 mg Cu), cupric sulfide (13.3 mg Cu), and cuprous sulfide (16 mg Cu), into thighs of 2- to 3-month-old Wistar rats caused no injection-site tumors after 20 months of observation. Other tumors were observed at a very low incidence in the rats receiving cupric sulfide (2/30) and cuprous sulfide (1/30) (148). The International Agency for Research on Cancer does not list copper or any copper compounds as suspected carcinogens for animals or humans.

Mutagenic data are equivocal for copper or its salts. No increases in mutations in *E. coli* and *S. typhimurium* strains (TA98, TA1535, TA1537, and TA1538) incubated with up to 5 mg copper quinolinolate/plate and in *S. typhimurium* TA98 and TA100 incubated with up to 5 mg copper sulfate/plate were found (149). Negative results were also obtained with copper sulfate or copper chloride in assays using *S. cerevisiae* (150) and *Bacillus subtilis* (151–153). Dose-related mutagenic effects in *E. coli* with 2–10 ppm copper sulfate in a reverse mutation assay were reported (154). Errors in DNA synthesis from poly-(c)templates have been induced in viruses incubated with copper chloride or copper acetate (155). Chromosomal aberrations were induced in isolated rat hepatocytes when incubated with copper sulfate (156). Casto et al. (157) showed enhanced cell transformation in Syrian hamster embryo cells infected with simian adenovirus following the addition of cuprous sulfide and copper sulfate. Law (158) reported increases in the percent of lethals observed in Drosophila larvae and eggs when exposed to copper by microinjection (0.1% copper sulfate) or immersion (concentrated aqueous copper sulfate), respectively.

3.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV of 0.2 mg/m^3 for copper as copper fume and 1 mg/m^3 for copper dusts and mists is to prevent irritation (20). The OSHA PEL for copper dusts and mists 1 mg/m^3 and for copper fume is 0.1 mg/m^3, as an 8-h TWA (159). OSHA declined to increase its PEL to the concentration recommended by ACGIH because the latter's TLV was based on a 1972 personal communication. This communication stated that workers in the United Kingdom that were exposed to copper fumes at concentrations up to 0.4 mg/m^3 during welding and copper metal refining operations failed to experience ill effects. OSHA's position was that the Agency must demonstrate that exposed workers will not be placed at increased risk even after the limit has been raised. The National Institute for Occupational and Health recommended exposure level (REL) of 1 mg/m^3 applies to copper dusts and mists, with a REL of 0.1 mg/m^3 for copper fumes. The ACGIH TLV for copper dusts and mists is 1 mg/Cu and for copper fume is 0.2 mg/m^3.

Initial physical examinations for workers likely to be exposed to copper in the course of their employment should include respiratory and liver function tests and a screening for Wilson's disease. Normal concentrations of copper in blood from nonexposed workers range from 0.8 to 1.6 mg/L, with an average copper blood concentration of 1.2 mg/L.

Germanium, Tin, and Copper

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Lead

Robert A. Goyer, MD

A. Inorganic Lead Compounds

1.0 Lead

1.0.1 CAS Number: [*7439-92-1*]

1.0.2 Synonyms: NA

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 207.19

1.0.5 Molecular Formula: Pb

1.0.6 Molecular Structure: Pb

1.1 Chemical and Physical Properties

Lead is a lustrous silvery metal that tarnishes in the presence of air and becomes a dull bluish gray.

The chemical symbol, Pb, is derived from *plumbum*, the Latin word for waterworks, because of lead's extensive use in ancient water pipes. Lead has four electrons in its valence shell, but only two ionize readily. The usual oxidation state of lead in inorganic compounds is therefore +2 rather than +4. Lead generally forms stable compounds. Four stable lead isotopes exist in nature (208, 206, 207, and 204 in order of abundance). Through the years lead mined from deposits of different geologic eras has entered the environment, so that today there are wide variations in isotopic ratios of lead in commerce and in the environment. These differences in isotopic ratios may be used as nonradioactive tracers in environmental and metabolism studies (14).

For the purposes of this chapter the toxicology of all lead compounds are considered similar once the lead has entered body tissues. Generally, it is the lead ion that interacts with the target organ or organelle. Solubility in body tissues affects rates of absorption. Exceptions are the industrially synthesized lead–carbon compounds such as tetraethyl lead (TEL) and tetramethyl lead (TML), which have major differences in the toxicological properties. These compounds were added to gasoline to improve engine efficiency and reduce gasoline consumption in automobiles. Although their use as fuel additives has diminished, there are still potential occupational exposures. Lead released from these compounds following combustion of gasoline forms inorganic lead compounds. The toxicology of TEL and TML is considered in a later section of this chapter. Chemical and physical properties of lead and some of its compounds are shown in Table 34.1 (15, 16).

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Titanium, Zirconium, and Hafnium

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A. Titanium and Titanium Compounds

Titanium (Ti) [*7440-32-6*] is a silvery gray metal that resembles polished steel. Titanium a transition element, was first discovered as its oxide by William Gregor in 1791 and named in 1795 by Martin H. Klaproth after the Titans, the giants of Greek mythology. Nevertheless, the pure metal was not isolated until 1910 and remained a laboratory curiosity until an economical purification process was developed in 1946.

Because titanium is as strong as steel and 45% lighter in weight, it is especially suitable for use in aviation and astronautics. About 50% of the titanium produced is used for jet engine components (rotors, fins, and compressor parts). Titanium alloys readily with other metals such as aluminum and tin. The alloy composition Ti + 2.5% tin + 5% aluminum is used when high strength at high temperatures is required, and the alloy Ti + 8% aluminum + molybdenum + vanadium is used in low temperature applications. Each supersonic transport contains about 270,000 kg of titanium.

The most important titanium compound is titanium dioxide, TiO_2 [*13463-67-7*], a white substance that has a high reflective index. TiO_2 forms the basis of the titanium pigment industry because of its opacifying property, ready availability, and relatively low cost. TiO_2 is processed at very high

temperatures into artificial rutile, which is used as a semiprecious stone (titania). Titania has a light yellow color and a higher index of refraction than diamond, but is rather soft. TiO_2 has been used to some degree since 1918, but its use expanded after technological improvements in ore processing and because of expanded industrial need. Fifty percent of the TiO_2 used is as pigments, 20% in paper, and 12% in plastics. It is also used in cosmetics and sun screens. Additional uses of TiO_2 are as a catalyst, a dielectric in capacitors, and a source of titanium metal.

The remaining titanium compounds have a variety of special uses.

Titanium trichloride, a dark-violet deliquescent solid that decomposes in air and water, is used as a cocatalyst for polyolefin polymerization and in organometallic synthesis. The tetrachloride is a colorless liquid that fumes in moist air and forms a dense, persistent, white cloud used in smoke screens. The tetrachloride is used extensively in TiO_2 production.

Titanium disulfide, a yellow solid, is used as a solid lubricant, and titanous sulfate, green in the crystalline state but dark purple in acid solution, is used in the textile industry as a reducing agent for stripping or discharging colors.

The toxicity of titanium varies with the chemical form. Metallic titanium and TiO_2 are insoluble, unreactive, nonmetabolized, and virtually devoid of acute toxicity, though prolonged exposure to high concentrations of TiO_2 causes lung tumors in rats. In contrast, the soluble inorganic titanium salts are absorbed and metabolized and do show appreciable acute toxicity. A third titanium form, the oil-soluble organotitanium complex, titanocene, is metabolized by a still different pathway and is both toxic and tumorigenic in animals.

The toxicology of two other titanium compounds, titanium diboride and titanium carbide, is not discussed in this chapter. Titanium diboride [*12045-63-5*], an extremely hard substance (Mohs hardness 9 +) with oxidative resistance up to 1400°C, is used as a metallurgical additive for super alloys and nuclear steels, as a high-temperature electrical conductor, and in coatings resistant to attack by molten metals. Titanium carbide is extremely hard and as a crystalline solid has its chief use as an additive to tungsten carbide in cutting tools and other parts that are subjected to thermal shock.

Table 35.2. Physical and Chemical Properties of Titanium (Ti) and its Compounds

Compound	CAS Number	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (°C)	Specific Gravity	Solubility
Titanium	[*7440-32-6*]	Ti	47.87	3287	1660	4.5	Insol. cold water; dec. hot water
Titanium dioxide	[*13463-67-7*]	TiO_2	79.87	2500–3000	1830–1850	3.90 (anatase) 4.23 (rutile)	Sol. hot H_2SO_4,HF, alkali; insol. HCl, water, alcohol
Titanium	[*12070-*	TiC	59.88	4820	3140	4.93	Insol.

carbide	*08-5*]						water; sol. aqua regia, HNO_3
Titanium trichloride	[*7705-07-9*]	$TiCl_3$	154.23	660	Dec. 440	2.64	Sol. water; HCl; v. sol. alcohol; insol. ether
Titanium tetrachloride	[*7550-45-0*]	$TiCl_4$	189.68	136.4	–25	Liq. 1.726	Sol. cold. water; HCl, alcohol
Titanium hydride	[*7704-98-5*]	TiH_2	49.88	Dec. 450	—	3.75	—
Titanium (IV) sulfide	[*12039-13-3*]	TiS_2	112.00	—	—	3.37	Hyd. sl. colder; dec. in steam, HCl; sol. dil. HNO_3, H_2SO_4
Titanium (III) sulfate	[*10363-61-0*]	$Ti_2(SO_4)_3$	383.93	—	—	—	Insol. water, alcohol; sol. dil. HCl

59) isolated impure zirconium by heating a mixture of potassium zirconium fluoride with potassium in an iron tube. Zirconium occurs abundantly in stars and has been identified in the sun and in meteorites. It is present as a minor impurity during the extraction of beryllium from its ore, bertrandite.

Occurrence

Zirconium, one of the more abundant elements, is widely distributed in the earth's crust and occurs as the oxide, baddeleyite (ZrO_2), or as part of a complex of oxides as in zircon, $ZrO_2 \cdot SiO_2$, elpidite, $Na_2ZrSi_6O_{13} \cdot 3H_2O$, and eudialyte, $Na_{13}(Ca \cdot Fe)_6 \cdot (Zr \cdot Si)_{20}O_{52}Cl$ (60). Zircon is the most important commercial ore and baddeleyite also has some importance. It has been estimated that zirconium constitutes about 0.017% of the lithosphere.

Major world sources of zircon are Australia, the Republic of South Africa, and the United States. France, Japan, and the United States are producers of nuclear- and commercial-grade zirconium metals. About 50,000 tons of the world demand of 184,000 tons (27%) of zircon were consumed by the United States in 1983. Zircon occurs worldwide as an accessory mineral in igneous, metamorphic, and sedimentary rocks from which it is mined.

Commercial deposits occur only in Brazil and the Republic of South Africa, but it is also found in

East Africa, Sri Lanka, and the former Soviet Union. Zircon sand is produced in Australia, Republic of China, Korea, South Africa, India, and Brazil. All commercial sources of zircon are derived from mining ancient, unconsolidated beach deposits, the largest of which are in Kerala, India, in Sri Lanka, the east and west coasts of Australia, on the Trail Ridge in Florida, and at Richards Bay in the Republic of South Africa. These heavy mineral sands are processed to recover the titanium-bearing minerals ilmenite, rutile, and leucoxene, and zircon is obtained as a coproduct. The output of zircon depends mainly on the market for titanium minerals used in producing titanium oxide white pigment and titanium metal (59, 61). The production of zirconium metal is only a minor use of zircon.

In the United States, the zirconium content of zircon in beach sand and placer deposits in Florida and Georgia is estimated at 4 million tons. In addition, 4 million tons of marginal reserves and subeconomic resources are located principally in Tennessee, New Jersey, South Carolina, and California. Zircon is recovered from mineral sands by dredging and mining.

Zirconium is associated with other metals in many minerals but is recovered only from zircon (ZrO_4SiO_2), baddeleyite (brazilite) (ZrO_2), eudialyte [$Na_{13}(CaFe)_6 \cdot (ZrSi)_{20}O_{52}Cl$]. Hafnium is invariably associated with zirconium. Zircon occurs in all igneous rocks but is more common in granite, sylnite (complex silicates), and diorite (alkaline earth silicates). Zircon is a common constituent of river gravels and beach sands, from whence it is recovered as a coproduct of ilmenite (FeO_4TiO_2), rutile (TiO_2), and monazite (thorium and lanthanum phosphates). Baddeleyite usually occurs in phenolite and is also found in river gravels and beach sands (59).

Because of its very high chemical activity at temperatures just above normal ambient temperature, zirconium occurs only in the combined state (61). Zirconium is found in at least 37 different mineral forms (62), but the predominant commercial source is the mineral zircon, zirconium orthosilicate.

Baddeleyite, a natural zirconium oxide, has been found in Brazil and in Transvaal, South Africa. The Brazilian ore occurs frequently with zircon and may contain 65–85% zirconium oxide, 12–18% silica, and 0.5% uranium oxide. Currently, very little Brazilian ore is exported because all radioactive minerals are under the close scrutiny of the Brazilian government. The Transvaal ore is a complex ore composed of different sections; these are mined to recover magnetite, apatite (a copper concentrate), vermiculite, and baddeleyite. The baddeleyite ore contains a zirconium oxide concentration of 0.2% but when concentrated, it yields about 96% zirconium oxide with a hafnium content (Hf/Zr + Hf) of about 2%. Zirconium and hafnium are geochemically associated in the principal ore mineral, zircon, in a ratio of 50 to 1. The two elements are separated only for nuclear applications.

Eudialyte [$Na_{13}(Ca \cdot Fe)_6 \cdot (Zr \cdot Si)_{20}O_{52}Cl$], a third ore, is the source of pure zirconium oxide from large deposits in southwest Greenland. Two zirconium-containing minerals have been discovered in the past 20 years, welognite $(Sr_{2.8}Ca_{0.2})ZrNa_2(CO_3)_6 \cdot 3H_2O$ and gittinsite $CaZrSi_2O_7$. Unlike zircon, the zirconium content of these minerals and eudialyte can be dissolved by strong acid.

Zircon is the primary zirconium mineral of commercial significance. It is recovered solely as a by-product of mining and extracting of the titanium minerals, ilmenite and rutile, for which there is a much larger demand. Zircon has been known as a gem mineral since biblical times and was called *Jargon* in Sri Lanka and Hyacinth in France. The name zircon comes from the Arabic “zargun,” meaning gold color, describing the gemstone now known as zircon. Zircons may be colorless, amber, red, reddish brown, blue, green, or black. Analysis of the gemstone Jargon from Sri Lanka in 1789 by Klaproth revealed 68% of an unknown earth which he called zirkonerde (63). In 1797, Vauquelin studied this new earth, gave it the name zirconia, and published the preparation and properties of some of its compounds (64). It was only in 1824 that Berzelius prepared the first crude zirconium metal, a black powder, by heating potassium and potassium hexafluorozirconate in a closed pot (61).

The mineral zircon is mainly used for facings on foundry molds; foundries consume approximately one-half of the domestic zirconium production, and the remaining one-half is consumed by refractory, abrasive, ceramic, metal, and other industries. Domestic zirconium is marketed in proprietary mixtures for use as weighting agents, Zr–TiO_2 blends for welding-rod manufacture, and zirconium-refractory heavy-mineral (kyanite, sillimanite, and staurolite) sand blends for foundry sand and sandblasting applications. The zirconium-bearing foundry sand was reportedly designed to provide consistent high-quality performance at low cost for critical casting applications (65).

Zircon is widely used in furnaces and hearths as refractory bricks and blocks for containing molten metals. Zircon is also used in manufacturing fused cast and bonded AZS (alumina-zirconia-silica-base) refractories for glass tank furnace use and in alumina–zirconia snagging wheels used in heavy grinding on rough metal surfaces. Zircon is also used as a refractory material for dies used to extrude various materials (59).

Table 35.3. Physical and Chemical Properties of Zirconium and Its Compounds[a]

Compound	CAS Number	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (°C)	Specific Gravity	Solubility in Water (68°F)	Ref.
Zirconium	[*7440-67-7*]	Zr	91.22	4409	1855	6.52	Insoluble	*a*
Zirconium beryllide	[*12010-33-2*]	$ZrBe_{13}$			1925	2.72		*a*
Zirconium beryllide		$ZrBe_{17}$			1980	3.08		*a*
Zirconium diboride	[*12045-64-6*]	ZrB_2	112.85		3040	6.17		*a,b*
Zirconium boride	[*12045-28-2*]	ZrB			2800			*b*
Zirconium boride (1:12)	[*12046-91-2*]	ZrB_{12}			Decomposes at 2250			*b*
Zirconium bromide, zirconium tetrabromide	[*13777-25-8*]	$ZrBr_4$	410.84	360*	450**	3.98		*a*
Zirconium carbide	[*12020-14-3*]	ZrC	103.24		3532	6.73		*a*
Zirconium chloride, zirconium tetrachloride	[*10026-11-6*]	$ZrCl_4$	233.04	331*	437**	2.80	Reacts with water	*a*
Zirconium dichloride	[*13762-26-0*]	$ZrCl_2$	162.13		Decomposes at 350	3.6		*c*
Zirconium fluoride, zirconium tetrafluoride	[*7783-64-4*]	ZrF_4	167.22	912*	932**	4.43	Slightly sol	*a*
Zirconium hydride	[*7704-99-6*]	ZrH_2	92.34			5.6	Insoluble	*a*

Zirconium hydroxide	[*14475-63-9*]	$Zr(OH)_4$	159.25		Decomposes	3.25	Insoluble	[a]
Zirconium iodide	[*13986-26-0*]	ZrI_4	598.84	431*	499**	4.85	Very soluble	[a]
Zirconium nitrate, pentahydrate	[*13746-89-9*]	$Zr(NO_3)_4 \cdot 5H_2O$	429.32		Decomposes at 100		Very soluble	[a]
Zirconium nitride	[*25658-42-8*]	ZrN	105.23		2960	7.09		[a]
Zirconium orthosilicate	[*10101-52-7*]	$ZrSiO_4$	183.31		Decomposes at 1540	4.56	Insoluble	[a]
Zirconium oxide	[*1314-23-4*]	ZrO_2	123.22		2710	5.68	Insoluble	[a]
Zirconium silicide	[*12039-90-6*]	$ZrSi_2$	147.40		1620	4.88	Insoluble	[a]
Zirconium sulfide	[*12039-15-5*]	ZrS_2	155.36		1480	3.82	Insoluble	[a]
Zirconium sulfate, tetrahydrate	[*7446-31-3*]	$Zr(SO_4)_2 \cdot 4H_2O$	355.41		Decomposes at 100	2.8	Very soluble	[a]
Zirconium sulfate	[*14644-61-2*]	$Zr(SO_4)_2$	283.3		Decomposes at 410	3.2		[d]
Zirconium chloride, octahydrate	[*13520-92-8*]	$ZrOCl_2 \cdot 8H_2O$	322.25		Decomposes at 400	1.91	Very soluble	[a]
Zirconium oxychloride	[*7699-43-6*]	$ZrOCl_2$	178.13					[d]

[a] a = Adapted from *CRC Handbook of Chemistry and Physics*, CRC Press, 78th ed., Boca Raton, FL., 1997–1998.
[b] b = Adapted from *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed., Vol. 4, John Wiley & Sons, 1992.
[*] * = sublimation point.
[**] ** = triple point.
[c] c = Adapted from *CRC Handbook of Chemistry and Physics*, CRC Press, 67th ed., Boca Raton, FL., 1986–1987.
[d] d = Adapted from CHEMFINDER.com

Table 35.4. Statistics of Zirconium Imports and Exports—United States, 1993–1997[a]

	Metric Tons				
	1993	**1994**	**1995**	**1996**	**1997 (est.)**
Imports					

Zirconium ores and concentrates (ZrO_2)	45,500	53,300	60,800	60,100	41,600
Zirconium alloys, waste and scrap (ZrO_2)	798	837	884	830	993
Zirconium oxide (ZrO_2)	1,990	2,400	4,370	5,240	3,870
Exports					
Zirconium ores and concentrates (ZrO_2)	23,400	20,800	26,200	22,780	24,900
Zirconium alloys, waste and scrap (ZrO_2)	2,020	1,640	1,680	1,480	1,690
Prices					
Zircon, dollars per ton:					
Domestic	NA[b]	278	319	419	400
Imported	200	220	325	411	400
Zirconium sponge, dollars per kg:	9–12	9–12	9–12	9–12	9–12

[a] Adapted from U.S. Geological Survey, *Mineral Commodity Summaries*, 1998.
[b] NA = not available.

Table 35.5. The Supply/Demand for Zirconia (Zirconium Oxide) in Metric Tons for 1991 and 1994[a]

	United States		**Western Europe**		**Japan**		**Total[b]**	
	1991	**1994**	**1991**	**1994**	**1991**	**1994**	**1991**	**1994**
Number of producers[c]	5	5	5	4	9	9	19	18
Production	9,747	12,100	4,100	4,400	6,750	6,280	19,850	22,780
Imports[d]	1,536	2,404	6,100	na[f]	650	900	8,286	na[f]
Exports[e]	1,495	1,222	300	na[f]	718	na[f]	3,213	na[f]
Consumption	9,788	13,282	9,845	10,175	7,400	7,190	23,421	30,641

[a] Adapted from *Chemical Economics Handbook*, SRI International, Menlo Park, CA, August 1996.

[b] Totals may not equal the sums of categories because of rounding.

[c] Data for United States and Western Europe do not include producers of zirconia metal and reprocessors of baddeleyite. Data for Japan include manufactured zirconia producers that use baddeleyite as a raw material.

[d] Data for United States and Western Europe include baddeleyite but not for Japan.

[f] Not available.

[e] Japan's export figures include germanium oxide which represents less than 5% of total volume.

10.1 Aluminum Zirconium Compounds
10.4.2 Human Experience 10.4.2.1 General Information

10.4.2.2 Clinical Cases Zirconium compounds have been associated with the development of hypersensitivity granulomas. However, aluminum zirconium complexes have not previously been shown to induce sensitization. The clinical and histologic findings of a case was described in which a patient developed an acute hypersensitivity reaction to an aluminum zirconium complex (134).

10.5 Standards, Regulations, or Guidelines of Exposure

NIOSH has a recommended exposure limit (REL) of 5 mg/m^3 as Zr and a STEL value of 10 mg/m^3 (45). As of July 1999, the OSHA TWA has remained at 5 mg/m^3 (43). The 2000 ACGIH TLV is 5 mg/m^3 and the STEL value is 10 mg/m^3 (44).

11.1 Zirconium Compounds (Combination Studies)
11.4.2 Human Experience 11.4.2.2 Clinical Cases Men who worked with zirconium compounds at one site in the North of England were monitored since 1975 to evaluate the effects of exposure on the lung (mainly < 10 mg/m^3) over many years. Chest radiographs (in 1975, 1978, and 1982) and lung function measurements (from 1975–1988) were carried out on all 178 men known to have worked with the compounds; an estimate of cumulative exposure was computed from job title and likely exposures. No evidence was found that zirconium exposure resulted in abnormal chest radiographs or impaired pulmonary function (135).

11.5 Standards, Regulations, or Guidelines of Exposure

NIOSH has a recommended exposure limit (REL) of 5 mg/m^3 as Zr and a STEL value of 10 mg/m^3 (45). As of July 1999, the OSHA TWA has remained at 5 mg/m^3 (43). The 2000 ACGIH TLV is 5 mg/m^3, and the STEL value is 10 mg/m^3 (44).

12.1 Sodium Zirconium Lactate
12.4.2 Human Experience 12.4.2.2 Clinical Cases By 1959 there were numerous reports of axillary granulomas following the use of stick deodorants containing NaZr lactate (136). These granulomas appear as underarm eruptions of small, indolent, flesh-colored papules, often in linear streaks. Several years later, zirconium oxide, as a cream, introduced as a treatment for poison ivy dermatitis, produced small papules in the skin which, on microscopic examination, revealed epithelioid cell granulomas (137). When the sensitizing Zr salt was removed from the preparation, healing occured.

12.5 Standards, Regulations, or Guidelines of Exposure

NIOSH has a recommended exposure limit (REL) of 5 mg/m^3 as Zr and a STEL value of 10 mg/m^3 (45). As of July 1999, the OSHA TWA has remained at 5 mg/m^3 (43). The 2000 ACGIH TLV is 5 mg/m^3 and the STEL value is 10 mg/m^3 (44).

13.1 Zirconium-Containing Aerosol Spray
13.4.2.2 Clinical Cases Epstein (138) developed a zirconium-containing aerosol spray that did not produce granulomas of the skin in an unsensitized person. However, Zr-containing antiperspirant sprays were ultimately banned following a panel statement of the FDA and subsequent hearings which concluded that (1) the respiratory tract is the deposition site for the antiperspirant in spray form, (2) no proof was presented on the metabolic fate or integrity of the deposited spray in the respiratory tract, and (3) zirconium chlorhydrate can elicit a hypersensitivity granulomatous response

in sensitized persons.
13.5 Standards, Regulations, or Guidelines of Exposure
NIOSH has a recommended exposure limit (REL) of 5 mg/m^3 as Zr and a STEL value of 10 mg/m^3 (45). As of July 1999, the OSHA TWA has remained at 5 mg/m^3 (43). The 2000 ACGIH TLV is 5 mg/m^3 and the STEL value is 10 mg/m^3 (44).
14.1 Lead Titanate Zirconate
14.2 Human Experience
14.4.2.2 Clinical Cases An Ontario plant with 101 workers who produced and used the ceramic compound lead titanate zirconate (LTZ), was the site of an investigation (139). Although air lead levels were high in most plant areas, 82 workers who were not exposed to lead oxide but to LTZ in the process had normal blood lead levels. In addition, no radiographic changes or abnormal pulmonary function test results were detected in 61 workers examined. The particle size of LTZ was less than 5 micrometers, and the solubility of LTZ in body fluids was significantly less than lead oxide. The authors postulated that the observed low toxicity of LTZ could be due to its low solubility in body fluids. Further studies of the toxicity of LTZ and other less soluble lead compounds were recommended by the authors (139).
14.5 Standards, Regulations, or Guidelines of Exposure
NIOSH has a recommended exposure limit (REL) of 5 mg/m^3 as Zr and a STEL value of 10 mg/m^3 (45). As of July 1999, the OSHA TWA has remained at 5 mg/m^3 (43). The 2000 ACGIH TLV is 5 mg/m^3 and the STEL value is 10 mg/m^3 (44).
15.1 Zircaloy
15.4.2 Human Experience 15.4.2.2 Clinical Cases A 51-year-old nonsmoking female suffered from relapsing progressive pneumonia for several years. She had worked for 16 years in the nuclear industry and was exposed to grinding particles and welding fumes from working with Zircaloy, an alloy that contains tin, iron, chromium, and zirconium. During an exacerbation of the pneumonia, radiography showed interstitial infiltration of both lower lobes. In addition, nodular and painful thickenings appeared in old operation scars on various parts of her body. Persistent infiltrations of the lung led to lobectomy of the right lower lobe to exclude a malignant disease in the worker. The histological picture of the lung tissue showed different stages of alterations and pronounced proliferation of the alveolar epithelium, epithelioid cell granulomas between well-preserved alveolar walls, and additional large areas of scar tissue (140). This observation was similar to that noted in another study published a few years previously, where the authors called it “Zirconium lung” (141).
15.5 Standards, Regulations, or Guidelines of Exposure
NIOSH has a recommended exposure limit (REL) of 5 mg/m^3 as Zr and a STEL value of 10 mg/m^3 (45). As of July 1999, the OSHA TWA has remained at 5 mg/m^3 (43). The 2000 ACGIH TLV is 5 mg/m^3, and the STEL value is 10 mg/m^3 (44).
15.6 Studies on Environmental Impact
Zircaloy hazards associated with the shear/leach operation at the second Thermal Oxide Reprocessing Plant (THORP) at the Sellafield factory were examined. Potential hazards of the process include Zircaloy dust explosions in the vicinity of the shear and either dry or submerged ignition layers. With respect to the development of the safety case for layer ignitions, the reaction kinetics were experimentally investigated by reproducing the conditions under which a thermal runaway could be seen. A mathematical model of the settled layer heat transfer characteristics was developed. It was shown that an oxide layer formed on particles of Zircaloy resulted in a slowing of explosive reactions of particulate Zircaloy (142).

Titanium, Zirconium, and Hafnium
Leela I. Murthy, Ph.D., David A. Dankovic, Raman C. Murthy

C. Hafnium and Hafnium Compounds

Hafnium (Hf), CAS Number: [*7440-58-6*], one of the transition elements, belongs to Group IV B of the periodic table along with titanium and zirconium. Hafnium is never found free in nature but is always associated with the more plentiful zirconium in natural minerals. Hafnium and zirconium are almost identical in nature and hence show close similarity in chemical properties not seen in any other pair of elements in the periodic table.

Hafnium is one of the less abundant elements in the earth's crust. It makes up 2% of the combined weight of hafnium and zirconium in zircon, $(ZrHf)O_2 \cdot SiO_2$, which is recovered from certain beach sands. Hafnium makes up about 0.5–2% of the combined weight with zirconium in the ore, baddeleyite, $(Zr.Hf)O_2$ (143). Because of its similarity to zirconium, no qualitative differences have been found that would permit separating them except for the production of hafnium-free nuclear-grade zirconium (61).

Hafnium was positively identified only in 1923 though zirconium was discovered in 1789. The theory that element 72 was tetravalent and not trivalent like the rare earth series elements was postulated by the Bohr atomic theory and by Moseley's X-ray spectra of several zircon concentrates (144). The name hafnium comes from Hafnia, the Latin name for Copenhagen where the discovery was made.

Hafnium was also identified by X-ray fluorescence analysis and by neutron activation analysis in a chronosequence of soils in the Indiana Dunes. It was leached along with titanium, selenium, and heavy lanthanides associated with heavy minerals, particularly, iron oxides, in the very fine sand fraction (0.05–0.1 mm) of the Indiana Dunes soils (145).

The primary commercial source of hafnium is zircon, zirconium orthosilicate, which is inert and refractory and is obtained during the mining of rutile and ilmenite mineral sands. Zircon sands contain 2% hafnium oxide but higher concentrations are found in altered zircons such as cyrtolite, malacon, alvite, and naëgite. The statistics of hafnium imports and prices for 1993–1997 are presented in Table 35.6.

Table 35.6. Statistics of Hafnium Imports and Prices—United States, 1993–1997[a]

	1993	1994	1995	1996	1997
Imports, metric tons					
Hafnium, unwrought, waste, and scrap	3	5	5	8	8
Prices	1993	1994	1995	1996	1997
Hafnium sponge, dollars per kilogram	165–210	165–210	165–210	165–210	165–210

[a] Adapted from U.S. Geological Survey, *Mineral Commodity Summaries*, 1998.

It is extremely difficult to separate hafnium from zirconium. Some of the methods used in the laboratory for separating it from zirconium are: (1) solvent extraction of thiocyanates by hexone, (2) solvent extraction of nitrates by tributyl phosphate and, (3) fractional crystallization of the double fluorides (146). Three industrial methods are normally used to separate hafnium and zirconium: (1) liquid-liquid extraction (2) molten salt distillation and (3) fluorozirconate crystallization. Different hafnium compounds are obtained from zircon using different procedures. Figure 35.1 presents a flowchart for obtaining the various hafnium compounds, as well as the different forms of hafnium

from zircon.

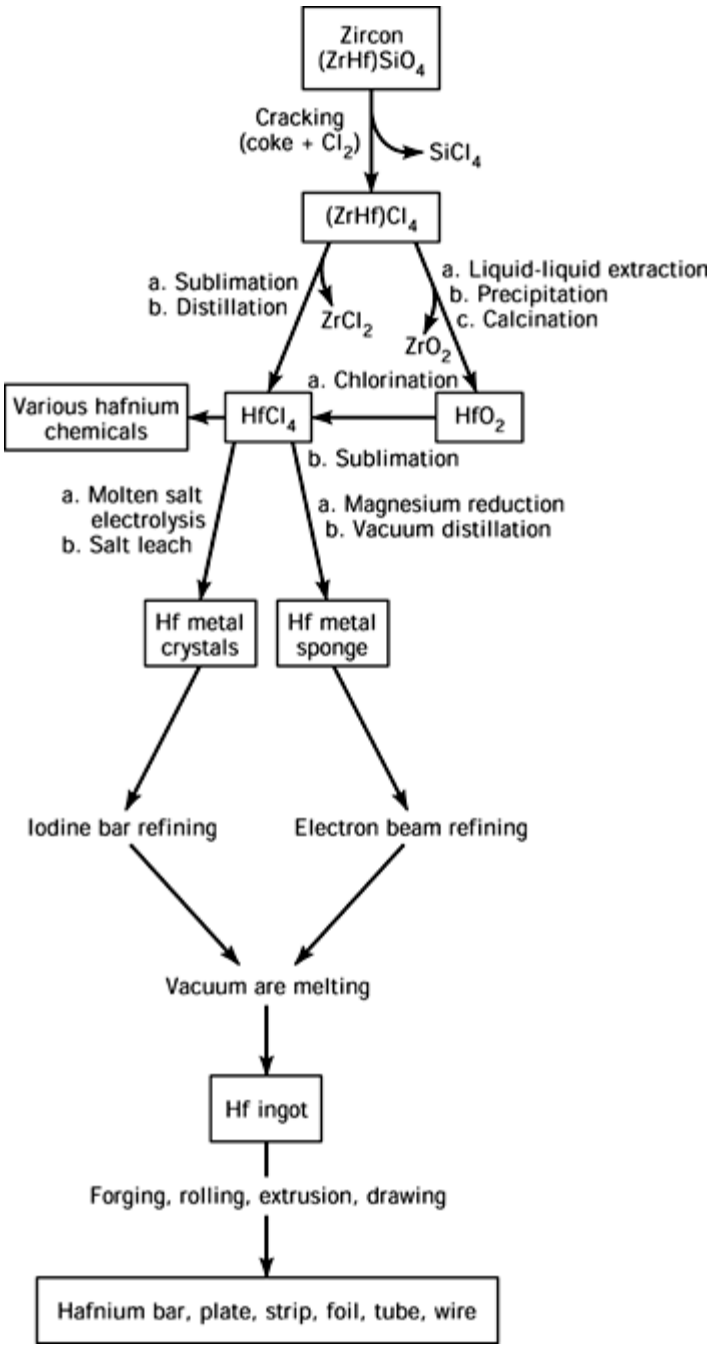

Figure 35.1. Flow sheet of hafnium production from zircon.

Another method used a pressurized ion-exchange column to separate hafnium from zirconium. Basically, the hafnium and zirconium sulfate complex was separated by chromatographic elution from Dowex 50W-X8 (15–25 mm) resin with sulfuric acid solutions. Fluorometric and colorimetric reagents were used to monitor the column effluents continuously. Because neither the fluorometric nor the colorimetric reagent was specific for either hafnium or zirconium, peak patterns were identified using the stable isotopes ^{90}Zr and ^{180}Hf as "fingerprints" of their elution position (147). An unseparated fraction was also obtained which was thought to be a polymeric hydrolytic product.

Some physical properties of hafnium and its compounds are presented in Table 35.7.

Table 35.7. Physical and Chemical Properties of Hafnium and Its Compounds[a]

Compound	CAS Number	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (°C)	Specific Gravity	Solubility in Water (68°F)	Ref.
Hafnium	[*7440-58-6*]	Hf	178.49	4603	2233	13.31	Insoluble	*a*
Hafnium beryllide		$HfBe_{13}$			1595	3.93		*a*
Hafnium beryllide		$HfBe_{17}$			< 1750	4.78		*a*
Hafnium diboride	[*12007-23-7*]	HfB_2	200.11		3100	10.5		*a*
Hafnium boride	[*12228-27-2*]	HfB	189.3		Dec. at 210			*b*
Hafnium dodecaboride	[*32342-52-2*]							*a*
Hafnium bromide, hafnium tetrabromide	[*13777-22-5*]	$HfBr_4$	498.11	323*	424**	4.90		*a*
Hafnium carbide	[*12069-85-1*]	HfC	190.50		≈3000	12.2		*a*
Hafnium chloride	[*13499-05-3*]	$HfCl_4$	320.30	317*	432**		Reacts with water	*a*
Hafnium fluoride, hafnium tetrafluoride	[*13709-52-9*]	HfF_4	254.48	970*	> 970	7.1		*a*
Hafnium hydride	[*12770-26-2*]	HfH_2	180.51			11.4		*a*
Hafnium iodide, hafnium tetraiodide	[*13777-23-6*]	HfI_4	686.11	394*	449**	5.6		*a*
Hafnium nitride	[*25817-87-2*]	HfN	192.50		3305	13.8		*a*
Hafnium ortho silicate	[*13870-13-8*]	$HfSiO_4$	270.57			7.0		*a*
Hafnium oxide	[*12055-23-1*]	HfO_2	210.49		2774	9.68	Insoluble	*a*
Hafnium oxychloride octahydrate	[*14456-34-9*]	$HfOCl_2 \cdot 8H_2O$	409.52		Decomposes		Soluble	*a*
Hafnium phosphide	[*12325-59-6*]	HfP	209.46			9.78		*a*
Hafnium selenide	[*12162-21-9*]	$HfSe_2$	336.41			7.46		*a*

Hafnium silicide	[*12401-56-8*] $HfSi_2$	234.66	≈1700	7.6	[a]
Hafnium sulfate	[*15823-43-5*] $Hf(SO_4)_2$	370.62	Decomposes > 500		[a]
Hafnium sulfide	[*18855-94-2*] HfS_2	242.62		6.03	[a]

[a] a = Adapted from *CRC Handbook of Chemistry and Physics*, CRC Press, 78th ed., Boca Raton, FL., 1997–1998.
[b] b = Adapted from *CRC Handbook of Chemistry and Physics*, CRC Press, 67th ed., Boca Raton, FL., 1986–1987.
[*] * = sublimation point.
[**] ** = triple point.

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(1990).

Arsenic, Antimony, and Bismuth
Lisa Gallicchio, Bruce A. Fowler Ph.D., Emily F. Madden

1.0 Arsenic
1.0.1 CAS Number:
[*7440-38-2*]
1.0.2 Synonyms:
Inorganic arsenic, arsenite, arsenate, arsenic acid, arsine gas
1.0.3 Trade Names:
NA
1.0.4 Molecular Weight:
74.9
1.0.5 Molecular Formula:
As
1.0a Arsenic Trioxide
1.0.1a CAS Number: [*1327-53-3*]

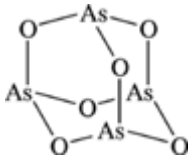
1.0.2a Synonyms: Arsenic oxide; arsenic (III) oxide; arsenous trioxide; arsenous acid; arsenous oxide; arsenic sesquioxide; white arsenic; diarsenic trioxide; crude arsenic; arsenic (white); arsenious oxide; arsenic (III) trioxide; arsenous anhydride; arsenite; arsenolite; arsenous acid anhydride; arsenous oxide anhydride; arsodent; claudelite; claudetite; arsenic oxide (3); arsenic oxide (As_2O_3); arsenic sesquioxide (As_2O_3); arsenicum album; diarsonic trioxide; diarsenic oxide; arsenious oxide, 99.999%

1.0.3a Trade Names: NA

1.0.4a Molecular Weight: 395.628

1.0.5a Molecular Formula: As_4O_6

1.0.6a Molecular Structure:



Arsenic, Antimony, and Bismuth
Lisa Gallicchio, Bruce A. Fowler Ph.D., Emily F. Madden

2.0 Antimony

2.0.1 CAS Number:
[*7440-36-0*]
2.0.1a Antimony Trioxide, [*1309-64-4*]
2.0.2 Synonyms:
Antimony is also known as stibine (gaseous form of antimony hydride).
2.0.3 Trade Names:
None.
2.0.4 Molecular Weight:
121.760
2.0.5 Molecular Formula:
Sb
2.1 Chemical and Physical Properties
2.1.1 General Sb as an element is a brittle, flaky, crystalline (hexagonal) silver-white metal. It does not react with air at room temperature but burns brightly when heated, and forms white fumes. It is a poor conductor of electricity and heat. Antimony occurs in tri- (+3) and pentavalent (+5) compounds and is found in the earth's crust mostly associated with sulfur as stibnite and in ores associated with arsenic. Antimony is a group VA element of the periodic table and it has many of the same chemical and biological properties as the element arsenic.

2.1.2 Odor and Warning Properties Stibine gas is odorless. Exposure to antimony at high levels may result in a variety of adverse health effects. For example, breathing high levels of antimony and some of its compounds can irritate the eyes and lungs and can cause problems with the heart, lungs, and stomach.
2.2 Production and Use
Antimony is used as a common constituent of metal alloys; antimony ores are mined and mixed with other metals such as lead and copper. Antimony is used frequently for hardening lead in lead storage batteries. Antimony is used in the manufacture of ceramics, paints, glass, solder, pewter, typemetal, bearings, castings, explosives, and semiconductors. Antimony compounds are also used as abrasives for flameproofing material such as textiles and plastics. Antimony trioxide is an important component of pigments and munitions primers (189).

Historically, antimony compounds were used as emetics and expectorants. Recently, antimony compounds, such as tartar emetic and sodium stibogluconate, are used as antihelminthic and antiprotozoic drugs in treating parasitic diseases and infections (190). It plays no role in nutrition and is a nonessential element.
2.3 Exposure Assessment
2.3.1 Air Antimony concentrations in the air of the order 1–10 mg/m^3 were reported from a number of different smelter operations (191). Average working zone concentrations of antimony ranging from 4.7 to 10.2 mg/m^3 have been reported in smelting works (192). In one abrasives plant, the average air concentration of antimony was 3.0 mg/m^3 (193). Currently, the Occupational Safety and Health Administration (OSHA) has set an occupational exposure limit of 0.5 mg of antimony per cubic meter of air for an 8-hour workday, 40-hour workweek.

2.3.2 Background Levels Data regarding daily intake of antimony are controversial. Reports range from about 10& mg in a Swedish study (194) (neutron activation), a weekly average of 23 mg in four normal German diets (195) (neutron activation) to 250–1250 mg in one U.S. study of institutional diets for children using atomic absorption spectrophotometry (AAS) without extraction (196). There is reason to believe that the AAS method may have given falsely high values (191). Antimony concentrations of 3 to 8 mg/kg have been found in milk and potato powder (195). Antimony occurs primarily as a suspended particulate in water, although hydrolysis is possible (197). Antimony is likely to accumulate in sediments, and although antimony concentrations have been observed in some marine and freshwater invertebrates (possibly in methylated forms), antimony does not biomagnify (198, 199). Antimony concentrations in fresh water fish are reportedly of the order of 3 mg/kg wet weight (200). Antimony levels of 0.2 mg/L were reported in

the northeastern Pacific Ocean, and in the Rhine River levels average 0.1 mg/L (201). The EPA currently allows 0.006 parts antimony per million parts of drinking water (ppm). In soil, antimony ranges from 0.1 to 10 mg/kg dry weight (202). Antimony is a common air pollutant and has an average concentration of 0.001 mg/m^3 (203). Antimony concentrations in air ranging from 1.4 to 55 ng per cubic meter (204) and an average of 32 ng per cubic meter (205) were reported in Chicago using neutron activation analysis. The combustion of fossil fuels and products that contain antimony compounds commonly release antimony into the air, most likely as the trioxide and possibly the tetroxide and pentoxide forms (198). In addition, antimony levels in cigarettes have been studied by neutron activation, and an average of 0.1 mg of antimony per kg dry weight of tobacco was estimated (206).

2.3.3 Workplace Methods The recommended method for determining workplace exposures to antimony is NIOSH Method PCAM #261 (207).

2.3.4 Community Methods: NA

2.3.5 Biomonitoring/Biomarkers 2.3.5.1 Blood Blood concentrations can be measured several days after antimony exposure by using atomic absorption spectrometry.

2.3.5.2 Urine Occupational exposure is monitored by measuring antimony in the urine and also for the clinical investigation of antimony therapeutics. Some tests are, however, not routinely performed in doctors' offices and may require specialized equipment and methods such as AAS to perform them.

2.4 Toxic Effects

The major targets in antimony poisoning are the gastrointestinal and respiratory tracts, and the effects have been documented in both animals and humans (203). Other targets include the liver and the hematopoietic system. Renal toxicity including histological changes have been observed in animals (203). Antimony is an irritant of the mucous membranes, skin, and eyes. Pulmonary injury is linked with heavy exposure to antimony trioxide and pentoxide, and antimony trisulfide is regarded as cardiotoxic. It has been suggested that the descending order of toxicity is the antimony metalloid (mainly as stibine gas), the trisulfide, the pentasulfide, the trioxide, and the pentoxide from (203). The chemical properties and biological activities of antimony are similar to arsenic, although it is considerably less toxic.

2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity Acute antimony poisoning is a rare occurrence but can result in death within several hours (203). The symptoms of acute antimony poisoning are similar to those of arsenic poisoning: vomiting, diarrhea, colic, and a metallic taste (203). For example, acute symptoms such as vomiting and diarrhea were produced in cats and dogs when administered antimony potassium tartrate in doses of the order of 10 mg/kg (191). In acute peroral exposure, antimony potassium tartrate is more toxic than antimony tri- and pentoxide. Cats and dogs exposed to doses of 100 mg/kg antimony trioxide and pentoxide for months exhibited no toxic manifestations (208, 209). Acute exposure to antimony compounds by inhalation can produce respiratory effects. For example, guinea pigs that inhaled antimony trioxide at an average concentration of 45 mg/m^3 for 33 to 609 hours exhibited signs of interstitial pneumonitis (210). Acute antimony exposures induce circulatory system effects. For example, an acute circulatory response, with a drop in blood pressure was observed after intravenous injections of antimony (211, 212). Pathological ECG changes were observed in dogs injected for four days with 5 mg of antimony potassium tartrate; the most prominent change was inversion of the T-wave (213). Liver and kidney effects have been observed with acute exposure; fatty degeneration occurred in the convoluted tubules of the kidney and the liver after a single dose of 60 mg of antimony potassium tartrate solution was given to rabbits (214). The pathological kidney changes occurred a few hours after the administration but preceding the changes observed in the liver. Fatty degeneration of the liver, but not the kidneys, was observed in one inhalation study of guinea pigs (210). Exposure to antimony and its compounds reportedly causes mild but inconsistent hematological effects in animals. Rats fed

894 mg/kg/day of antimony trioxide for up to one month showed an increased red blood cell count (215). In contrast, decreased red blood cell counts were reported for rats that received antimony trioxide in doses of 418 mg/kg/day for 24 weeks (216). In addition, decreased hematocrit and hemoglobin levels, as well as decreased plasma protein concentrations were observed for rats exposed orally to metallic antimony at 500 to 1000 mg/kg/day for 12 to 24 weeks. The odorless toxic gas stibine (antimony hybride), like arsine, is a potent hemolytic agent. The lethal concentration of stibine in air for mice is reportedly about 100 ppm for 1.6 hours (217). The formation of Heinz bodies in red blood cells was associated with acute stibine exposure that may underlie its hemolytic effects.

2.4.1.2 Chronic and Subchronic Toxicity Antimony potassium tartrate is more toxic in chronic peroral exposure than antimony tri- and pentoxide (191). Rats given 5 mg/L antimony potassium tartrate in drinking water in a long term study showed a significant decrease in survival and average life span (about 15%) compared to control animals (218). Rats given a diet containing 0.5 to 2% antimony or antimony trioxide had a decreased weight gain (216). Rats and rabbits exposed to antimony trioxide for periods up to 14 months at 90 to 125 mg/m^3 of air during 100 h/month exhibited pneumonitis, lipoid pneumonia, fibrous thickening of alveolar walls, and focal fibrosis (219, 220). In this study, rabbits appeared more susceptible than rats (220). A study of the long-term toxicity of inhaled antimony trioxide using female CDF-rats and miniature swine, where animals were exposed to low (1.6 mg/m^3) and high (4.2 mg/m^3) doses for 6 hours a day at 5 days per week for one year, showed pronounced morphological changes in the lung in rats, but not in miniature pigs (221). The changes in the lung included focal fibrosis, adenomatous and pneumonocytic hyperplasia, and cholesterol clefts, and the changes were more pronounced in the high-exposure group. Circulatory system and cardiovascular effects from chronic antimony exposures were observed. Chronic effects, including parenchymatous degeneration in the myocardium, were reported upon histopathological examination of hearts from rabbits and rats exposed to 3.1 and 5.6 mg/m^3 antimony trisulfide for 6 weeks (193). In contrast, Watt (221) found no evidence of cardiovascular effects in his long-term study of miniature swine exposed to antimony trioxide. Long-term peroral exposure to high doses of antimony may induce liver toxicity in animals. For example, rats exposed to 0.5 to 2% antimony and antimony trioxide in the diet for up to 24 weeks had elevated serum levels of liver enzyme GOT for the higher exposure (216).

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 2.4.1.3.1 Absorption Antimony is poorly absorbed from the gastrointestinal tract but is more readily absorbed through the respiratory tract (203). For example, at least 15% of a single oral dose of labeled antimony potassium tartrate given to mice is absorbed when recovered in the urine and tissues (222).

2.4.1.3.2 Distribution Antimony is distributed nonspecifically, although trivalent compounds tend to react with red blood cells and the liver, and the pentavalent form tends to remain in the plasma (203). Two hours after an intraperitoneal injection of 3 mg trivalent antimony in rats, more than 95% of the amount in blood was incorporated in the red blood cells, whereas for pentavalent antimony, 90% was mainly recovered in the plasma (223). After acute or chronic oral or parenteral exposure to antimony, the highest levels are recovered in the thyroid, adrenals, and kidneys. A study of rats fed a diet that contained 2% antimony for 1.5 months showed that highest antimony concentrations were found in the thyroid and adrenals at values of 88.9 and 67.8 mg/kg, respectively. For spleen, liver, lungs, and kidneys, the antimony concentrations ranged between 6.7 and 18.9 mg/kg (224). For humans, body surface scanning of persons given intravenous injections of labeled sodium antimony dimercaptosuccinate revealed highest antimony amounts in the thyroid, liver, and heart (225, 226). Forty-three days after the last injection, the liver showed values about one-sixth the maximum value reached one day after the last injection.

2.4.1.3.3 Excretion The rate and route of excretion depend on the valency of the antimony compounds, and certain species differences have also been observed (191). Pentavalent organic antimony is excreted mainly in the urine in a rapid manner, and trivalent is eliminated mainly

through the feces (223, 227). Antimony is also excreted in bile primarily conjugated to glutathione (228). For hamsters administered tri- and pentavalent antimony by intraperitoneal injection, after 24 hours about 15% of the trivalent and 65% of pentavalent antimony were found in the urine (229). For fecal excretion over the same period of time, about 50% of trivalent antimony and less than 10% pentavalent antimony was recovered. In addition, 6% of the trivalent and 88% of pentavalent antimony dose given to rats was eliminated via the urine within 24 hours of administration (223). No methylation of antimony has been reported in humans or in animals (228).

2.4.1.4 Reproductive and Developmental: NA

2.4.1.5 Carcinogenesis Existing data to date suggest that antimony may be an animal carcinogen; however, the data are not sufficient for a quantitative estimate of cancer potency (203). Inhalation of antimony dust in laboratory rats may increase the risk of lung cancer, but there is no evidence of an increased risk in animals fed an antimony-containing diet or drinking water. Female rats exposed to antimony trioxide at 4.2 and 3.2 mg/m^3 for 6 h/day, 5 days/week for one year, developed lung tumors after one additional year of observation (232). Similar results were reported in another study in which 27% of female rats were exposed to 45 mg/m^3 antimony trioxide for one year, and 25% of female rats exposed to 38 mg/m^3 antimony ore containing mostly antimony trisulfide developed lung neoplasms (233). In addition, no lung tumors were observed in male rats exposed to either antimony compound, or in the controls. The International Agency for Research on Cancer (IARC) has concluded that antimony trioxide is a possible carcinogen (234); antimony trioxide production has been given an A2 suspected human carcinogen designation by the ACGIH but no TLV has been assigned to date (207). There is still limited evidence for the carcinogenicity of antimony trisulfide (234).

2.4.1.6 Genetic and Related Cellular Effects Studies Both negative and positive results have been reported in genotoxic assays of antimony and its compounds (189).

2.4.2 Human Experience 2.4.2.1 General Information Most acute and chronic information about antimony toxicity, was obtained primarily from industrial airborne exposures; occupational exposures are usually by inhalation of dust containing antimony compounds, antimony tri- and pentachloride, trioxide, and trisulfide (235). Data on the adverse effects from treating parasitic diseases with antimony compounds were also reported.

2.4.2.2 Clinical Cases 2.4.2.2.1 Acute Toxicity Respiratory effects may be acute, particularly from airborne tri- and pentachloride exposures that induce rhinitis and even acute pulmonary edema (235). Acute respiratory exposure to antimony trichloride (73 mg/m^3) produced irritation and soreness of the upper respiratory tract in several workers (236). Cordasco and Stone (237) reported three cases, two of them fatal, of severe pulmonary edema induced by antimony pentachloride exposure, although no air concentrations were available. Gastrointestinal effects were recorded upon acute exposure to antimony compounds. Inhalation of dust containing antimony by factory workers induced gastrointestinal irritation, probably the result of antimony dust transported via the mucociliary escalator and swallowed (189). Acute symptoms, including abdominal cramps, diarrhea, and vomiting, among smelter workers subjected to heavy exposure to antimony fumes were reported by Renes (192). Potassium antimony tartrate at a dose of 0.53 mg/kg can induce vomiting (238). Vomiting, nausea, and diarrhea were reported in 150 children who drank an antimony-contaminated lemon drink (239). Acute antimony poisoning is rare but can result in death within several hours (203). Various toxic side effects and cases of sudden death were recorded in connection with medical treatment of tropical diseases using antimony compounds (240). Common features during treatment with antimony compounds are nausea and vomiting (241–243).

Acute antimony poisoning is rare, and hence little documentation is available. Symptoms such as vomiting, diarrhea, colic, and a metallic taste have been described in a number of reports of acute antimony poisoning. Seventy people became ill after drinking a lemonade drink containing 0.013%

antimony, and 56 people were taken to the hospital with burning stomach pains, nausea, vomiting and colic (238, 262). Werrin (239) reported acute antimony poisoning of 150 children who ingested a contaminated lemon drink (about 30 mg/L). In former times, drinks stored in antimony cups were used as expectorants and emetics, the dose ranged from 30 to 60 mg to induce vomiting (263).

2.4.2.2.2 Chronic and Subchronic Toxicity Workers chronically exposed to airborne antimony and antimony compounds can develop persistent symptoms such as dermatitis, eye irritation, obstructive lung alterations, and emphysema with increased pneumoconiosis (244, 245). Chronic respiratory effects related to antimony were reported among 78 smelter workers exposed to antimony concentrations ranging from 4.7 to 11.8 mg/m^3 for periods exceeding two weeks (192). Symptoms suffered by the workers included rhinitis (20%), pharynigitis (8%), pneumonitis (5.5%), and tracheitis (1%). In addition, 70% of the workers experienced soreness in the nose and nosebleeds. It must be noted that the workers were also exposed to arsenic concentrations around 0.7 mg/m^3, and hence several of the symptoms may have been caused by arsenic, considering the more toxic properties of the metal (246). Respiratory tract irritation was not mentioned by Brieger et al. (193) in an extensive study of workers exposed to antimony trisulfide ranging from 0.6 to 5.5 mg/m^3. Pneumoconiosis-like X-ray pictures obtained from workers who had long-term occupational exposure to antimony have been noted by several authors (244, 245, 247–251). It is likely that silica may have been present in some of these instances (191). An X-ray method for measuring inhaled antimony trioxide was developed by McCallum et al. (252), and a significant correlation between estimated lung antimony and the period of employment was found upon examining 113 antimony process workers. A report of the examination of 51 Yugoslavian antimony smelter workers showed X-ray changes that indicated antimony pneumoconiosis (antimoniosis); the X-ray findings were characterized by the presence of diffuse, densely distributed, punctate opacities whose diameter was less than 1 mm (245). In addition, pulmonary function tests showed obstructive changes and mixed restrictive-obstructive changes, along with increases of airway resistance and decreased forced expiratory flow rates. Chronic coughing was also another major complaint of the exposed workers. Other investigators also observed lung changes among antimony workers exposed to antimony trioxide for up to 28 years (247, 253); the prevalence of pneumoconiosis and symptoms of emphysema were given as 21 and 42%, respectively, among the workers (253). Antimony pneumoconiosis has been commonly regarded as a benign condition that had no detrimental effects upon health or life expectancy (251), but chronic respiratory effects were reported in a number of studies, and therefore heavy antimony exposure cannot be regarded as harmless (191). Skin effects from chronic antimony exposures have been reported. Pruritic skin papules progressing to skin eruptions, referred as “antimony spots,” are occasionally seen in workers chronically exposed to antimony and its salts. Of thirty-two antimony smelter workers examined by Potkonjak and Pavlovich (245), 67.2% had developed “antimony dermatosis.” The skin eruptions are transient and mainly affect skin areas exposed to heat and where sweating occurs (192, 248, 254, 255). Circulatory system and cardiovascular effects were reported by Brieger et al. (193) upon examining 124 abrasive industry workers exposed to airborne antimony trisulfide ranging from 0.6 to 5.5 mg/m^3 for 8 to 24 months. Six workers died suddenly, and two died from chronic heart disease during this period. In addition, ECG changes, mostly of the T-wave, were seen in 37 out of 75 workers examined. It must be noted that no control group was examined in this study. Cardiovascular effects, including arrhythmia, were also reported among antimony exposed persons in clinical settings (256, 257).

2.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Single intramuscular or intravenous injections in human volunteers produced higher 24-hour urinary excretion of pentavalent (80%) than of trivalent (25%) antimony compounds, a similar pattern found in animal data (225, 258, 259). A study of elimination of a single intravenous administered dose of labeled antimony potassium tartrate (trivalent antimony) showed urinary excretion about four times higher than fecal elimination, and in one patient about 73% of the total dose was eliminated within 4 weeks (260). When pentavalent antimony in the form of sodium stibgluconate was administered intramuscularly to patients, about 95% of the dose is recovered in urine within 6 hours indicating that the initial excretion of antimony in humans is rapid (190). A study by Mansour et al. (261) suggested there may be a long-term

component of antimony elimination. They found average blood and urine antimony levels of 6.7 and 27.6 mg/L, respectively, in three patients clinically treated one year earlier for bilharzia with antimony. Because antimony is a group VA element, it has many of the same chemical and toxicological properties as arsenic, although it is less toxic. For example, the toxicity of trivalent compounds is greater than the pentavalent compounds. Hence, the metabolism of antimony is similar to that of arsenic, and antimony tends to bind to sulfhydryl groups of respiratory enzymes (203).

Much of the data from the studies of industrially exposed persons give information regarding the excretion of antimony by monitoring antimony levels in the urine of workers. Workers exposed to air containing around 3 mg/m^3 antimony showed urinary antimony values ranging from 0.08 to 9.6 mg/L, which are higher compared to normal values (193). Smith and Griffiths (269) found higher urinary concentrations of antimony ranging from 10–220 mg/L in urine samples from exposed workers compared to urine samples of nonexposed persons (less than 1 to 5 mg/L). A number of studies also examined the half-life of antimony retention in the lungs of industrial workers exposed to airborne antimony. A study by Gerhardsson and his group (270) of lung tissue obtained from former exposed smelter workers found that inhaled antimony may be deposited and retained in the lungs up to several years. Exposed workers had an average of 12 times higher lung concentrations of antimony (315 mg/kg) compared to nonexposed persons (26 mg/kg). Leffler and co-workers (271) studied lung retention of antimony and arsenic in hamsters after intratracheal instillation of industrial dust neutron-activated from a Swedish copper smelter. In this study, two phases in lung clearance of antimony were found: the half-life for the initial phase was 40 hours for antimony trioxide and 30 hours for antimony dust, and the half-life for the second phase was approximately 20 to 40 days for antimony trioxide and antimony dust. The low solubility of antimony in factory dust along with its long biological half-life may explain the observed lung accumulation and retention of antimony in industrially exposed workers (191).

2.4.2.2.4 Reproductive and Developmental A report from Russia reported an increase in the number of spontaneous abortions in women exposed to antimony in the workplace, but no exposure levels were available (189, 230). The often-cited Balyaera report (231) indicates an increase in the number of spontaneous abortions and menstrual cycle disturbances among female workers exposed to antimony-containing aerosols. In animal studies, no effects were observed in the offspring of rats administered low doses of antimony trichloride in drinking water.

Gynecological examinations were performed on women who were exposed to dust that contained metallic antimony, antimony trioxide, and antimony pentasulfide during a two-years period (231), and a higher incidence of “various sexual disturbances” was reported in exposed women compared to the controls (77.5% vs. 56.0%). Disturbances of the menstrual cycle, inflammatory disease, and other ailments of the sexual organs were reported. The incidence of spontaneous abortions was 12.5% in the exposed women as compared with 4.1% in the controls, and the incidence of premature births was 3.4% versus 1.2% in controls. Birth weights of children born to exposed women were comparable to the controls, but the body weight of children of exposed women began to lag after one year. It must be noted that the level of antimony exposure in this study was not specified, and it is not known how the control group was selected, whether confounding factors were controlled for, and if exposures to other toxic substances occurred.

The often cited Balyaera study (231) indicated that women workers exposed to dust containing antimony and antimony compounds experienced a greater incidence of spontaneous abortions than a control group of non-exposed females. Aiello (272) observed a high rate of premature deliveries among women workers in an antimony smelting and processing plant.

2.4.2.2.5 Carcinogenesis Existing experimental data suggest that antimony may be an animal carcinogen, but there is lack of data on the possible carcinogenic properties of antimony and antimony compounds for human exposures. The ACGIH (246) refers to unpublished data on a large antimony smelter in the United Kingdom in the 1960s where workers were exposed to antimony

trioxide ranging from 0.5 to 40 mg/m^3. The data may indicate increased mortality in lung cancer among the heavily exposed workers, but the workers were also exposed to zirconium making the data cited difficult to interpret (191, 246).

2.4.2.2.6 Genetic and Related Cellular Effects Studies No genotoxic effects from human exposure to antimony and antimony compounds were reported.

2.4.2.3 Epidemiology Studies Most epidemiological findings come from the studies of occupationally exposed industrial workers and of persons clinically exposed to antimony compounds for treating tropical diseases and parasitic infections.

Epidemiologic data regarding chronic antimony toxicity comes mainly from studies of occupationally exposed workers in the mining and extraction industries. Renes' (192) study of 78 smelter workers relates chronic respiratory effects, such as rhinitis, pharyngitis, pneumonitis, trachetiis, and chronic cough to antimony exposures. However, the workers were also exposed to arsenic concentrations that may have influenced the results. Brieger and co-workers (193) reported excess mortality and morbidity among 124 workers in the abrasive industry. The report describes respiratory, cardiovascular, and gastrointestinal effects among workers exposed to antimony trisulfide ranging from 0.6 to 5.5 mg/m^3 for 8 to 24 months. A study by McCallum and co-workers (252) using X-ray spectrometry for measuring inhaled antimony trioxide found a significant correlation between estimated antimony levels in the lung and the period of employment in years among 113 antimony process workers. X-ray changes indicating antimoniosis and altered pulmonary function tests were reported among 51 Yugoslavian smelter workers exposed for 9 to 31 years to dust containing antimony trioxide antimony pentoxide, and free silica (245). They also describe the development of “antimony dermatosis” among 62.7% of the workers. Two other groups reported lung effects (including pneumoconiosis and emphysema) in antimony workers (247, 253). Adverse effects during clinical antimony treatment for parasitic infections were described. ECG changes, particularly in the T-wave, were reported frequently during long-term treatments (264–268).

There are no epidemiological data available to suggest that antimony is genotoxic in humans.

2.5 Standards, Regulations, or Guidelines of Exposure

Approaches used to limit exposure to arsenic apply also to antimony and antimony compounds. The OSHA permissible exposure limit (PEL), the NIOSH recommended exposure limit (REL), and the ACGIH threshold limit value-weighted average (TLV-TWA) for antimony and its compounds 0.5 mg/m^3 (207). The ACGIH has listed antimony trioxide as a suspected source of human carcinogenicity with an A2 designation.

2.6 Studies on Environmental Impact

Antimony is a common air pollutant that occurs at an average concentration of 0.001 mg/m^3 (203). Antimony is released into the environment from burning fossil fuels and from industry (198). In the air, antimony is rapidly attached to suspended particles and thought to stay in the air for 30 to 40 days (198). Antimony is found at low levels in some lakes, rivers, and streams, and may accumulate in sediments. Although antimony concentrations have been found in some freshwater and marine invertebrates, it does not biomagnify in the environment (198, 199). The impact of antimony and antimony compounds on the environment has not been extensively studied to date.

Arsenic, Antimony, and Bismuth

Lisa Gallicchio, Bruce A. Fowler Ph.D., Emily F. Madden

3.0 Bismuth

3.0.1 CAS Number:

[*7440-69-9*]

3.0.2 Synonyms:
None
3.0.3 Trade Names:
None
3.0.4 Molecular Weight:
208.980
3.0.5 Molecular Formula:
Bi
3.1 Chemical and Physical Properties
3.1.1 General Bismuth is a brittle, white, crystalline metal that has a pinkish tint. It is the most diamagnetic of all metals, and its thermal conductivity is lower than any metal except mercury. In addition, bismuth has high electrical resistance and the highest Hall effect of any metal. Inorganic salts of bismuth are poorly water soluble; solubility is influenced by the acidity of the medium and the presence of additional certain compounds containing sulfhydryl or hydroxyl groups (273). Bismuth belongs to the VA group of the periodic system together with arsenic and antimony, and it forms compounds in the +3 and +5 oxidation states. Bismuth occurs in the native form; however, it is found largely in nature in minerals such as bismite, bismuthinite, and bismutite and is usually associated with sulfide ores of lead and copper and tin dioxide.

3.1.2 Odor and Warning Properties Human exposure to bismuth and bismuth compounds is quite limited, except for its use in medicine where it has been prescribed for more than a century. Occupational and environmental exposure to bismuth and its toxicological significance are still unknown.
3.2 Production and Use
Bismuth is used in low-melting alloys and metallurgical additives, including thermoelectric and electronic applications. It is also used for catalysts, pearlescent pigments in cosmetics, in industrial chemicals, and in pharmaceuticals. Bismuth compounds have been used as antiseptics, astringents, antacids, dusting powders, and as radio-opaque agents in X-ray diagnosis.

Organic bismuth compounds such as tartrate, gallate, nitrate, and salicylate were used in the treatment of syphilis before the advent of penicillin in the 1940s (274). Inorganic bismuth compounds such as Bi subnitrate, subcarbonate, and subgallate, are still used today in some countries for treating gastrointestinal complaints including diarrhea, constipation, cramps, and flatulence. Bi subsalicylate (BSS) is the principal ingredient of Pepto-Bismol, and is consumed worldwide in large quantities (275). Colloidal Bi subcitrate (CBS) is available by prescription for treating of peptic ulcer and has prove to be effective as a histamine H2-antagonist for treating gastric and duodenal ulcer when given in 4- to 8-week courses (273, 276). Bismuth subgallate (BSG) is still used as a topical antiseptic for the skin and as a hemostatic agent after adenotonsillectomy (273, 276). Bismuth subsalicylate (BSS) is used in treating and the preventing traveler's diarrhea in the United States (277), and also for treating *Helicobacter pylori* associated with gastritis (278).
3.3 Exposure Assessment
3.3.1 Air The concentration of bismuth in the air outside cities is less than 1 mg/m^3 (275). Bismuth concentrations in urban air range from 1 to 66 ng/m^3, and concentrations in rural air from 0.1 to 0.6 ng/m^3 (279). It is estimated that the daily intake of bismuth via inhalation is <0.01–0.76 mg (280, 281).

3.3.2 Background Levels Investigation of ambient concentrations of bismuth is limited because industrial and environmental bismuth poisonings are rare (275). Bismuth levels in seawater have been reported at 0.2 mg/L (282), and much lower values in the range of 0.053–0.63 ng/L have been reported for ocean surface waters (283). Levels of bismuth in soil have been reported at 1 mg/kg, and in rocks bismuth levels range from 0.1 mg/kg in coal to 3 mg/kg in sandstone (284). The daily intake of bismuth from food and water ranges from 5 to 20 mg (283). Representative food samples pooled from the main regions of the United Kingdom were analyzed, and it was estimated that the daily intake of bismuth is less than 5 mg (285). Woolrich (280) reported that the daily intake of bismuth

from food and water is about 20 mg, but data on bismuth concentrations in specific food items were not given in this report.

3.3.3 Workplace Methods Exposure to bismuth and bismuth compounds can occur in the manufacture of pharmaceuticals, cosmetics, and industrial chemicals. Information regarding occupational exposures to bismuth is lacking, but it may soon gain attention because bismuth is being increasingly used to replace lead in many chemical and technical applications (286). NIOSH Analytical Method #0500 is recommended for determining workplace exposures to bismuth telluride doped with selenium sulfide and undoped (10a).

3.3.4 Community Methods Human exposure to bismuth and bismuth compounds is frequently through the use of bismuth-containing medications, and consumption worldwide is often under uncontrolled situations. Though evidence shows that the risk of bismuth-related toxicity is low in the general population, clinicians should be aware of the possibility that bismuth is involved in neurotoxicity, although not much is known regarding its mechanisms (287).

3.3.5 Biomonitoring/Biomarkers 3.3.5.1 Blood Concentrations of Bi measured in the blood are not predictive of the severity of Bi-induced encephalopathy (288), but concentrations in the CSF and may reflect the clinical condition of an exposed individual better (289). It is unlikely to detect bismuth levels in the blood of persons recently exposed to Bi therapy for gastric ulcers (290).

3.3.5.2 Urine High Bi concentrations in the urine can also support the diagnosis of Bi-induced encephalopathy, but such measurements are more difficult to relate to the severity of the clinical condition (287). The methods of choice at present for quantifying bismuth in urine, blood, and serum are either electrothermal AAS or AAS with hydride generation (273). For the analysis, sample pretreatment is usually necessary because of matrix effects.

3.3.5.3 Other Intracellular inclusion bodies (metal-protein complexes), observed after exposure to bismuth occurs most frequently in the nuclei of cells in the proximal renal tubule (291–293). It is unclear what role the formation of these metal-protein complexes have in bismuth-induced nephrotoxicity (273). The clinical significance of these inclusion bodies may be as a diagnostic indicator of exposure (293).

3.4 Toxic Effects

The main target organs of bismuth toxicity are the brain, kidney, and bone. Common toxic effects that have been attributed to bismuth and bismuth compounds in humans are encephalopathy, nephropathy, osteoarthropathy, gingivitis, stomatitis, and colitis. (273). The liver could be a target organ of Bi toxicity, and whether hepatitis is an adverse side effect of bismuth intoxication is still in dispute (273). Adverse side effects on the various organ systems may depend on the chemical and biological characteritics of the bismuth compound. For example, neurotoxicity, it has been found, is caused by “insoluble” inorganic bismuth compounds, whereas bismuth compounds used in the past for treating syphilis caused nephrotoxicity and bone disease (273).

3.4.1 Experimental Studies 3.4.1.1 Acute Toxicity Application of trimethyl- and triethylbismuth to the skin of rabbits and rats reportedly produced intense inflammation and edema. In addition, local necrosis was also observed at the injection sites. Another local effect was eye irritation after inhalation exposure to alkylbismuth (294). Acute local effects of inhalation, including pulmonary edema, were observed after inhalation of trimethylbismuth by dogs, rats, and cats. Acute administration of bismuth salts produced both liver and kidney toxicity in both humans (274, 295–298) and animals (299). Toxicity in the kidney is observed primarily in the renal proximal tubule cells by the development of phosphaturia, amino aciduria, and glucosuria (296). More recent studies (299) demonstrated marked inhibition of enzymes in the heme biosynthetic pathway in both liver and kidney. The mechanisms of bismuth toxicity and target organelle damage are complex and involve disrupting a number of biochemical systems. Liver toxicity was observed as cloudy swelling, nuclear degeneration, and random small foci of necrosis after rabbits were given lethal injections of sodium and potassium tartro-bismuthate (i.v. 10–30 mg/kg; i.m. 150–350 mg/kg) and bismuth trioxide (i.m.

450 and 500 mg/kg) (300). Exposure to bismuth tri- or thioglycollamate and bismuth diallylacetate induced acute renal toxicity, and these compounds are no longer used in medicine (287). In some cases, bismuth-induced acute nephrotoxicity is reversible (295–297, 301–305). Kidney damage was produced in rats given single intramuscular injections of 13 different bismuth compounds at concentrations ranging from 0.03 to 1.5 g/kg (274). Histological examination of 104 rats showed that 36 or 37 of the animals that died before 21 days had varying degrees of nephritis as had 11 of the 67 surviving animals. The most prominent site of toxicity was the proximal tubule. Bismuth thioglycollate was the least toxic compound, although doses of 0.04–0.080 g/kg produced severe nephritis. Subcutaneous injections of 5 g bismuth subnitrate daily for up to 3 days produced degenerative changes, and intranuclear and cytoplasmic inclusion bodies were found in the renal proximal tubules of rabbits (291). The formation of pathognomonic bismuth-containing intranuclear inclusion bodies (291–293) in renal proximal tubule cells (Figure 36.2) is hence an important diagnostic indicator of elevated bismuth exposure. The relationship of the formation of these structures to bismuth binding to metallothionein-line proteins (306, 307) in the kidney is presently not clear but may be related to a process similar to that observed in renal lead-binding proteins (308, 309, 310, 311), and the formation of pathognomonic lead-containing intranuclear inclusions. The toxicological significance of the inclusion body phenomenon rests with the intracellular storage of these toxic metals in a target cell population such as the renal proximal tubular epithelium. They appear as sharply defined, round structures whose diameter is up to 5 mm and are found mainly in the cell nuclei, in the cytoplasm, and possibly in the lysosomes. Inclusion bodies were observed in 86% of the kidneys of syphilis patients medically treated with bismuth compounds (291). These inclusions contained bismuth, proteins, carbohydrates, lipids, and sulfur (292, 293, 312–314). Their implication in bismuth-induced renal toxicity still remains unclear (287). Enzymes in the heme biosynthetic pathway were highly sensitive to inhibition by bismuth both *in vivo* and *in vitro* (299). Specifically, rats injected with bismuth subnitrate over a dose range of 0, 20, 40, and 80 mg Bi/kg and sacrificed 16 hours later showed marked mitochondrial swelling and distortion of the inner mitochondrial membranes of both liver and kidney at the 40 and 80 mg Bi/kg dose levels. These morphological effects were associated with dose-related decreases in the activities of the mitochondrial enzymes ALA synthetase and heme synthetase and the cytosolic enzyme ALA dehydratase in liver. In kidneys, similar dose-related decreases in the activities of ALA synthetase and ALA dehydratse but not heme synthetase were observed. *In vitro* studies using bismuth concentrations from 0–0.4 mM for 1 hour demonstrated that the observed effects on the mitochodrial heme pathway enzymes are the result of both membrane distortion and the direct inhibitory action of bismuth on these essential enzymatic activities.

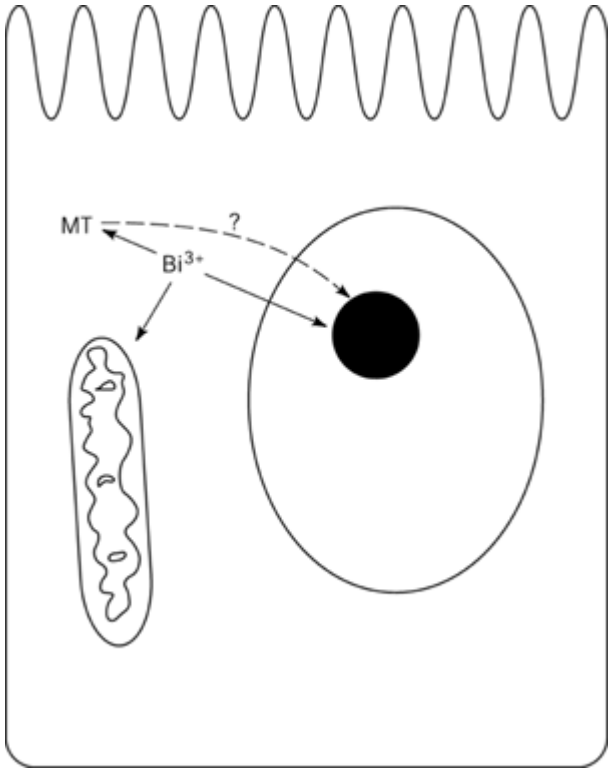


Figure 36.2. Diagram of renal proximal tubule cell showing a pathognomonic bismuth-containing intranuclear inclusion body, bismuth binding to methallothionein-like proteins, and reaction with heme biosynthetic pathway enzymes.

3.4.1.2 Chronic and Subchronic Toxicity With chronic ingestion, bismuth accumulates in a number of tissues until both nephrotoxicity and neurotoxicity develop (275). It has been found that patients who died of Bi encephalopathy had Bi concentrations in the gray matter (1.2 to 29 mg/g) that were generally twice as high as that in the white matter (1.3 to 15.9 mg/g) (315). The highest concentrations of Bi were found in the thalamus, frontal, and cerebellar cortex. In another body, the highest Bi concentrations were found in the brain stem and the pons (316). The precise mechanisms of Bi-induced neurotoxicity, including Bi encephalopathy, still remain unclear. One *in vitro* study showed that astrocytes are much more sensitive to Bi sodium tartrate than nerve cells in cultures of brain, meninges, and neuronal retina cells from chicks (317). Damage to astrocytes may be responsible for the early "vague" symptoms of Bi neurotoxicity, whereas nerve cells are damaged only after prolonged Bi exposure. Neuronal cell degradation in rat hippocampal slices was demonstrated from prolonged Bi exposures, whereas no effects on the bioelectric activity of pyramidal cells were observed for acute exposures (317). Chronic nephrotoxicity from bismuth exposure was observed in a number of animal studies. Hemorrhages in the cortical and cerebral layer of the kidney and lymphohistiocytic infiltrations were found in rats after 6 months of peroral treatment with potassium bismuthate and bismuth sulfate (0.025–5.0 mg/kg) (318). The administration of bismuth trichloride by subcutaneous injection at doses of 1.0, 2.0, and 3.0 mg/kg every other day for up to 2 weeks greatly increased renal concentrations of copper and concomitant levels of metallothionein-like proteins (306).

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 3.4.1.3.1 Absorption Bismuth compounds are considered slightly to moderately absorbed through the respiratory and gastrointestinal tracts, depending on their solubility. Slikkeveer and de Wolff (319) divided pharmacologically active bismuth compounds into four toxicological groups: Groups 1: water-insoluble organic salts and subsalts that are absorbed minimally from the gut and cause no toxicity; Group 2: absorbable lipid-soluble organic compounds that can elevate Bi blood levels and cause neurotoxicity and hepatoxicity; Group 3: absorbable water-soluble organic compounds that elevate Bi blood levels and

cause nephrotoxicity; and Group 4: water-soluble complexes that hydrolyze in the gastrointestinal tract with some absorption of Bi and the hydrolyzed radical, elevating Bi and complex radical levels. The absorption of inorganic Bi compounds, it is suggested, depends on their solubility in the gastrointestinal tract (320–322). In one study, the bioavailability of radiolabeled Bi compounds corresponded with the solubility in artificial duodenal juice but not with the solubility in gastric juice (323). Citrate enhanced intestinal absorption of bismuth from Bi subnitrate, Bi subsalicylate, Bi citrate, $BiCl_3$, and colloidal Bi subcitrate during *in vivo* perfusion of rat intestine (273). In addition, the simultaneous intake of citrate and Bi subnitrate by human volunteers increased bismuth absorption significantly, and the absorption profiles for Bi in blood and citrate in serum were parallel, suggesting the formation of a bismuth citrate complex (273). A notable rise in bismuth blood levels was seen after oral administration of Bi subnitrate and sulfhydryl-containing compounds, the increase was largest for 3-mercaptopropionic acid, penicillamine, cysteine, and homocysteine (324). No effect on bismuth absorption was found for serine, alamine, and methione. Bismuth absorption was also increased by the simultaneous intraperitoneal administration of Bi subnitrate and cysteine (325). Promotion of bismuth absorption has also been suggested for several other hydroxy-containing compounds (287), for sorbitol (326), and for lactic acid (327), but experimental proof is lacking. Because bismuth is not an essential element, it is thought to share absorption routes with other different substances (287). Several unidentified bismuth species may form in the intestine that may then partake in counterion absorption, but the actual sites of bismuth absorption are not known (287).

3.4.1.3.2 Distribution The chemical form of bismuth in the blood is not known, and there are no data available on the specific carriers of bismuth in the blood after oral intake of bismuth compounds (287). It has been shown *in vitro* that 17% of radioactive bismuth citrate was associated with erythrocytes, and the remainder of the concentration was bound to serum proteins (328). Twenty days after an oral dose of colloidal Bi subcitrate, a relatively considerable amount was associated with red blood cells (about 8.7% of the dose) (323). Two hours after the addition of bismuth subnitrate to whole blood, about 82.3% was found in red blood cells at 25 mg/L, and about 97.7% was found at 2500 mg/L (329). For concentrations below 200–300 mg/L, overall binding to the blood components seemed to be stronger than above the level. Gel filtration of blood after incubation with bismuth subsalicylate exhibited an association of bismuth with the higher molecular weight fraction (>200,000 Da): a_2-macroglobulin, IgM, b-lipoprotein, and haptoglobulin (322). The distribution of bismuth in the various organs is mostly independent of the Bi compound administered or the route of administration because the highest concentration per gram wet weight was always recovered in the kidneys (328, 330–335). However, with more detailed studies of bismuth distribution, exceptions have been found. For example, when bismuth was administered as a colloid or adsorbed onto charcoal, the distribution after intravenous delivery depended on particle size where Bi-containing particles were found mainly in the lung and in the reticuloendothelial system (328, 336, 337). In a study of tissue distribution of Bi subnitrate, Bi subsalicylate, colloidal Bi subcitrate, Bi citrate, and Bi subnitrate with added citrate buffer in rats fed for 14 days to reach comparable Bi concentrations in the blood, it was found that rats fed Bi subsalicylate had lower Bi levels in the kidney and higher levels in the liver compared to other Bi compounds (273). Although Bi subsalicylate intake led to the lowest bismuth levels in the kidneys, it was the only compound to show transient kidney toxicity at the highest blood concentration. For dogs orally administered trimethylbismuth, the concentration of Bi was higher in the liver than in the kidneys, which is most likely due to the organic characteristics of the compound (294). The kidneys had the longest retention time of bismuth compared with any other organ (287). Russ et al. (328) found that 144 hours after intravenous injection of ^{206}Bi citrate, 12% of the injected dose remained in the kidneys, 0.9% in the bone, and no or very little of Bi remained in other organs. For rats exposed for 14 months to colloidal Bi subcitrate, bismuth levels ranked from high to low in the kidney, lung, spleen, liver, brain, and muscle respectively (338). The wet weight concentrations of Bi in the kidney were 13.9 mg/g and 0.13 mg/g in the muscle. In other studies where bismuth concentrations in the bone were measured, the concentrations in bone were usually 10 to 20 times lower than in the kidney (335, 339, 340). Elevated bismuth concentrations in the brain were observed in a number of studies

and may account for its neurotoxic effects. In animals and humans that received bismuth, the concentration in the brain tissue was higher than in the controls, showing that Bi can pass through the blood–brain barrier, although in small quantities (338, 341–343). In rats administered radiolabeled bismuth citrate intravenously, the highest activity was found in the spinal cord, medulla oblongata, hypothalamus, and pons after 2 hours (333).

3.4.1.3.3 Excretion Bismuth is eliminated from the body through the urine and feces, and the route may depend on the Bi compound and the dose (287). In one study where rats were intravenously injected with ^{206}Bi nitarte, 38% of the metal was excreted in four days: 21% in the urine and 17% in the feces (340). After intramuscular injection of bismuth butylthiolaureate to rats, equal amounts of Bi were excreted in the urine and feces after 90 days, and 10% of the dose remained in the body (344). In humans, the elimination of different Bi compounds was showed no differences; 99.9% of an oral dose of several radiolabeled Bi compounds was excreted in the feces (323). On day 12 after exposure, the ratio of Bi in the urine and feces (bile) was 1:1. In the presence of biliary drainage, Bi could still be found in the intestine after intravenous delivery, implying that Bi is eliminated into the intestine, partly through intestinal and partly through bile secretion (334). The cecum in rats is suggested as a location for intestinal secretion because after intravenous injection, a high amount of Bi was recovered there (333, 344, 345). A number of studies suggest a two- or three-compartment model to describe the elimination kinetics of Bi, and the kidney is the major compartment (287). For example, in one study of two human volunteers intravenously administered ^{206}Bi and of three patients recovered from Bi-induced encephalopathy, the half-lives of 3.5 min, 0.25 min, and 3.2 hours were established (346). For rats exposed to a single oral dose of ^{205}Bi as colloidal Bi subcitrate, a three-compartment model was used to describe urinary and fecal elimination; the biological half-lives were estimated at 10, 36, and 295 hours, respectively (323). The elimination half-life in human plasma after multiple dosing was estimated at about 20.7 days (347). It must be noted there is considerable variation and little consistency in the data, possibly due to the use of different bismuth compounds in the studies, some of them even unnamed (287).

3.4.1.4 Reproductive and Developmental There is no evidence to date that bismuth has any reproductive and developmental effects in humans or in animals.

3.4.1.5 Carcinogenesis An old life time study with rats fed 2% bismuth subcarbonate (BSC) in the diet did not show an increase of tumors or a decrease of survival (348).

3.4.1.6 Genetic and Related Cellular Effects Chromosomal aberrations with gaps were observed in the mouse bone marrow after an oral uptake of an aqueous suspension of Bi_2O_3 for up to 21 days (349). In addition, no abnormal sperm were detected in this experiment. It must be noted that in this mutagenicity study, no measurements of Bi blood levels were taken to ensure that bismuth had indeed reached the bone marrow because Bi_2O_3 absorption from the gastrointestinal tract is considered negligible (287).

3.4.1.7 Other Neurological, Pulmonary, Skin Sensitization Blood pressure of dogs, received hypodermic or intramuscular injections of trimethylbismuth (at 4 doses of 350 mg/kg) dropped to shock level without alteration of heart rate, arrhythmia, or blockage. The animals were anesthetized with barbiturates (294). A slight decrease of blood pressure and amplitude in heart rate was observed after intravenous injection of elemental bismuth (0.50 mg/kg). Higher bismuth doses of 1.8 mg/kg resulted in heart block, and all fundamental heart functions were affected, including excitability, conductivity, and contractility (350).

3.4.2 Human Experience 3.4.2.1 General Information There are very few reports of occupational exposure to bismuth and its compounds. An important source of bismuth exposure in the past has been through the therapeutic use of bismuth compounds to treat infections such as syphilis and gastrointestinal complaints. Because of problems associated with acute and chronic bismuth toxicity,

the medical use of bismuth compounds has been restricted in Europe, Canada, and Australia (275).

3.4.2.2 Clinical Cases 3.4.2.2.1 Acute Toxicity Clinical manifestations of acute bismuth intoxication are similar to those caused by mercury and lead: neurological abnormalities which include encephalopathy, and renal dysfunction with nephrotic syndrome that may progress to acute failure (275). The blood levels may reach 1500 to 2000 mg/L when large amounts of bismuth compounds are ingested acutely, resulting in encephalopathy with obtundation that can progress to coma, myoclonus, and abnormal electroencephalographic readings (351). Daily doses of 5 to 10 g of bismuth subsalicylate caused encephalopathy after 7 days in one patient, whose blood bismuth levels reached 200 mg/L and urine bismuth concentration was 2960 mg/L. Chelators such as British antilewisite or dimercaprol can be used for severe bismuth poisoning. Clinical symptoms of bismuth toxicity may resolve over a course of several weeks to months after a patient ceases using bismuth compounds (275). There are no reports of occupational exposure effects of bismuth (352).

Application of trimethylbismuth to human skin produced no effects, but irritation developed when the exposed skin had been scratched. Irritations of the eye and upper respiratory tract were also observed for humans (294).

3.4.2.2.2 Chronic and Subchronic Toxicity Chronic ingestion of bismuth compounds produces bismuth lines (pigmentation) on the gums and way cause stomatitis, excess salivation, osteoarthropathy, and pathological fractures (275). Generalized osteoporosis, sometimes in combination with osteomalacia, was observed after bismuth treatment for syphilis (287), Lesions were often localized in the pelvis, the head of the femur, and the vertebrate. It has been mentioned that the presence of bismuth in the bone can aggravate a preexisting tendency toward osteoporosis (353–355). Hepatotoxicity from bismuth intoxication is suggested from one case study of 121 inmates in an American prison who had liver damage after receiving bismuth therapy for syphilis (356). It must be noted that no bismuth concentrations were measured in this study, and hence the association of bismuth intake with hepatotoxicity is viewed as unconvincing (287). There are numerous cases that report the neurotoxicity of bismuth compounds, the clinical cases usually include Bi encephalopathy. Before the onset of encephalopathy, a “prodromal period” occurs of other varying symptoms such as deterioration of memory, impairment of walking, standing and writing, insomnia, changes in behavior, depression, anxiety, hallucinations, and excitation (287). The observed characteristic symptoms of Bi encephalopathy are myoclonia, changes of awareness, astasia and/or abasia, and dysarthria. Myoclonias were frequently observed in the distal parts of the arms but were also observed in the legs, trunk, face and tongue (287). One case history described a 69-year-old German patient who developed depression, insomnia, lack of concentration, nervousness, and panic attacks after the intake of Bi nitrate at 8 g/day for a period of 3 weeks. After 12 months of bismuth intake, he was diagnosed as suffering from major depression, and he gradually developed difficulty with short- and long-term memory, difficulty in reading and writing, tremor, vertigo, and dysarthria. After 15 months of bismuth intake the syndrome progressed into full myoclonic Bi encephalopathy. Another case hisotry describes a German woman who used a Bi subgallate containing stomach powder for more than 15 years and suffered from dementia, abnormal coordination, occasional tremors, and dysarthria. The Bi concentration in her blood was 70 mg/L six days after discontinuing Bi subgallate intake. The patient was discharged from the hospital after 4½ months in good medical condition, indicating the reversibility of Bi-induced encephalopathy. In France, where a wide range of bismuth compounds on the French market were used for gastrointestinal complaints, an epidemic outbreak of encephalopathy possibly related to bismuth intake drew public attention in 1974 (357). Bismuth subnitrate was involved most frequently in bismuth-induced encephalopathy because it was used by the majority of patients (358). Legal restrictions on the sale of Bi-containing compounds in France were imposed, overall Bi sales declined, and indirectly the number of patents who had Bi encephalopathy declined (359). In 1980, a total of 942 cases was reported in France, 72 of which ended in death (360). It has never been proven that these deaths were directly associated with bismuth intake.

3.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms There is very little known regarding the

mechanisms of toxicity of bismuth and bismuth compounds. Because the clinical signs of acute bismuth toxicity are similar to those of lead and mercury, the curent knowledge of the mechanisms of toxicity of these two metals may help to elucidate the mechanisms behind bismuth toxicity in animals and in humans (275).

3.4.2.2.4 Reproductive and Developmental Although bismuth can penetrate the placenta (361) there are no clinical reports of teratogenicity in humans.

3.4.2.2.5 Carcinogenesis There is no evidence of carcinogenicity of bismuth compounds in humans.

3.4.2.2.6 Genetic and Related Cellular Effects Studies Besides one animal study that may implicate bismuth as a possible mutagen (349), there is no evidence that bismuth is mutagenic in humans.

3.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization Pityriasis, rosea-like eruptions, and other skin manifestations such as the “erythema of the ninth day” syndrome (Milian's syndrome) have been occasionally reported as a result of therapy with bismuth compounds (362, 363). Ulcerative stomatitis has been observed after bismuth treatment (364, 365). Bismuth pigmentation has been found in the colon, vagina, and the skin (366). Colitis, gastrointestinal bleeding, purpura, agranulocytosis, and aplastic anemia have also been reported after bismuth treatment (367).

3.4.2.3 Epidemiology Studies There are numerous case reports of bismuth toxicity, mostly of its medicinal use for treating syphilis and gastrointestinal complaints, but there have been no clearly defined epidemiologic studies of bismuth toxicity in the general population. An outbreak of encephalopathy in France in 1974 may possibly be related to Bi intake, but no cases were reported in the United States, the United Kingdom or in the Netherlands where large amounts of Bi were sold (289). It has never been proven that the etiology of this outbreak of encephalopathy can be attributed exclusively to Bi intake (287).

3.5 Standards, Regulations, or Guidelines of Exposure

The 1999 ACGIH threshold limit value-time weighted average (TLV-TWA) is 5 mg/m^3 for “doped” bismuth telluride, which is used in semiconductors and is “doped” with selenium sulfide to alter its conductivity and 10 mg/m^3 for undoped bismuth telluride. NIOSH has the same recommended exposure levels. OSHA has a PEL of 15 mg/m^3 for total undoped bismuth telluride and 5 mg/m^3 for respirable undoped bismuth telluride. Industrial bismuth poisoning is considered uncommon (275).

3.6 Studies on Environmental Impact

There is no evidence to date that bismuth in the environment alters the health of humans, other animals, or plants. The presence of bismuth in various organisms is not considered significant and probably results from its presence in trace amounts in soil, water, and food. Solubilization of bismuth in ground water by acid rain may increase its biological concentration and human exposure, but there is no evidence to date to suggest that this is occurring.

Arsenic, Antimony, and Bismuth

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The Halogens

Daniel Thau Teitelbaum, MD

A. Fluorine and its Compounds

1.0 Fluorine

1.0.1 CAS Number: [*7782-41-4*]

1.0.2 Synonyms: Fluorine-19

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 37.99680

1.0.5 Molecular Formula: F_2

1.0.6 Molecular Structure:

1.1 Chemical and Physical Properties

Because of the small atomic radius (Table 48.1), the effective surface charge density of the fluorine atom is greater than that of any other element, making fluorine the most electronegative and the most reactive of the elements (1–3). Under appropriate conditions, it forms compounds with all other elements except argon, helium, and neon (4). Fluorine is univalent, and no compounds are known in which fluorine has a valence of > 1. Asbestos and finely dispersed water, glass, ceramics, carbon, and metals all burn in fluorine. In contact with massive mild steel, copper, nickel, or Monel metal, fluorine forms a film that prevents further attack, which means that these materials can be used to handle fluorine at ordinary temperatures (3). Fluorine reacts with water to form hydrogen fluoride and the highly toxic oxygen difluoride, OF_2. Fluorine in combination exists in either the ionic form or the covalent tetrahedral form. Compounds resulting from the interaction of fluorine and metals are usually ionic and have high melting and boiling points. Many fluorides, for example, the fluorides of lithium, aluminum, strontium, barium, magnesium, and manganese, are sparingly soluble or insoluble in water. Nonmetallic elements react with fluorine to yield covalent compounds, for examples are silicon tetrafluoride, sulfur hexafluoride, and complex anionic forms. These covalent compounds are characterized by low melting points and high volatility. The inorganic chemistry of fluorine is discussed in detail by Glemser (5) and by the World Health Organization in its Environmental Health Criteria 36 (6).

1.2 Production and Use

Fluorine is the most reactive of all the elements. Free fluorine is rarely, if ever, found in nature. Elemental fluorine is produced on a commercial scale by the electrolysis of anhydrous hydrogen fluoride in a molten solution of potassium fluoride (essentially the same process as that used by Moissan in 1886 to isolate fluorine for the first time). Fluorine gas is formed at the anode and hydrogen at the cathode. The principal impurity is hydrogen fluoride, most of which is removed by passing the gas stream through a condensation trap; the remaining traces are converted to sodium bifluoride ($NaHF_2$) on exposure to sodium fluoride pellets.

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B. Chlorine and its Compounds

Table 48.12. Properties of Chloride Salts[a]

Compound	CAS Number	Mol. Wt.	Specific Gravity	MP (°C)	BP (° C)	Solubility
Ammonium chloride	[*12125-02-9*]	53.5	1.527^{25}	Sublimes without melting	—	283 g/L H_2O, 25° C, 396 g/L H_2O, 80°C; soluble in methanol, ethanol; insoluble in acetone, ether
Potassium chloride	[*7447-40-7*]	74.55	1.98	773	—	357 g/L H_2O, 25° C, 555 g/L H_2O, 100°C; 0.4% in alcohol; insoluble in acetone, ether

Sodium chloride	[*7647-14-5*]	58.45	2.17^{25}	804–1600	—	357 g/L H_2O, 25° C, 385 g/L H_2O, 100°C; slightly soluble in alcohol; insoluble in HCl

[a] From Ref. 222.

Table 48.13. Properties of Chlorine Dioxide and Fluorides[a]

Compound	Description	Mol. Wt.	MP (°C)	BP (° C)	Sp. Gr. (Liquid)	Solubility
Chlorine dioxide	Yellow to reddish-yellow gas; unpleasant odor similar to that of chlorine	67.46	–59.00	11	1.642	Soluble in water, alkalies, H_2SO_4
Chlorine trifluoride	Corrosive, odorless gas; sweet, suffocating odor	92.46	–76.34	11.75	1.77^{13}	Violently hydrolyzed by water
Chlorine pentafluoride	Colorless gas with a suffocating odor	130.45	—	—	—	Reacts explosively with water

[a] From Refs. 222 and 223.

Table 48.14. Properties of Chlorine Salts Containing Oxygen[a]

Compound	Formula	Description	Mol. Wt.	Sp. Gr.	MP (° C)	Solubility
Calcium chlorate	$Ca(ClO_3)_2$	Hygroscopic	206.99	2.71	100	Soluble in water, alcohol
Potassium chlorate	$KClO_3$	Colorless, lustrous crystals	122.55	2.32	368	60.6 g/L H_2O, 25°C; 555 g/L H_2O, 100°C; almost insol. in alcohol
Sodium chlorate	$NaClO_3$	Colorless crystals	106.45	2.5	248	Soluble in 1 part water, 0.5 parts boiling water; slightly soluble in

						alcohol
Sodium hypochlorite	NaOCl	Crystals; anhydrous form is explosive	74.44	—	18	293 g/L H_2O, 0°C
Sodium chlorite	$NaClO_2$	Slightly hygroscopic crystals or flakes	90.45	—	Dec. at 180–200°C	390 g/L H_2O, 30°C
Ammonium perchlorate	NH_4ClO_4	Orthorhombic crystals	117.49	1.95	Dec. on heating	Soluble in water, methanol; slightly soluble in ethanol, acetone; insoluble in ether
Potassium perchlorate	$KClO_4$	Colorless crystals or white powder	138.55	2.52	Dec. at 400°C	Soluble in 65 parts water; practically insoluble in alcohol
Sodium perchlorate	$NaClO_4$	White, deliquescent crystals	122.44	2.02	Dec. at 130°C	Very soluble in water

[a] From Ref. 222.

Table 48.15. Estimated Number of Workers Exposed to Oxygen-Containing Chlorine Salts in 1983[a]

Compound	Number of Workers
Calcium chlorate	19,597
Potassium chlorate	8,679
Sodium chlorate	28,583
Calcium hypochlorite	39,878
Sodium hypochlorite	562,423
Sodium chlorite	18,585
Ammonium perchlorate	1,445
Potassium perchlorate	2,640
Sodium perchlorate	1,452

[a] From Ref. 7.

Table 48.16. Acute Toxicity Values for Oxygen-Containing Chlorine Salts[a]

Compound	Species	Oral LD_{50} (mg/kg)
Calcium chlorate	Rat	4500
Potassium chlorate	Rat	1870
Sodium chlorate	Rat	1200
	Mouse	8350
	Rabbit	7200
Sodium chlorite	Rat	165
	Mouse	350
	Guinea pig	300
Sodium hypochlorite	Rat	8910
Sodium perchlorate	Rat	2100

[a] From Ref. 151.

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C. Bromine and its Compounds

Table 48.17. Chemical Properties of Bromine Compounds and Estimated Number of Workers Exposed[a]

Compound	Formula	Description	Mol. Wt.	Sp. Gr.	MP (°C)	BP (° C)	Solubility	Number of Workers Exposed in 1983
Hydrogen bromide	HBr	Colorless gas	80.92	3.5 g/l	–86.9	–66.8	Saturated solution at 66% HBr	20,571
Ammonium bromide	NH_4Br	White, slightly hygroscopic crystals	97.96	2.43^{25}	Sublimes	—	Soluble in water, alcohol, acetone; slightly soluble in ether	—
Potassium	KBr	Colorless	119.01	2.75	730	—	Soluble in	50,375

bromide		crystals or white powder					water; slightly soluble in alcohol	
Sodium bromide	NaBr	White crystals	102.91	3.21	755	—	Soluble in water, alcohol	124,815
Potassium bromate	$KBrO_3$	White crystals	167.01	3.27	350 (dec. 370)	—	Soluble in water; slightly soluble in alcohol	26,562
Sodium bromate	$NaBrO_3$	Colorless crystals	150.91	3.34	381 (dec.)	—	Soluble in water	27,921
Bromine trifluoride	BF_3	Colorless or pale yellow liquid	136.92	2.80^{25}	8.77	125.75	Very reactive	357
Bromine pentafluoride	BF_5	Fuming liquid	174.92	2.46^{25}	–60.5	40.76	Explodes on contact with water	357

[a] From Refs. 7 and 222.

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D. Iodine and Its Compounds
15.0 Iodine
15.0.1 CAS Number: [*7553-56-2*]

15.0.2 Synonyms: NA

15.0.3 Trade Names: NA

15.0.4 Molecular Weight: 253.8090

15.0.5 Molecular Formula: I_2

15.0.6 Molecular Structure:

I—I

15.1 Chemical and Physical Properties
Iodine is the heaviest of the halogens that are of industrial interest. Under ordinary conditions, iodine takes the form of gray-black plates or granules that have a metallic, crystalline luster. It volatilizes at

room temperature to yield a sublimed, violet vapor. Iodine's physical properties are shown in Table 48.1.

Although iodine resembles other members of the halogen group, it is the least electronegative; it is thus the least chemically reactive of the halogens and forms the weakest bonds with more electropositive elements. Like other halogens, iodine unites with all elements except sulfur, selenium, and the noble gases. It reacts directly with most elements (except carbon, nitrogen, oxygen, and some of the more unreactive metals), and reacts with numerous organic compounds that are of pharmaceutical interest. Iodine also forms compounds with other halogens, such as iodine bromide and iodine monochloride; these interhalogen compounds are used in organic synthesis (131). Iodine occurs in valence states from 1 to 7 (223). The most stable of the positive iodine compounds are the iodates, in which the valence of iodine is +5, and the periodates, in which it is +7. Thirty isotopes of iodine have been identified, although only one, 127I, occurs in nature (2).

15.2 Production and Use

Iodine is the 47th most abundant element in the earth's crust (133). The name iodine derives from the Greek word for violet-colored, *ioeides*, which was used to describe the purple vapor generated by heating iodine (133).

The major U.S. sources of iodine are natural and oil-field brines, such as those near Shreveport, Louisiana (oil field), in the Los Angeles basin of California, and in the natural brines of Midland, Michigan and Woodward, Oklahoma. Iodine occurs in trace quantities in seawater and igneous rocks (223).

Large iodine resources exist in foreign countries. Japan's natural gas-well brines are credited with as much as four-fifths of the world's iodine reserve. An estimate of the indicated reserve of Chilean nitrate minerals, from which iodine is obtained as a by-product, is about 1 billion short tons (~ 0.04% I_2). Unmeasured quantities of iodine are contained in brines in Indonesia, Germany, France, Italy, the United Kingdom, Norway, Ireland, and the former Soviet Union (297). In the United States, the principal method used to recover iodine from oil brines involves the oxidation of iodide by chlorine, followed by removal of the volatile iodine from solution with an airstream. The iodine is reabsorbed in solution and reduced to hidrotic acid with sulfur dioxide. The solution is then chlorinated to precipitate free iodine, which is further purified by treatment with concentrated sulfuric acid. The same process is used to recover iodine from natural brines. In the recovery of iodine from Chilean nitrate deposits, solutions containing the iodates are reduced with sodium bisulfite to precipitate the iodine, which is then purified by sublimation.

In 1984, an estimated 500 trillion lb of crude or resublimed iodine products were produced in the United States, and more than 2 billion lb were imported in 1985 (263). Approximately 22% of this total was used in organic synthesis, and another 20% found use in pharmaceutical applications. Other uses, and their percentages of total consumption, were as follows in 1984: animal feed supplements (18%), sanitary and industrial disinfectants (12%), stabilizers (11%), inks and colorants (6%), photographic chemicals (5%), and miscellaneous uses (6%) (263).

Iodine is used both in animal and human medicine, where its disinfectant and antiseptic properties are valued. The lack of iodine causes goiter (compensatory hypertrophy of the thyroid gland), and iodine is used both to treat iodine deficiency and hyperthyroidism (131). Table 48.18 shows the principal iodine compounds and their industrial uses. NIOSH has estimated that in 1983, 204,902 workers were exposed to iodine (7).

Table 48.18. Principal Iodine Compounds and Their Uses[a]

Compound	Principal Uses

Sodium iodide	Photography, organic chemical cloud seeding, iodized salt, medication, wet extraction of silver, feed additive, laboratory reagent
Potassium iodide	Photographic emulsions, treatment of radiation accidents, laboratory analysis, animal and poultry feed
Hidrotic acid	Reducing agent, manufacture of organic iodides, laboratory analysis, disinfectant
Potassium iodate	Oxidizing agent in chemical analysis, topical antiseptic, nutrient iodine source
Iodine chloride	Organic synthesis, laboratory analysis
Iodine monobromide	Organic synthesis
Iodine trichloride	Chlorinating agent, oxidizing agent, topical antiseptic
Iodine pentafluoride	Fluorinating agent, component of explosives
Hydrogen iodide	Manufacture of hidrotic acid and organic iodo compounds

[a] From Refs. 2, 131, 222.

16.0 Inorganic Compounds

The inorganic iodine compounds of commercial interest, and their physical properties, are shown in Table 48.19. The iodides, an important class of inorganic iodine compounds, have less tendency to form complexes than the other halides. Chlorine and bromine freely displace iodine from the iodides (133). Iodine forms industrially useful and important compounds with hydrogen, metals, the other halogens, and oxygen. The ones presented below are typical.

Table 48.19. Properties of Industrially Useful Inorganic Iodine Compounds

Compound	CAS Number	Formula	Mol. Wt.	Physical Properties	Sp. Gr. (°C)	MP (°C)	BP (°C)	Solubility
Hydrogen iodide (hidrotic acid)	[*10034-85-2*]	HI	127.91	Colorless gas	Gas 5.66°	–50.8	–35.88	425 cm^3/L H_2O, 0°C; soluble alcohol
Ammonium iodide	[*12027-06-4*]	NH_4I	144.94	Colorless, cubic, hygr.	2.514^{25}	Subl. 551	220 vac.	1.542 kg/L H_2O, 0°C; 2.503 kg/L, H_2O, 100°C; very soluble alcohol, acetone, NH_3
Potassium iodide	[*7681-11-0*]	KI	166.01	Colorless or white, cubic	3.13	681	1330	1.275 kg/L H_2O, 0°C; 2.08 kg/L, H_2O, 100°C; 18.8 g/L,

								alcohol, 25° C; slightly soluble ether
Sodium iodide	[*7681-82-5*]	NaI	149.89	Colorless cubic	3.667^{25}	661	1304	1.84 kg/L H_2O, 25°C; 3.02 kg/L H_2O, 100°C; 425 g/L, 25° C; sol. alcohol
Iodic acid	[*7782-68-5*]	HIO_3	175.91	Colorless or pale yellow cryst.	4.629^{0}	Dec. 110	—	2.8 kg/L H_2O, 0°C; 4.73 kg/L H_2O, 80°C; very soluble alcohol 87%
Potassium iodate	[*7758-05-6*]	KIO_3	214.0	Colorless, monoclinic	3.93^{32}	560	Dec.>100	47.4 g/L H_2O, 0°C; 323 g/L H_2O, 100°C; soluble KI; insol. alcohol
Sodium iodate	[*7681-55-2*]	$NaIO_3$	197.89	White, rhombic	$4.277^{17.5}$	Dec.	—	90 g/L H_2O, 20°C; 340 g/L H_2O, 100°C; insoluble. alcohol; soluble acetic acid
Periodic acid	[*10450-60-9*]	H_5IO_6	191.91	Colorless	—	Subl. 110	Dec. 138	Very soluble (decomposes) cold H_2O
Iodine bromide	[*7789-33-5*]	IBr	206.81	Dark gray cryst.	4.4157^{0}	(42) subl. 50	Dec. 116	Soluble (dec.) cold H_2O; soluble alcohol, ether, chloroform, CS_2
Iodine chloride	[*7790-99-0*]	ICl	162.36	Dark red needles	3.1822^{0}	27.2	97.4	Decomposes to HIO_3 cold H_2O; soluble alcohol, ether, CS_2, HCl
Iodine tribromide	—	IBr_3	366.63	Brown liquid	—	—	—	Soluble cold

								H_2O; soluble alcohol
Iodine pentafluoride	[*7783-66-6*]	IF_5	221.90	Colorless liquid	3.75	9.6	98	Decomposes cold H_2O; dec. acid, alkali

16.0a Hydrogen Iodide

Hydrogen iodide [HI (hidrotic acid)] gas dissolves in water at 10°C and 1 atm pressure to the extent of 70 wt% to form hidrotic acid. The technical grade, 47% HI, is a highly corrosive liquid that fumes in moist air. Its solutions, like others containing the iodide ion, can dissolve in large quantities of iodine (e.g., tincture of iodine, KIúI$_2$). Hidrotic acid is more stable than the gas and is one of the strongest acids; it dissolves metals, oxides, carbonates, and salts of the other weak, monoxidizing acids, causing the formation of iodides. The major uses of hidrotic acid are shown in Table 48.18.

16.0b Iodides

Of the commercially available iodides, potassium iodide (KI) is the most important. All iodides are highly water-soluble, stable, and high melting solids (Table 48.19). The tetraiodides of titanium and zirconium, however, decompose to their elements at elevated temperatures, yielding very high purity zirconium metal. According to NIOSH (7), there were 243,989 workers exposed to potassium iodide in 1983.

16.0c Iodates and Periodates

The iodates and periodates are among the most stable and well known of the iodine compounds. Except for the salts of the alkali metals, most iodates are sparingly soluble in water. Both iodates and periodates are powerful oxidizers in acid solution and are thus used as disinfectants. Other uses are as feed additives and in medicine. Approximately 193,692 workers were exposed to potassium iodate in 1983; the corresponding figure for sodium iodate is 8972 (7).

16.0d Iodine Halides

The four iodine halides of interest, iodine monobromide, iodine chloride, iodine trichloride, and iodine pentafluoride, are shown in Table 48.19.

16.1 Chemical and Physical Properties

Table 48.19 show their physical properties. All are high density substances.

16.2 Production and Use

The chief use of these halides is in organic synthesis and as halogenation catalysts. Iodine pentafluoride is a fluorinating and incendiary agent. The reaction of iodine pentafluoride with organic substances must be carefully controlled because explosions may occur.

16.3 Exposure Assessment

Occupational exposure to airborne iodine can be measured using a charcoal tube impregnated with alkali-metal hydroxide. The iodine is desorbed using sodium nitrate, and analysis is conducted by ion chromatography (143). This method has a limit of detection of 0.01 ppm for a 7.5-L air sample. The overall precision of the method (coefficient of variation) is 0.11. At iodine concentrations of 0.5 times the OSHA PEL of 0.1 ppm, the overall error of the method is 27%, which is slightly above the maximum acceptable error of 25%. At iodine concentrations of 1 and 2 times the limit, overall error is acceptable.

The NIOSH method for sampling iodine (method 6005) is similar to that described above, except that sodium carbonate is used as the desorption agent (25). The estimated limit of detection for this method is 1 mg per sample, and the overall precision is slightly better (coefficient of variation 0.085) than is obtained from the use of sodium nitrate as the desorption agent.

16.4 Toxic Effects

Because iodine is an essential nutrient that is required for the healthy development and functioning of the thyroid gland, it has been the subject of numerous metabolic studies in human volunteers and

experimental animals. However, information on the toxic effects of iodine and iodine compounds in the occupational setting is scarce.

In general, the vapor of iodine is reported to be more irritating than that of chlorine or bromine (129, 130), although case reports are few because iodine does not find wide industrial use. In one of the few available animal studies, dogs exposed to iodine vapor (concentration not specified) developed signs of pulmonary edema (129, 130). In humans, exposure to the vapor causes irritation of the eyes and eyelids, upper respiratory tract, lungs, and skin (129, 130).

Four volunteers exposed to a 0.57-ppm concentration of iodine vapor for 5 min reported no ill effects; at a concentration of 1.63 ppm, however, all volunteers reported experiencing eye irritation after 2 min (298). Exposures to the vapor have also been associated with headaches, lacrimation, chest tightness, and sore throat (129, 130). In a study of workers exposed to vapors emanating from a tank containing an iodine solution, concentrations of 1.0 ppm were reported to be ‘highly' irritating (129, 130), and early studies report that working in an atmosphere containing 0.15–0.2 ppm of the vapor was difficult and that work had to be discontinued when the concentration reached 0.3 ppm (129, 130).

Topical applications of iodine solutions have caused redness and inflammation; strong solutions may cause thermal burns (129, 130). There are reports of fatalities caused by skin absorption of iodine tinctures applied to wounds (298), and a fatality has been attributed to the use of an iodine solution to provide continuous postoperative irrigation of a hip wound (33). Two Dutch eel fishermen developed contact dermatitis attributed to the iodine in Japanese Sargasso weed in the local lake; both cases were confirmed by patch test (299).

Matt studied the effects of halogen gases on humans and animals. In a series of open-room exposure experiments he confirmed the known cutaneous, mucosal, and respiratory toxicities of the halogen gases, at relatively low concentrations. He estimated that workers could tolerate iodine exposures of 0.001%, but that concentrations of 0.005% could not be tolerated. He observed preferential irritation of the ocular membranes by iodine in this study (300).

Chronic absorption of iodine can lead to “iodism,” a condition characterized by sleeplessness, tremor, rapid heart rate, diarrhea, weight loss, conjunctivitis, rhinitis, and bronchitis (298). However, this syndrome is usually associated with long-term ingestion of iodine-containing medications (expectorants, diuretics) rather than with occupational exposure (129, 130).

There is little information on the acute toxicity of iodine and its compounds. Table 48.20 shows the available data, as well as the signs and symptoms associated with exposure to each substance.

Table 48.20. Acute Toxicity and Exposure-Related Signs and Symptoms for Iodine and Some of Its Compounds[a]

Substance	Acute Toxicity Data (Route, Species)	Signs and Symptoms of Exposure
Iodine	Oral LD_{50}, rat: 14 g/kg Inhalation LC_{LO}, rat: 800 mg/m^3 for 1 hr	Tearing, nasal secretions, sore throat, chest tightness, headache, skin burns, rash, allergic dermatitis
Iodine		Severe eye, skin, and respiratory tract

monochloride	Oral LD_{LO}, rat: 50 mg/kg Dermal LD_{LO}, rat: 500 mg/kg	irritation; pulmonary edema; burns of the eye and skin
Potassium iodate	Oral LD_{LO}, guinea pig: 400 mg/kg	Dust causes eye, skin irritaion
Potassium iodide	Oral LD_{LO}, mouse: 1862 mg/kg	Eye, skin irritation; in animals, teratogenic effects
Sodium iodide	Oral LD_{LO}, rat: 4340 mg/kg	Eye, skin irritation; cough
Hydrogen iodide	—	Severe eye, nose, throat irritation; laryngeal and broanchial spasms (sometimes fatal); pulmonary edema; necrosis of skin
Iodine pentafluoride	—	Severe eye, nose, and throat irritation, bronchial and laryngeal edema
Hidrotic acid	—	Lacrimation, sore throat, difficult breathing, cough, edema; burns, blisters, and necrosis of the skin

[a] From Refs. 129, 130, 151, 223, and 298.

The most significant concerns about iodine and iodine exposure have arisen from air contamination and food and waterborne radioiodine (radioactive iodine) from nuclear releases. These releases from atmospheric nuclear testing, and from accidents such as that at Three Mile Island (Pennsylvania, USA) and Chernobyl (Russia) have profound implications for the occurrence of thyroid cancer in the surrounding populations. Drift of radioiodine and contamination of potable-water and food supplies at great distances from the source of the material is also a major concern. The kinetics of these exposures, and their impact is beyond the scope of this chapter, but in any discussion of iodine as an industrial poison, the radioiodine forms produced and released by all of the uses of nuclear energy should be considered.

16.5 Standards, Regulations, or Guidelines of Exposure

OSHA (174), NIOSH (175), and the ACGIH (22) all have established a ceiling limit of 0.1 part per million (ppm) for iodine. NIOSH has also calculated an IDLH value for this element of 2 ppm (21). No limits have been established for the principal compounds of iodine.

The Halogens
Daniel Thau Teitelbaum, MD

E. Astatine

17.0 Astatine

17.0.1 CAS Number: [*7440-68-8*]

17.0.2 Synonyms: NA

17.0.3 Trade Names: NA

17.0.4 Molecular Weight: 210

17.0.5 Molecular Formula: At

17.1 Chemical and Physical Properties

The fifth halogen—astatine—is little known and has to date found few uses. The physical and chemical properties of astatine are as follows:

Atomic number	85
Atomic weight	210
Melting point	302°C
Boiling point	337°C (est.)

The name *astatine* derives from the Greek word for unstable, *astatos*. Astatine is believed to have four valence states: 1, 3, 5, and 7. Twenty-four isotopes have so far been identified, and the longest-lived of these, (301), At, has a half-life of only 8.1 h. The total amount of astatine in the earth's crust is believed to be less than 1 ounce (2).

Astatine behaves chemically in a manner much like iodine; however, it is believed to be more metallic than iodine. It is likely to accumulate in the thyroid gland, although this has not been demonstrated (2).

The Halogens

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Aliphatic Hydrocarbons

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A. Alkanes (Saturated Hydrocarbons, Paraffins)

The alkanes have the generic formula of C_nH_{2n+2}. All the carbons have single covalent bonds between them. They are also called *saturated hydrocarbons*, which means that all the carbons have the maximum number of bonds (four). The alkane series is composed of gases (methane, ethane, propane, and butanes), liquids from pentanes (C5–C16 compounds), and longer-chain solids (1).

The toxicity of the alkanes is generally related to vapor pressure, viscosity, surface tension, and lipid solubility. Physical properties of saturated aliphatic hydrocarbons are listed in Table 49.1.

Table 49.1. Physicochemical Properties of Alkanes[a]

Compound	Molecular Formula	Molecular Weight	Boiling Point (°C)	Melting Point (°C)	Density (mg/cm^3) (at °C)	Refractive Index n_D	Solubility	Flash Point (°C)	I
Methane		16.042	–161.5	–182.5	0.4228 (–	—	w 3, al 3,	–187.8	

	CH_4				162)		et 3, ac 2	(open cup)
Ethane	C_2H_6	30.07	–88.63	–183.23	0.5446 (–89)	—	bz 4	–135
Propane	C_3H_8	44.09	–42.1	–187.7	0.493 (25)	—	w 3, al 3, et 4, ac 2	–104.0
Butane	C_4H_{10}	58.12	–0.5	–138.35	0.573 (25)	1.3326 (20)	w 3, al 4, et 4, ch 4	–60.0 (closed cup)
2-Methylpropane	C_4H_{10}	58.12	–11.7	–159.6	0.5510 (25)	1.3518 (–25)	w 2, al 3, et 3, ch 3	–82.8 (closed cup)
Pentane	C_5H_{12}	72.15	36.1	–129.8	0.6262 (20)	1.3575 (20)	w 2, al 5, et 5, ac 5	–49.0
2-Methylbutane	C_5H_{12}	72.15	27.8	–159.8	0.6201 (20)	1.3537 (20)	w 1, al 5, et 5	–51.0
2,2-Dimethylbutane	C_6H_{14}	86.177	49.7	–100	0.6444 (25)	1.3688 (20)	w 1, al 3, et 3, ac 4	–48.0
2,3-Dimethylbutane	C_6H_{14}	86.177	58	–128.5	0.6616 (20)	1.3750 (20)	w 1, al 3, et 3, ac 4	–29.0
2,2-Dimethylpropane	C_5H_{12}	72.15	9.5	–16.6	0.5258 (25)	1.3476 (6)	w 1, al 3, et 3, ct 3	–6.67
Hexane	C_6H_{14}	86.10	68.95	–95	0.6548 (25)	1.3749 (20)	w 1, al 4, et 3, ch 3	–22.0 (closed cup)
2-Methylpentane	C_6H_{14}	86.177	62	–154	0.650 (25)	1.3715 (20)	w 1, al 3, et 3, ac 5	–23.0
3-Methylpentane	C_6H_{14}	86.177	64	–118.0	0.6598 (25)	1.3765 (20)	w 1, al 3, et 5, ac 5	–6.0
Heptane	C_7H_{16}	100.20	98.4	–90.7	0.6837 (20)	1.3878 (20)	w 1, al 4, et 5, ac 5	–4.4 (closed cup)
2-Methylhexane	C_7H_{16}	100.20	90.0	–118.2	0.6787 (20)	1.3848 (20)	w 1, al 3, et 5, ac 5	–1.0
3-Methylhexane	C_7H_{16}	100.20	92.0	–119.0	0.6860 (20)	1.3887 (20)	w 1, al 3, et 5, ac 5	–4.0
Octane	C_8H_{18}	114.22	125.7	–56.8	0.6986 (25)	1.3974 (20)	w 1, al 3, et 3, ac 5	–13.0 (closed cup)
								22 (open cup)
2,5-Dimethylhexane	C_8H_{18}	114.23	109.1	–91.0	0.6901 (25)	1.3925 (20)	w 1, al 5, et 3, ac 5	—
2,2,4-Trimethylpentane	C_8H_{18}	114.22	99.2	–116	0.6877 (25)	1.3915 (20)	w 1, al 5, et 3, ac 5	–12.0
2,3,4-Trimethylpentane	C_8H_{18}	114.23	113.5	–109.2	0.7191 (20)	1.4042 (20)	w 1, al 4, et 5, ac 5	–12.0
Nonane	C_9H_{20}	128.26	150.8	–53.5	0.7176	1.4054	w 1, al 4,	31.0

					(20)	(20)	et 4, ac 5		
2,2,5-Trimethylhexane	C_9H_{20}	128.26	124.0	–105.7	0.7072 (20)	1.3997 (20)	w 1, al 4, et 4, ac 4	13.0	-
Decane	$C_{10}H_{22}$	142.28	174.1	–29.7	0.7300 (20)	1.4102 (20)	w 1, al 5, et 3, ct 2	46	
2,7-Dimethyloctane	$C_{10}H_{22}$	142.28	159.9	–54.9	0.7202 (25)	1.4086 (20)	et 3, aa 3	—	-
Undecane	$C_{11}H_{24}$	156.31	195.9	–25.59	0.7402 (20)	1.4398 (20)	w 1, al 5, et 5	60.0	
Dodecane	$C_{12}H_{26}$	170.34	216.3	–9.6	0.7487 (20)	1.4216 (20)	w 1, al 4, et 4, ac 4	71.0	
Tridecane	$C_{13}H_{28}$	184.36	235.4	–5.5	0.7564 (20)	1.4256 (20)	w 1, al 4, et 4, ct 3	79.0	-
Tetradecane	$C_{14}H_{30}$	198.39	253.7	5.89	0.7628 (20)	1.4290 (20)	w 1, al 4, et 4, ct 3	99	
Pentadecane	$C_{15}H_{32}$	212.42	270.63	9.9	0.7685 (20)	1.4315 (20)	w 1, al 4, et 4	132	-
Hexadecane	$C_{16}H_{34}$	226.44	287	18.17	0.7733 (20)	1.4345 (20)	w 1, al 2, et 5, ct 3	135	
Heptadecane	$C_{17}H_{36}$	240.47	302.0	22.0	0.7780 (20)	1.4369 (20)	w 1, al 2, et 3, ct 2	—	-
Octadecane	$C_{18}H_{38}$	254.50	316.3	28.2	0.7768 (28)	1.4390 (20)	w 1, al 2, et 3, ac 3	>100.0	-
Nonadecane		$C_{19}H_{40}$	268.53	329.9	32.1				
Pristane	$C_{19}H_{40}$	268.53	296.0	—	0.783 (20)	1.4379 (20)	et 4, bz 4, ch 4, pe 4	—	-
Eicosane	$C_{20}H_{42}$	282.55	343.0	36.8	0.7886 (20)	1.4425 (20)	w 1, et 3, ac 4, bz 3	>100.0	-

[a] Molecular Formula—in Hill notation; molecular Weight—relative molar mass; Density—mass per unit volume in g/cm^3 at the temperature indicated in parentheses; Refractive Index—at the temperature indicated in parentheses, unless otherwise indicated, all values refer to a wavelength of 589 nm; Solubility—solubility in common solvents (w—water, al—ethanol, et—ethyl ether, ac—acetone, bz—benzene, ch—chloroform, ct—carbon tetrachloride, aa—acetic acid, pe—petroleum ether, os—organic solvents) on a relative scale: 1 = insoluble, 2 = slightly soluble, 3 = soluble, 4 = very soluble, 5 = miscible, 6 = decomposes; Flammability Limits—explosive limits (in percent by volume) at ambient temperature and pressure.

The aliphatic hydrocarbons are practically nontoxic for single exposures below the lower flammability limit. In general, the saturated hydrocarbons from propane through the octanes show increasingly narcotic properties. The margin between narcosis and lethal depression of vital centers is too narrow, and because of their explosive characteristics, these compounds are not used as surgical anesthetics. Narcotic effects may be accompanied by exhilaration, dizziness, and headache (1).

Virtually all paraffins will cause nausea, vomiting, abdominal pain, and occasionally diarrhea when ingested (2–4). Dermatitis, CNS depression, anesthesia, and cardiac sensitization have also been noted for many paraffins. Acutely, the most common toxic effects are CNS depression and asphyxia following inhalation and chemical pneumonitis after the aspiration of ingested alkanes. Asphyxia occurs when the oxygen in air is displaced by high concentrations of a gas or vapor. When the

oxygen concentration is lowered from ambient levels to ≤10%, hypoxia results and the body is starved for oxygen. At this level of oxygen deprivation, death occurs swiftly.

Dermal irritation and CNS depression are common problems with liquid aliphatic hydrocarbons in chronic exposures. Dermal irritation occurs in workers repeatedly exposed to liquid hydrocarbons as solvents. The paraffins are lipid solvents and dissolve or extract the fats from the skin, resulting in painful drying and cracking of the skin, that is, chronic eczematoid dermatitis, with itching and inflammation.

CNS depression occurs as the inhaled vapor or gas crosses the alveolar–capillary membrane to be absorbed into the bloodstream. At levels that cause CNS depression, the lung itself is spared injury (2–4). The CNS depressant properties of some alkanes have led to substance abuse in the form of "glue sniffing," usually toluene or *n*-hexane. Other abusers have utilized gasoline; paints containing solvents such as xylene, methyl ethyl ketone, acetone, ethyl acetate, ethyl benzene, and isobutyl acetate; typewriter correction fluids; aerosol can propellants, including propane and isobutane; and exhaust emissions. Abusers often exhibit a drunken appearance and suffer from learning or memory impairment, personality disorders, seizures, neuropsychological disorders, and tachycardia (2–4).

In general, branched-chain derivatives are less toxic than the corresponding parent straight-chain alkanes. Odorant properties increase whereas analgesic properties decrease with increasing chain length. Both dermal and pulmonary irritant properties increase with increasing chain length up to C14 derivatives (5).

Table 49.2. Occupational Exposure Limits for Propane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH Exposure Limit	ACGIH TLV
Time-weighted average	1000 ppm (1800 mg/m^3)	1000 ppm (1800 mg/m^3)	2500 ppm (4508 mg/m^3)
Short-term exposure limit	—	—	—
Ceiling limit	—	—	—

[a] OSHA and ACGIH—8-h TWA; NIOSH—10-h TWA. From Ref. 19.

Table 49.3. Occupational Exposure Limits for Propane in Different Countries[a]

Country	Exposure Limit
Australia	Asphyxiant
Belgium	Asphyxiant
Denmark	TWA 1000 ppm (1800 mg/m^3)
Finland	TWA 800 ppm (1100 mg/m^3)
Germany	TWA 1000 ppm (1800 mg/m^3)

Hungary	Asphyxiant
The Netherlands	Asphyxiant
The Philippines	TWA 1000 ppm (1800 mg/m^3)
Switzerland	TWA 1000 ppm (1800 mg/m^3)
United Kingdom	Asphyxiant

[a] From Ref. 19.

Table 49.4. Occupational Exposure Limits for Butane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH Recommended Exposure Limit	ACGIH TLV
Time-weighted average	—	800 ppm (1900 mg/m^3)	800 ppm (1900 mg/m^3)
Short-term exposure limit	—	—	—
Ceiling limit	—	—	—

[a] ACGIH—8-h TWA; NIOSH—10-h TWA. From Ref. 19.

Table 49.5. Occupational Exposure Limits for Butane in Different Countries[a]

Country	Exposure limit
Australia	TWA 800 ppm (1900 mg/m^3)
Austria	TWA 1000 ppm (2300 mg/m^3)
Belgium	TWA 800 ppm (1900 mg/m^3)
Denmark	TWA 500 ppm (1200 mg/m^3)
Finland	TWA 800 ppm (1900 mg/m^3); STEL 1000 ppm (2350 mg/m^3)
France	TWA 800 ppm (1900 mg/m^3)
Germany	TWA 1000 ppm (2350 mg/m^3)
Hungary	TWA 300 ppm; STEL 900 ppm
India	TWA 800 ppm (1900 mg/m^3)
Ireland	TWA 600 ppm (1430 mg/m^3); STEL 750 ppm (1780 mg/m^3)
Japan	TWA 500 ppm (1200 mg/m^3)
Mexico	TWA 800 ppm (1900 mg/m^3)
The Netherlands	TWA 600 ppm (1430 mg/m^3)

Poland	TWA 1900 mg/m^3; STEL 3000 mg/m^3
Russia	TWA 500 ppm; STEL 300 ppm
Switzerland	TWA 800 ppm (1900 mg/m^3)
United Kingdom	TWA 600 ppm (1450 mg/m^3); STEL 750 ppm (1810 mg/m^3)

[a] From Refs. 19 and 20.

Table 49.6. Summary of Subchronic Toxicity Studies in Animals Exposed to Mixtures Containing 2-Methylpropane

Species	Exposure route	Chemical mixture	Approximate Dose	Treatment regimen	Observed Effect	Ref.
Fischer rats	Inhalation	50–50 (wt%) *n*-butane:*n*-pentane	1000, 4500 ppm	6 h/day, 5 days/week, 13 weeks	Mild–transient kidney effects not exposure-related	76
		50–50 (wt %) isobutane:isopentane	1000, 4500 ppm	6 h/day, 5 days/week, 13 weeks	Mild–transient kidney effects not exposure-related	
		Unleaded gasoline blend	1200, 5200 ppm	6 h/day, 5 days/week, 13 weeks	No nephrotoxicity observed	
Sprague–Dawey rats	Inhalation	25 (wt%) *n*-butane, *n*-pentane, isobutane, isopentane	0, 44, 432, 4437 ppm	6 h/day, 5 days/week, 3 weeks	No clinical signs of toxicity and no nephrotoxicity observed	77
Rabbits	Inhalation	Hairspray with 22% isobutane	2 daily—30-s aerosol bursts	3 days/week, 90 days	No changes in body weight, hematology, clinical chemistry, and urinalysis	46

Table 49.7. Occupational Exposure Limits for 2-Methylpropane in Different Countries[a]

Country	Exposure Limit

Germany	TWA 1000 ppm (2350 mg/m^3)
Switzerland	TWA 800 ppm (1900 mg/m^3)
United Kingdom	TWA 600 ppm (1430 mg/m^3); STEL 750 ppm

[a] From Ref. 19.

Table 49.8. Occupational Exposure Limits for Pentane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH Exposure Limit	ACGIH TLV
Time-weighted average	1000 ppm (2950 mg/m^3)	120 ppm (350 mg/m^3)	600 ppm (1770 mg/m^3)
Short-term exposure limit	750 ppm (2250 mg/m^3)	610 ppm (1800 mg/m^3)	—
Ceiling limit	—	—	—

[a] OSHA and ACGIH—8-h TWA; NIOSH—10-h TWA. From Ref. 19.

Table 49.9. Occupational Exposure Limits for Pentane in Different Countries[a]

Country	Exposure Limit
Australia	TWA 600 ppm (1800 mg/m^3); STEL 750 ppm (2250 mg/m^3)
Belgium	TWA 600 ppm (1770 mg/m^3); STEL 750 ppm (2210 mg/m^3)
Denmark	TWA 500 ppm (1500 mg/m^3)
Finland	TWA 500 ppm (1500 mg/m^3); STEL 625 ppm (1800 mg/m^3)
France	TWA 600 ppm (1800 mg/m^3)
Germany	TWA 1000 ppm (3000 mg/m^3)
Hungary	TWA 500 mg/m^3; STEL 1500 mg/m^3
Ireland	TWA 600 ppm (1800 mg/m^3); STEL 750 ppm (2250 mg/m^3)
Japan	TWA 300 ppm (880 mg/m^3)
Mexico	TWA 600 ppm (1800 mg/m^3); STEL 760 ppm (2250 mg/m^3)
The Netherlands	TWA 600 ppm (1800 mg/m^3)
The Philippines	TWA 1000 ppm (2950 mg/m^3)
Poland	TWA 1800 mg/m^3; STEL 2300 mg/m^3

Russia	TWA 300 ppm; STEL 300 mg/m^3
Sweden	TWA 600 ppm (1800 mg/m^3); STEL 750 ppm (2000 mg/m^3)
Switzerland	TWA 600 ppm (1800 mg/m^3)
Turkey	TWA 1000 ppm (2950 mg/m^3)
United Kingdom	TWA 600 ppm (1800 mg/m^3); STEL 750 ppm

[a] From Refs. 19 and 20.

Table 49.10. Summary of Subchronic Toxicity Studies in Animals Exposed to Hexane

Species	Exposure Route	Chemical	Approximate Dose (ppm)	Treatment Regimen	Observed Effect	Ref.
Fischer rat	Inhalation	Hexane	0, 3000, 6500, 10,000	6 h/day, 5 days/week, 13 weeks	Depression of body weight gain, lower brain weight, and axonopathy in males	130
B6C3F$_1$ mice	Inhalation	Hexane	0, 500, 1000, 4000, 10,000	6 h/day, 5 days/week, 13 weeks	No effect in survival	131
			0, 500, 1000, 4000, 10,000	6 h/day, 5 days/week, 13 weeks	Morphological alterations in the respiratory tract	
			1000	22 h/day, 5 days/week, 13 weeks	Paranodal axonal swelling in the tibial nerve	
SM-A male mice	Inhalation	Commercial-grade hexane	0, 100, 250, 500, 1000, 2000	6 days/week, 1 year	Peripheral neuropathy by electromyographic analysis	132
Sprague–Dawley rats	Inhalation	Hexane	0, 6, 26, 129	6 h/day, 5 days/week, 26 weeks	No signs of nervous system degeneration	133
			0, 5, 27, 126	21 h/day, 7 days/week, 26 weeks	No signs of nervous system degeneration	
Sprague–Dawley rats	Inhalation	Hexane	0, 126, 502	22 h/day, 7 days/week, 6 month	Abnormal gait, axonal degeneration, myelin vacuolization	134
		Hexane + hexane mixtures	125 + 125, 375, 1375	22 h/day, 7 days/week, 6 month	No neuropathic/myopathic alterations	
Wistar male rats	Inhalation	Hexane	0, 500, 1200, 3000	12 h/day, 7 days/week, 16 weeks	Dose-dependent peripheral neurotoxicity and body weight decrease	135
Sprague–Dawley	Inhalation	Hexane	0, 500, 1500, 5000	9 h/day, 5 days/week,	Decrease in weight gain, axonal	91

rats			14–30 weeks	degeneration, swelling of axons	
		2500	10 h/day, 6 days/week, 14–30 weeks	Axonal degeneration, swelling of axons	
Rabbits	Inhalation Hexane	3000	8 h/day, 5 days/week, 24 weeks	Ocular and upper respiratory tract irritation, respiratory difficulties	136

Table 49.11. Summary of Neurotoxicity Studies in Human Exposed to Hexane

Type of Facility/Population	Mixture Composition	Exposure Levels	Persons Affected	Findings	Ref.
Laminating plant	Solvents containing 65–95% hexane	500–2000 ppm	17 cases	Polyneuritis	159
Vinyl sandal manufacture	Glues containing 70% hexane	500–25007 ppm, 48 h/week	93 of 296	Progressive polyneuropathy, symmetrical sensorimotor disorder, no deaths	171
Shoe industry	Hexane and other solvents	196 ppm, 1–25 years	15 studied	Reductions in maximal motor and distal sensory nerve conduction velocities Changes in somatosensory evoked potentials	172
Press proofing workers	Solvents containing hexane	190 ppm	15 of 59 studied	Overt peripheral neuropathy, CNS malfunction, residual abnormalities after exposure removal; no neuropathy at <100 ppm	173–175
Tungsten carbide	Tungsten	58 ppm 8-h	14 + 5	No signs of	176

milling	carbide + hexane or acetone	TWA/2 years	past exposed	neuropathy; headaches, hyperaesthesia of limbs, and muscle weakness	
Printers and spray painters	Solvents containing hexane	1–39 ppm, 6 years	16% of 240 exposed	Not clinically significant signs of peripheral neuropathy	177

Table 49.12. Occupational Exposure Limits for Hexane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	500 ppm (1800 mg/m^3)	50 ppm (180 mg/m^3)	50 ppm (176 mg/m^3)
Short-term exposure limit	—	—	—
Ceiling limit	—	—	—

[a] OSHA and ACGIH—8-h TWA; NIOSH—10-h TWA. From Ref. 19.

Table 49.13. Occupational Exposure Limits for Hexane in Different Countries[a]

Country	Exposure Limit
Australia	TWA 50 ppm (180 mg/m^3)
Belgium	TWA 50 ppm (180 mg/m^3)
Denmark	TWA 50 ppm (180 mg/m^3)
Finland	TWA 50 ppm (180 mg/m^3); STEL 150 ppm (530 mg/m^3)
France	TWA 50 ppm (180 mg/m^3)
Germany	TWA 50 ppm (180 mg/m^3)
Hungary	TWA 100 mg/m^3; STEL 200 mg/m^3
Ireland	TWA 20 ppm (70 mg/m^3)
Japan	TWA 40 ppm (140 mg/m^3)
Mexico	TWA 100 ppm (360 mg/m^3)

The Netherlands	TWA 25 ppm (90 mg/m^3)
The Philippines	TWA 500 ppm (1800 mg/m^3)
Poland	TWA 100 mg/m^3; STEL 400 mg/m^3
Russia	TWA 40 ppm; STEL 300 mg/m^3
Sweden	TWA 25 ppm (90 mg/m^3); STEL 50 ppm (180 mg/m^3)
Switzerland	TWA 50 ppm (180 mg/m^3); STEL 100 ppm (360 mg/m^3)
Turkey	TWA 500 ppm (1800 mg/m^3)
United Kingdom	TWA 20 ppm (72 mg/m^3)

[a] From Refs. 19 and 20.

Table 49.14. Occupational Exposure Limits for Heptane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	500 ppm (2000 mg/m^3)	85 ppm (350 mg/m^3)	400 ppm (1640) mg/m^3
Short-term exposure limit	—	440 ppm (1800 mg/m^3)	500 ppm (2050) mg/m^3
Ceiling limit	—	—	—

[a] OSHA and ACGIH—8-h TWA; NIOSH—10-h TWA. From Ref. 19.

Table 49.15. Occupational Exposure Limits for Heptane in Different Countries[a]

Country	Exposure Limit
Australia	TWA 400 ppm (1600 mg/m^3); STEL 500 ppm (2000 mg/m^3)
Belgium	TWA 400 ppm (1640 mg/m^3); STEL 500 ppm (2050 mg/m^3)
Denmark	TWA 400 ppm (1600 mg/m^3)
Finland	TWA 300 ppm (1200 mg/m^3); STEL 500 ppm (2000 mg/m^3)
France	TWA 400 ppm (1600 mg/m^3)
Ireland	TWA 400 ppm (1600 mg/m^3); STEL 500 ppm (2000 mg/m^3)
Germany	TWA 500 ppm (2100 mg/m^3)
Japan	TWA 200 ppm (820 mg/m^3)
Mexico	TWA 400 ppm (1600 mg/m^3); STEL 500 ppm (2000 mg/m^3)
The Netherlands	TWA 300 ppm (1200 mg/m^3); STEL 400 ppm (1600 mg/m^3)

The Philippines	TWA 500 ppm (2000 mg/m^3)
Poland	TWA 1200 mg/m^3; STEL 2000 mg/m^3
Russia	TWA 200 ppm
Sweden	TWA 200 ppm (800 mg/m^3); STEL 300 ppm (1250 mg/m^3)
Switzerland	TWA 400 ppm (1600 mg/m^3); STEL 800 ppm
Turkey	TWA 500 ppm (2000 mg/m^3)
United Kingdom	TWA 400 ppm (1600 mg/m^3); STEL 500 ppm

[a] From Refs. 19 and 20.

Table 49.16. Occupational Exposure Limits for Octane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	500 ppm (2350 mg/m^3)	75 ppm (350 mg/m^3)	300 ppm (1401) mg/m^3
Short-term exposure limit	—	—	375 ppm (1750) mg/m^3
Ceiling limit	—	385 ppm (1800 mg/m^3)	—

[a] OSHA and ACGIH—8-h TWA; NIOSH—10-h TWA. From Ref. 19.

Table 49.17. Occupational Exposure Limits for Octane in Different Countries[a]

Country	Exposure Limit
Australia	TWA 300 ppm (1450 mg/m^3); STEL 375 ppm (1800 mg/m^3)
Belgium	TWA 300 ppm (1400 mg/m^3); STEL 375 ppm (1750 mg/m^3)
Denmark	TWA 300 ppm (1450 mg/m^3)
Finland	TWA 300 ppm (1400 mg/m^3); STEL 375 ppm (1750 mg/m^3)
France	TWA 300 ppm (1450 mg/m^3)
Germany	TWA 500 ppm (2400 mg/m^3)
Hungary	TWA 500 mg/m^3; STEL 1500 mg/m^3
Ireland	TWA 300 ppm (1450 mg/m^3); STEL 375 ppm (1800 mg/m^3)
Japan	TWA 300 ppm (1400 mg/m^3)
Mexico	TWA 300 ppm (1450 mg/m^3); STEL 375 ppm (800 mg/m^3)

The Netherlands	TWA 300 ppm (1450 mg/m^3)
The Philippines	TWA 500 ppm (2350 mg/m^3)
Poland	TWA 1000 mg/m^3; STEL 1800 mg/m^3
Russia	TWA 300 ppm
Sweden	TWA 200 ppm (900 mg/m^3); STEL 300 ppm (1400 mg/m^3)
Switzerland	TWA 300 ppm (1400 mg/m^3); STEL 600 ppm
Turkey	TWA 400 ppm (1900 mg/m^3)
United Kingdom	TWA 300 ppm (1450 mg/m^3); STEL 375 ppm

[a] From Refs. 19 and 20.

Table 49.18. Occupational Exposure Limits for Nonane in Different Countries[a]

Country	Exposure Limit
Denmark	TWA 200 ppm (1050 mg/m^3)
Finland	TWA 200 ppm (1050 mg/m^3); STEL 250 ppm (1315 mg/m^3)
France	TWA 200 ppm (1050 mg/m^3)
Ireland	TWA 200 ppm (1050 mg/m^3)
Mexico	TWA 200 ppm (1050 mg/m^3); STEL 250 ppm (1300 mg/m^3)
Japan	TWA 200 ppm (1050 mg/m^3)
The Netherlands	TWA 200 ppm (1050 mg/m^3)
Switzerland	TWA 200 ppm (1050 mg/m^3)

[a] From Refs. 19 and 20.

Aliphatic Hydrocarbons
Tania Carreón, MS

B. Alkenes (Olefins)
Alkenes differ from alkanes in the presence of a double covalent bond in the carbon chain. They have the generic formula C_nH_{2n}. They represent the simplest of the *unsaturated hydrocarbons*.

Alkenes are chemically more reactive than alkanes, primarily through addition reactions across the double bonds (5). When heated or in the presence of catalysts, most olefins will polymerize. They have higher boiling points than the parent paraffins as shown in Table 49.19.

Table 49.19. Physicochemical Properties of Alkanes[a]

Compound	Molecular formula	Molecular weight	Boiling point (°C)	Melting point (°C)	Density (mg/cm^3) (at °C)	Refractive index n_D	Solubility	Flash Point (°C)	Fla L
Ethene	C_2H_4	28.0	–103.7	–169.2	0.5678 (–104)	1.363 (100)	w 1, al 2, et 3, ac 2	–130 (closed cup)	2.7
Propene	C_3H_6	42.08	–47.4	–185.24	0.505 (25)	1.3567 (–70)	w 4, al 4, aa 4	–108	2.0
1-Butene	C_4H_8	56.107	–6.1	–185.3	0.588 (25)	1.3962 (20)	w 1, al 4, et 4, bz 3	—	1.6
cis-2-Butene	C_4H_8	56.107	3.7		0.616 (25)	1.3931 (–25)	w 1, al 4, et 4, bz 3	—	1.7
trans-2-Butene	C_4H_8	56.107	0.88		0.599 (25)	1.3848 (–25)	bz 3	—	1.8
2-Methylpropene	C_4H_8	56.107	–6.9	–140.3	0.589 (25)	1.3926 (–25)	w 1, al 4, et 4, bz 3	—	1.8
1-Pentene	C_5H_{10}	70.134	30	–165	0.6405 (20)	1.3715 (20)	w 1, al 5, et 5, bz 3	–28	1.5
cis-2-Pentene	C_5H_{10}	70.13	36.9	–151.4	0.6556 (20)	1.3830 (20)	w 1, al 5, et 5, bz 3	<–20.0	—
trans-2-Pentene	C_5H_{10}	70.13	36.3	–140.2	0.6431 (25)	1.3793 (20)	w 1, al 5, et 5, bz 3	< –20.0	—
3-Methyl-1-butene	C_5H_{10}	70.13	20.1	–168.5	0.6213 (25)	1.3643 (20)	w 1, al 5, et 5, bz 3	–7.0	1.5
1-Hexene	C_6H_{12}	84.16	63.3	–139.8	0.6731 (20)	1.3837 (20)	al 4, et 4, bz 4, pe 4	15 (closed cup)	1.2
cis-2-Hexene	C_6H_{12}	84.16	68.8	–141.1	0.6869 (20)	1.3979 (20)	w 1, al 3, et 3, bz 3	–21.0	—
trans-2-Hexene	C_6H_{12}	84.16	67.9	–133.0	0.6732 (25)	1.3936 (20)	w 1, al 3, et 3, bz 3	—	—
2-Methyl-2-pentene	C_6H_{12}	84.16	67.3	–135.0	0.6863 (20)	1.4004 (20)	w 1, al 3, bz 3, ct 3	<–7.0	—
1-Heptene	C_7H_{14}	98.188	93.3	–119	0.6970 (20)	1.3998 (20)	w 1, al 3, et 3, ct 2		—
1-Octene	C_8H_{16}	112.22	121.2	–101.7	0.7149 (20)	1.4087 (20)	w 1, al 5, et 3, ac 3	21.0	—
2-Methyl-2-heptene	C_8H_{16}	112.22	122.6	—	0.7200 (25)	1.4170 (20)	w 1, et 3, bz 3, ct 3	—	—
1-Nonene	C_9H_{18}	126.24	146.9	–81.3	0.7253 (25)	1.4257 (20)	—	26.0	—
Propadiene	C_3H_4	40.06	–34.4	–136.2	0.584 (25)	1.4168 (20)	bz 4, pe 4	—	2.1
1,3-Butadiene	C_4H_6	54.09	–4.4	–108.9	0.6149 (25)	1.4292 (–25)	w 1, al 3, et 3, ac 4	–76	2.0

2-Methyl-1,3-butadiene	C_5H_8	68.118	34.0	–120	0.679 (20)	1.4219 (20)	w 1, al 5, et 5, ac 5	–48	1.5
cis-1,3-Hexadiene	C_6H_{10}	82.15	73.1	—	0.7033 (25)	1.4379 (20)	—	—	—
trans-1,3-Hexadiene	C_6H_{10}	82.15	73.2	–102.4	0.6995 (25)	1.4406 (20)	—	—	—
1,4-Hexadiene	C_6H_{10}	82.15	65.0	—	0.7000 (20)	1.4150 (20)	w 1, et 4	–21.0	2.0
1,5-Hexadiene	C_6H_{10}	82.15	59.4	–140.7	0.6878 (25)	1.4042 (20)	w 1, al 3, et 3, bz 3	—	—
1,7-Octadiene	C_8H_{14}	110.20	115.5	—	0.734 (20)	1.4245 (20)	—	9.0	—
Squalene	$C_{30}H_{50}$	410.73	280.0	< –20.0	0.8584 (20)	1.4990 (20)	w 1, al 2, et 3, ac 3	—	—
Lycopene	$C_{40}H_{56}$	536.88	—	175.0	—	—	al 2, et 3, bz 4, ch 4	—	—
b-Carotene	$C_{40}H_{56}$	536.88	—	183.0	1.00 (20)	—	w 1, al 2, et 3, ac 3	—	—

[a] Molecular Formula—in Hill notation; Molecular Weight—relative molar mass; Density—mass per unit volume in g/cm^3 at the temperature indicated in parentheses; Refractive Index—at the temperature indicated in parentheses, unless otherwise indicated, all values refer to a wavelength of 589 nm; Solubility—solubility in common solvents (w—water, al—ethanol, et—ethyl ether, ac—acetone, bz—benzene, ch—chloroform, ct—carbon tetrachloride, aa—acetic acid, pe—petroleum ether, os—organic solvents) on a relative scale: 1 = insoluble, 2 = slightly soluble, 3 = soluble, 4 = very soluble, 5 = miscible, 6 = decomposes; Flammability Limits—explosive limits (in percent by volume) at ambient temperature and pressure.

Alkenes, except for butadiene, are only slightly more toxic than alkanes. Ethene, propene, butene, and isobutene are weak anesthetics and simple asphyxiants. Pentene has been used for surgical anesthesia. Because of increasing mucous membrane irritancy and cardiac effects with increasing chain length, the hexylenes and higher members are unsuitable as anesthetic agents. The higher members may cause CNS depression, but are not sufficiently volatile to be considered vapor hazards at room temperature (267). Branching decreases the toxicity of C3 alkenes, does not appreciably affect the C4 and C5 alkenes, and increases the toxicity of C6–C18 alkenes. Unlike the hexanes, the olefins do not produce axonopathy. Repeated exposure to high concentrations of the lower members of the alkenes results in hepatic damage and hyperplasia of the bone marrow in animals. However, no corresponding effects have been noted in humans. Alpha olefins are more reactive and toxic than beta isomers. The alkadienes are more irritant and generally more toxic than the corresponding alkanes (268).

1,3-Butadiene is probably the most toxic member of the alkene family. The toxicological properties of butadiene have been studied extensively in both experimental animals and humans. Epidemiological studies on cancer among people exposed to butadiene have suggested increased risks for leukemia and lymphoma (269).

Table 49.20. Summary of Carcinogenicity Studies and Tumors Developed in Animals Exposed to 1,3-Butadiene

Exposure	Approximate Treatment

Species	Gender	Route	Dose (ppm)	Regimen	Neoplasm	Ref.
Sprague–Dawley rats	Female	Inhalation	0, 1000, 8000	6 h/day, 5 days/week, 105 weeks	Mammary gland adenoma and carcinoma Thyroid follicular cell adenoma Uterine sarcoma Zymbal gland carcinoma	362
Sprague–Dawley rats	Male	Inhalation	0, 1000, 8000	6 h/day, 5 days/week, 111 weeks	Pancreatic exocrine adenoma Testicular Leydig cell tumors	362
$B6C3F_1$ mice	Female	Inhalation	0, 625, 1250	6 h/day, 5 days/week, 60–61 weeks	Lethal thymic lymphomas Acinar cell carcinomas of the mammary gland Granulosa cell neoplasms of the ovary Hepatocellular neoplasms Heart hemangiosarcomas Malignant lymphomas Alveolar–bronchiolar neoplasms Squamous-cell neoplasms of the forestomach	388
$B6C3F_1$ mice	Male	Inhalation	0, 625, 1250	6 h/day, 5 days/week, 60–61 weeks	Lethal thymic lymphomas Heart hemangiosarcomas Alveolar–bronchiolar neoplasms Squamous-cell neoplasms of the forestomach	388
$B6C3F_1$ mice	Female	Inhalation	0, 6.25, 20, 62.5, 200, 625	6 h/day, 5 days/week, 104 weeks	Lethal thymic lymphomas Heart hemangiosarcomas Alveolar–	389

					bronchiolar neoplasms Hepatocellular neoplasms Harderian gland adenoma and carcinoma Granulosa cell neoplasms of the ovary Mammary gland carcinomas Squamous-cell neoplasms of the forestomach	
$B6C3F_1$ mice	Male	Inhalation	0, 6.25, 20, 62.5, 200, 625	6 h/day, 5 days/week, 104 weeks	Lethal thymic lymphomas Alveolar–bronchiolar neoplasms Harderian gland adenoma and carcinoma Heart hemangiosarcomas Hepatocellular neoplasms Squamous cell neoplasms of the forestomach Preputial gland adenoma or carcinoma	389

Table 49.21. Summary of Mutation Induction Studies in Transgenic Animals Exposed to 1,3-Butadiene

Species	Exposure route	Approximate Dose (ppm)	Treatment	Gene Mutation	Ref.
$CD2F_1$ transgenic mice	Inhalation	625	6 h/day, 5 days/week, 1 weeks	Increased mutant frequency of the *lacZ* transgene from the lung, no increase in bone marrow and liver	407

$B6C3F_1$ mice	Inhalation	625	6 h/day, 5 days/week, 2 weeks	Increased frequency of *hprt* mutant T lymphocytes	408
$(102/E_1$ X C3H/E1)F_1 mice	Inhalation	200, 500, 1300	6 h/day, 5 days/week, 1 weeks	Increased frequency of *hprt* mutant T lymphocytes at higher dose	409
$B6C3F_1$ transgenic mice	Inhalation	62.5, 625, 1250	6 h/day, 5 days/week, 4 weeks	Concentration-dependent increase in bone marrow *lacI* mutant frequency	410
$B6C3F_1$ transgenic mice	Inhalation	62.5, 625, 1250	6 h/day, 5 days/week, 4 weeks	Increase in bone marrow *lacI* mutant frequency at all levels of exposure	411
$B6C3F_1$ mice	Inhalation	20, 62.5, 625	6 h/day, 5 days/week, 4 weeks	Increased frequency of *hprt* mutant T lymphocytes	412
F344 rats	Inhalation	20, 62.5, 625	6 h/day, 5 days/week, 4 weeks	Increased frequency of *hprt* mutant T lymphocytes, rate of mutation accumulation greater in rats	412

Table 49.22. Summary of Epidemiological Studies in Human Exposed to 1,3-Butadiene[a]

Study Design	Industry	Workers (*N*)	Study Period	Main Result—SMR (95% C1) unless indicated	Ref.
Cohort	SBR	2756	11943–1976	All LHC: 1.3 (0.9–1.4) Leukemia: 1.7 (0.8–1.5) Lymphosarcoma: 1.7 (0.7–1.7)	437, 438
Cohort	BDM	2795	1943–1994	All LHC: 1.5 (1.1–2.0) Leukemia: 1.1 (0.6–1.9) Lymphosarcoma: 1.9 (0.9–3.6)	439
Cohort	SBR	12,110	1943–1982	All LHC: 1.0 (0.9–1.4) Leukemia: 1.0 (0.8–1.5) Lymphosarcoma: 0.6 (0.7–1.7)	440
Case-control	SBR	59 (LHC cases)	1943–1982	OR (95% CI)	441

		193 (controls)		All LHC: 2.3 (1.1–4.7) Leukemia: 9.4 (2.1–22.9) Lymphosarcoma: 0.5 (0.1–4.2)	
Case-control	SBR	59 (LHC cases) 1242 (controls)	1943–1982	OR (95% Cl) at 1 ppm butadiene Leukemia: 1.5 (1.1–2.1)	442
Cohort	SBR	15,649	1943–1991	All LHC: 1.1 (0.9–1.3) Leukemia: 1.3 (1.0–1.7) Lymphosarcoma: 0.8 (0.4–1.4)	443
Cohort	SBL	420	1947–1986	All LHC: 1 obs, 2.2 exp Leukemia: 1 obs, 0.9 exp	444
Cohort	BDM	614	1948–1989	All LHC: 0 obs, 1.2 exp	445
Cohort	BDM	364	1943–1970	All LHC: 1.7 (0.7–3.6) Leukemia: 1.2 (0.2–4.4) Lymphosarcoma: 5.8 (1.6–14.8)	446

[a] Key: ABS—acrylonitrile-butadiene-styrene plastic; BDM—butadiene monomer; CI—confidence integral; exp.—expected; LHC—lymphohematopoietic cancer; obs—observed; OR—odds ratio, SBL—styrene–butadiene latex; SBR—styrene–butadiene rubber; SMR—standardized mortality ratio.

Table 49.23. Occupational Exposure Limits for 1,3-Butadiene in the United States[a]

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	1 ppm (2.2 mg/m^3)	Lowest feasible concentration	2 ppm (4.4 mg/m^3)
Short-term exposure limit	5 ppp (11 mg/m^3)	—	—
Ceiling limit	—	—	—

[a] OSHA and ACGIH—8-h TWA; NIOSH—10-h TWA.

Table 49.24. Occupational Exposure Limits for 1,3-Butadiene in Different Countries[a]

Country	Exposure Limit

Australia	TWA 10 ppm (22 mg/m^3); carcinogen
Belgium	TWA 10 ppm (22 mg/m^3); carcinogen
Denmark	TWA 10 ppm (22 mg/m^3); carcinogen
Finland	TWA 50 ppm (73 mg/m^3); carcinogen
France	TWA 10 ppm (22 mg/m^3)
Germany	Carcinogen
Hungary	STEL 10 mg/m^3; carcinogen
Ireland	TWA 10 ppm (22 mg/m^3); carcinogen
Mexico	TWA 1000 ppm (2200 mg/m^3); STEL 1250 ppm (2750 mg/m^3)
The Netherlands	TWA 21 ppm (46.2 mg/m^3)
The Philippines	TWA 1000 ppm (2200 mg/m^3)
Poland	TWA 10 mg/m^3; STEL 40 mg/m^3; carcinogen
Russia	STEL 100 mg/m^3
Sweden	TWA 10 ppm (22 mg/m^3); STEL 20 ppm (40 mg/m^3); carcinogen
Switzerland	TWA 5 ppm (11 mg/m^3); carcinogen
Turkey	TWA 1000 ppm (2200 mg/m^3)
United Kingdom	TWA 10 ppm (22 mg/m^3)

[a] From Refs. 19 and 20.

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C. Alkynes

The presence of a triple covalent bond in the carbon chain gives rise to the compounds called *alkynes*. They have the generic formula C_nH_{2n-2}. Physical properties for selected alkynes are listed in Table 49.25.

Table 49.25. Physicochemical Properties of Alkanes[a]

Compound	Molecular formula	Molecular weight	Boiling point (°C)	Melting point (°C)	Density (mg/cm^3) (at °C)	Refractive Index n_D	Solubility	Flash Point (°C)	Flan Lir
Acetylene	C_2H_2	26.02	–84	–80.8	0.337	—	w 2, al 2,	–17.7	2.5–

			(subl. pt.)	(trip. pt.)	(25)		ac 3, bz 3	(closed cup)	
Propyne	C_3H_4	40.07	–23.2	–103	0.607 (25)	1.3863 (–40)	w 2, al 4, bz 3, ch 3	—	2.1–
3-Methylbutyne	C_5H_8	68.12	26.3	–89.7	0.6660 (20)	1.3723 (20)	w 1, al 5, et 5	—	—
1-Buten-3-yne	C_4H_4	52.08	5.1	—	0.7094 (0)	1.4161 (1)	w 1, bz 3	—	21.0
1,6-Heptadiyne	C_7H_8	92.14	112.0	–85.0	0.8164 (17)	1.4510 (17)	w 1, bz 3, aa 3	—	—
1-Decyne	$C_{10}H_{18}$	138.25	174.0	–44.0	0.7655 (20)	1.4265 (20)	w 1, al 3, et 3, os 3	—	—

[a] Molecular Formula—in Hill notation; Molecular Weight—relative molar mass; Density—mass per unit volume in g/cm^3 at the temperature indicated in parentheses; Refractive Index—at the temperature indicated in parentheses, unless otherwise indicated, all values refer to a wavelength of 589 nm; Solubility—solubility in common solvents (w-water, al-ethanol, et-ethyl ether, ac-acetone, bz-benzene, ch-chloroform, ct-carbon tetrachloride, aa-acetic acid, pe-petroleum ether, os-organic solvents) on a relative scale: 1 = insoluble, 2 = slightly soluble, 3 = soluble, 4 = very soluble, 5 = miscible, 6 = decomposes; Flammability limits—explosive limits (in percent by volume) at ambient temperature and pressure; subl. pt.—sublimation point; trip. pt.—triple point.

The alkynes do not exert any acute local toxicity. The lower members are anesthetics and cause CNS depression. They are practically nonirritating to the skin, but cause pulmonary irritation and edema at very high concentrations. The higher molecular weight members can be aspirated into the lungs when ingested (5).

Table 49.26. Occupational Exposure Limits for Propyne in the United States

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	1000 ppm (1650 mg/m^3)	1000 ppm (1650 mg/m^3)	1000 ppm (1640) mg/m^3)
Short-term exposure limit	—	—	—
Ceiling limit	—	—	—

OSHA and ACGIH—8-h TWA; NIOSH—10-h TWA. From Ref. 19.

Table 49.27. Occupational Exposure Limits for Propyne in Different Countries[a]

Country	Exposure Limit
Australia	TWA 1000 ppm (1650 mg/m^3); STEL 1250 ppm

Belgium	TWA 1000 ppm (1650 mg/m^3); STEL 1250 ppm (2050 mg/m^3)
Denmark	TWA 1000 ppm (1650 mg/m^3)
Finland	TWA 1000 ppm (1650 mg/m^3); STEL 1250 ppm (2065 mg/m^3)
France	TWA 1000 ppm (1650 mg/m^3)
Germany	TWA 1000 ppm (1650 mg/m^3)
Ireland	TWA 1000 ppm (1650 mg/m^3)
Mexico	TWA 1000 ppm (1650 mg/m^3); STEL 1250 ppm (2040 mg/m^3)
The Netherlands	TWA 1000 ppm (1650 mg/m^3)
The Philippines	TWA 1000 ppm (1650 mg/m^3)
Poland	TWA 1500 mg/m^3; STEL 2000 mg/m^3
Switzerland	TWA 1000 ppm (1650 mg/m^3)
Turkey	TWA 1000 ppm (1650 mg/m^3)

[a] From Refs. 19 and 20.

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Alicyclic Hydrocarbons
C. Stuart Baxter, Ph.D.

A. Cycloalkanes or Cycloparaffins

The alicyclic hydrocarbons include the cycloalkanes, also called *cycloparaffins*, *cyclanes*, and

naphthenes, and the cycloalkenes, also known as *cycloolefins* and *cyclenes*, and their alkyl and alkenyl derivatives. Some of these derivatives occur naturally in plants and are commonly known as *terpenes*. Other compounds can be isolated from crude petroleum refinery distillates or catalytically cracked petroleum products. Cycloalkanes are extensively used to produce re-formed aromatics (1) and as solvents or synthesis intermediates. Some physical properties of the cycloalkanes are given in Table 50.1 (2–18).

Table 50.1. Physical and Chemical Properties of Cycloalkanes

Compund	Molecular Weight	Boiling Point (° C)	Melting Point (° C)	Refractive Index (20° C)	Vapor Pressure (mm Hg) (°C)	Density g/mL, at 20 ° C	Flash Point (°C)	Solubilit w/al/et[a]
Cyclopropane	42.08	–76	–128	1.37	—	0.6769	—	s/v/v
Cyclobutane	56.10	13	–91	1.426	—	0.72	<10	i/v/v
Cyclopentane	70.13	49	–94	1.4065	400 (31)	0.7454	–37	i/v/v
Methylcyclopentane	84.16	71.8	–142.4	1.4097	100 (17.9)	0.7486	–10	i/v/v
Ethylcyclopentane	98.18	103	–138	1.4198	—	0.7665	15	i/v/v
Cyclohexane	84.16	80.74	6.6	1.4262	100 (60.8)	0.7786	–18	i/v/v
Methylcyclohexane	98.19	100.93	–126.3	1.42056	43 (20.5)	0.7694	–3	i/s/s
Ethylcyclohexane	112.21	131.78	–111	–33.5	—	0.788	18	i/s/s
1,1-Dimethylcyclohexane	112.21	120	—	1.428	—	0.781	7	i/s/s
1,2-Dimethylcyclohexane	112.21	124	—	1.432	10 (10.2)	0.778	15	i/s/s
1,3-dimethylcyclohexane	112.21	121-4	—	1.426	—	0.767	9	i/s/s
1,4-Dimethylcyclohexane	112.21	120	–87	1.426	—	0.773	15	i/s/s
Cycloheptane	98.19	118.4	–12	1.445	—	0.8098	6	i/v/v
Cyclooctane	112.21	151/740 m	15	1.458	—	0.836	30	i/v/v
Cyclononane	126.24	126.24	11	—	—	0.854	—	i/v/v
Cyclododecane	168.32	239	61	—	—	0.863	—	i/v/v

[a] Solublity in water/alcohol/ether: v = very soluble; s = soluble; i = insoluble.

A.1 Toxicity

Cyclopropane and cyclobutane are gases and have been used as anesthetics. Cyclopentane and higher members are liquids with low acute and chronic toxicity overall, but still able to induce many toxic responses characteristic of lipophylic compounds, including central nervous system (CNS) depression, dizziness, and headache. For cyclohexane and higher analogs, the margin of safety between CNS depression and death is very narrow and symptomatically barely recognizable. Following ingestion or inhalation cycloalkanes are exhaled in unchanged form or rapidly metabolized into water-soluble metabolites, usually glucuronides. Exposure of humans and laboratory animals to high concentrations may cause excitement, loss of equilibrium, stupor, and

coma, but rarely death. Oral administration of high doses to animals has additionally resulted in severe diarrhea, vascular collapse, and heart, lung, liver, and brain degeneration. Cycloparaffins and cycloalkenes are also ocular and dermal irritants since, as lipophylic agents, they defat the skin. In many cases they are also skin sensitizers; their sensitizing activity increases with the number of double bonds. The liquid members up to cyclooctane, and to a lesser exent cyclododecane, are aspiration hazards.

A number of alicyclic hydrocarbons are nephrotoxic in male rats. Repeated dose oral (19) or inhalation (20) studies result in tubular degeneration characterized by hyaline droplet formation, necrosis, intratubular casts, and medullary mineralization. These effects are associated with the presence of a_2-u-globulin in the males of a number of rat strains including Fischer 344, Sprague–Dawley, Wistar, Buffalo, and Norway Brown. It is not produced in the NCI–Black–Reiter (NBR) strain (21) or in female rats (22), and nephropathy is not produced by alicyclic hydrocarbons in these animals. This type of hydrocarbon nephropathy has been produced by cyclohexane (23, 24), 2,2,4-trimethylpentane (25), JP-5 jet fuel (25), JP-10 jet fuel (26), *d*-limonene (27), decalin (22, 28), and tetralin (29). The nephropathy has been studied extensively using a short-term decalin inhalation model (20). The nephropathy is not seen in mice or dogs (24).

This protein was of primary interest in carcinogenesis studies of unleaded gasoline (30). Kidney tumors were produced only in males and were associated with a_2-u-globulin. Further study revealed that humans do not produce this protein. On this basis, the National Toxicology Program stated that the kidney tumors seen in male rats were not relevant to carcinogenesis in man (31). Unleaded gasoline did not produce kidney tumors in male NBR rats (32).

Alicyclic Hydrocarbons
C. Stuart Baxter, Ph.D.

B. Cycloalkenes or Cycloolefins

The cyclic olefins are more highly reactive than their paraffin counterparts. They contribute to photochemical smog by reacting with ozone and other small molecular or ionic species (105). Selected physical properties are given in Table 50.2 (2–17). In C4–C7 cycloalkenes, toxicity increases with molecular weight. Cycladienes and polyenes appear to possess increasingly irritant, toxic, and sensitizing properties, peaking somewhat higher for cycladienes than for monocyclic alkenes. The aspiration hazard also appears higher for the cycloalkenes than the cycloalkanes (53).

Table 50.2. Physical and Chemical Properties of Cycloalkenes and Polycyclic Hydrocarbons

Compund	Molecular Weight	Boiling Point (°C) (mm Hg)	Melting Point (°C)	Refractive Index (20°C)	Vapor Pressure (mm Hg) (°C)	Density g/mL, at 20°C	Flash Point (°C)	Vapor Density
Cyclopentene	68.12	44.24	–135	1.4225	—	0.772	–30	2.3
Cyclohexene	82.15	82.98	–104	1.4465	162 (38)	0.811	–20	2.8
Cycloheptene	96.17	114.6	–56	1.4552	—	0.824	–6	—
1-Vinylcyclohexene	108.18	145	—	1.4915	—	0.8623	—	—
4-Vinylcyclohexene	108.18	126	–101	1.4639	25.8 (38)	0.8229	14	3.76

Limonene	136.24	176	–74.35	1.473	—	0.8411	46	—
1,3-Cyclopentadiene	66.10	42	–85	1.44	—	0.8021	32.2	—
Methylcyclohexa-1,4-diene	94.156	114–115	—	1.471	—	0.8354	10	—
1,3,5-cycloheptatriene	92.14	116	–79.49	1.519	—	0.888	5	—
Cycloocta-1,5-diene	108.18	150.8	–69	1.493	—	0.8803	45	—
Cyclooctatetraene	104.15	143	–27	1.537	7.9 (25)	0.925	22	—
cis-Decalin	138.25	193	–43.01	1.481	1 (22.5)	0.8965	58	4.76
trans-Decalin	138.25	195.65	–30.7	1.4695	10 (47.2)	0.8699	52	4.76
Tetralin	132.20	207.57	–35	1.5414	—	0.973	77	4.6
Dicyclopentadiene	132.20	170	–1	1.505	10 (47.6)	0.9302	26	4.55
a-Pinene	136.24	155	–64	1.4658	10 (37.3)	0.857	32	4.7
Turpentine	136.23	150–180	–60	—	—	0.854–68	35-9	4.6–4.84
Vinyl norbornene	120.19	141	–80	—	—	—	27	—
Ethylidene norbornene	120.19	67	—	—	—	0.893	38	4.2
Camphene	136.24	318	114	1.475	—	0.839	36	—
a-Caryophyllene	204.35	123 (10)	—	1.5004	—	0.8905	—	—

Alicyclic Hydrocarbons
C. Stuart Baxter, Ph.D.

C. Alkenyl Cycloalkenes
C.1 Vinylcyclohexenes
13.0 1-Vinylcyclohex-1-ene
13.0.1 CAS Number: [*2622-21-1*]

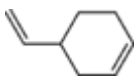
13.0.2 Synonyms: Cyclohexenylene, 1-ethenylcyclohexene, or tetrahydrostyrene

13.0.3 Trade Names: NA

13.0.4 Molecular Weight: 108.18

13.0.5 Molecular Formula: C_8H_{12}

13.0.6 Molecular Structure:



13.1 Chemical and Physical Properties
13.1.1 General Vinylcyclohex-1-ene is a flammable liquid (33). Selected physical properties are given in Table 50.2.
13.2 Production and Use
Vinylcyclohex-1-ene is a common component of tobacco smoke thought to be formed by dimerization from butadiene (119). It serves as an important chemical intermediate.
13.3 Exposure Assessment:
NA
13.4 Toxic Effects
13.4.1 Experimental Studies 13.4.4.1 Acute Toxicity Vinylcyclohex-1-ene is an irritant and CNS depressant at high concentrations. In mice exposed to 1-vinylcyclohexene, CNS depression was noted at a concentration of 7.5 mg/L. The 4-h LC_{50} in mice is 13.7 mg/L (120). It has a low degree of toxicity following ingestion or dermal absorption.

13.4.2 Human Experience No information is available; CNS depressant activity anticipated.
14.0 4-Vinylcyclohexene
14.0.1 CAS Number: [*100-40-3*]

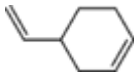
14.0.2 Synonyms: Butadiene dimer; 4-ethenylcyclohexene; cyclohexene, 4-ethenyl-; cyclohexene, 4-vinyl-; cyclohexenylethylene; ethenyl-1-cyclohexene; ncic54999; 1,2,3,4-tetrahydrostyrene; vinylcyclohexene; 1-vinylcyclohexene-3; 4-vinylcyclohexene; 4-vinylcyclohexene-1

14.0.3 Trade Names: NA

14.0.4 Molecular Weight: 108.18

14.0.5 Molecular Formula: C_8H_{12}

14.0.6 Molecular Structure:



14.1 Chemical and Physical Properties
14.1.1 General 4-Vinylcyclohexene is a colorless liquid. Selected physical properties are given in Table 50.2.
14.2 Production and Use
4-Vinylcyclohexene produced by dimerization of butadiene, as a by-product of chlorination of butadiene, or from butadiene on long storage (121). It is present in the offgases from tire curing (122) and is used as an intermediate for the production of vinylcyclohexene dioxide, which is used as a reactive diluent in epoxy resins. Previous uses of 4-vinyl-1-cyclohexene include comonomer in the polymerization of other monomers and for halogenation to polyhalogenated derivatives that are used as flame retardants. It is a precursor for ethyl cyclohexyl carbinol plasticizers, and is used as an intermediate for thiocyamate insecticides and as an antioxidant (122)
14.3 Exposure Assessment
14.3.1 Air Gas chromatography was used to determine the quantity formed from butadiene by its dimerization in the GC (123).

14.3.2 Background Levels: NA

14.3.3 Workplace Methods: NA

14.3.4 Community Methods: NA

14.3.5 Biomonitoring/Biomarkers No information is available. Metabolites may be quantitated in tissues and urine following exposure.

14.4 Toxic Effects

14.4.1 Experimental Studies 14.4.1.1 Acute Toxicity 4-Vinylcyclohexene is an irritant and CNS depressant at high concentrations, with a low degree of toxicity following ingestion or dermal absorption. The oral LD_{50} in the rat is 3080 mg/kg, and the dermal LD_{50} in the rabbit is 20 mL/kg. Time to death for rats was 15 min in the saturated vapor, and a concentration of 8000 ppm for 4 h proved lethal to four of six rabbits (107). The 4-h LC_{50} in mice is 27 mg/L (124).

14.4.1.2 Chronic and Subchronic Toxicity In one study, 1 g/m^3 administered by inhalation for 6 h/day over 4 months, inhibited weight increase and caused leukocytosis, leukopenia, and impairment of hemodynamics in rats and mice. Exposure of rats and mice to 1000 mg/m^3 (226 ppm) by inhalation for 6 h per day over 4 months was reported to inhibit weight gain and to cause leukocytosis, leukopenia, and impairment of haemodynamics (122).

14.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Incubation *in vitro* with liver microsomal enzymes yields the major metabolic products 4-vinyl-1,2-epoxycyclohexane and 4-epoxyethyl-1,2-dihydroxycyclohexane, with trace amounts (<0.001%) of vinylcyclohexene diepoxide (125). Metabolism in mice was reported to proceed to the mono- and diepoxides, and the latter was proposed to be the ultimate ovotoxic metabolite (126). To further investigate the role of metabolism in 4-vinylhexene toxicity, microsomal preparations were prepared from liver, lung, and ovaries obtained from female Crl:CD rats and B6C3F1 mice, rat, and mouse liver and lung, but not ovarian microsomes, metabolized 4-vinylcyclohexene to the 1,2-epoxide at detectable rates. Compared to the rat, the mouse appeared to be more efficient at metabolism to epoxides, and less efficent at hydrolysis of epoxides to diols, which may explain the higher ovotoxicity of 4-vinylcyclohexene to this species (125).

14.4.1.3.1 Adsorption See Section 14.4.1.3.2.

14.4.1.3.2 Distribution No information is available, but facile absorption and distribution of nonpolar compounds of this type is expected.

14.4.1.3.3 Excretion Excretion of the compound as conjugated metabolites is expected in the urine.

14.4.1.4 Reproductive and Developmental 4-Vinylcyclohexene is toxic to ovaries; following intraperitoneal administration to $B6C3F_1$ mice for 30 days a signicant deletion of ovarian follicles was reported (127).

14.4.1.5 Carcinogenesis A dose of 145 g/kg applied to mouse skin for 54 weeks provided weak evidence of carcinogenicity (109). Administration by gavage of doses of 0, 200, or 400 mg/kg body weight, 5 days per week, to groups of 50 F344/N rats for 103 weeks induced a slightly increased incidence of epithelial hyperplasia of the forestomach (1/50; 3/50; 5/47) and squamous-cell papillomas or carcinomas (combined) of the skin, in males receiving the highest dose. Low dose female rats whose survival was more similar to that of the vehicle controls had a marginally increased incidence of adenomas or squamous-cell carcinomas (combined) of the clitoral gland. Under these conditions, the 2-year gavage studies in male and female rats were considered inadequate because of extensive and early mortality at the high dose or at body doses and the lack of conclusive evidence of a carcinogenic effect (125).

14.4.1.6 Genetic and Related Cellular Effects Studies No mutagenicity was observed in *Salmonella*

typhimurium strains TA100, TA1535, TA1537, or TA98 in the presence or absence of Aroclor 1254–induced male Sprague–Dawley rat or male Syrian hamster liver S9 when tested according to the preincubation protocol. Several recognized metabolites, including 4-vinylcyclohexene diepoxide, 4-vinyl-1,2-epoxycyclohexane, and 4-epoxyethyl-1,2-dihydroxycyclohexane, were mutagenic in *Salmonella* and/or produced chromosomal damage *in vitro* (124). 4-Epoxyethyl-1,2-epoxycyclohexane, but not 4-vinyl-1,2-epoxycyclohexane or 4-epoxyethycyclohexane-1,2-diol, induce 6-thioguanine-resistant mutants in cultured Chinese hamster V79 cells when tested at 0.3–20 mM. 4-Vinyl-1,2-epoxycyclohexane and 4-epoxyethylcyclohexane-1,2-diol, tested at 2.0 mM, induced micronuclei, but 4-epoxyethyl-1,2-epoxycyclohexane did not; all three metabolites induced chromosomal damage (bridges and lagging chromosomes in anaphase) in V79 cells(109).

14.4.2 Human Experience 14.4.2.1 General Information 4-Vinylcyclohexene is an irritant in high concentrations, and possibly a CNS depressant. It has a low degree of toxicity via ingestion and skin penetration (128).

14.4.2.2 Clinical Cases 14.4.2.2.1 Acute Toxicity Exposed workers experienced keratitis, rhinitis, headache, hypotonia, leukopenia, neutrophilia, lymphocytosis, and impairment of pigment and carbohydrate metabolism (129).

14.4.2.2.2 Chronic and Subchronic Toxicity: NA

14.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms: NA

14.4.2.2.4 Reproductive and Developmental: NA

14.4.2.2.5 Carcinogenesis There is inadequate evidence in humans for carcinogenicity (109). Classification is A2: Suspected human carcinogen (130).
14.5 Standards, Regulations, or Guidelines of Exposure
Neither NIOSH nor OSHA have established limits for this chemical. The ACGIH has establish an 8 h TWA TLV of 0.1 ppm with an A3 notation. The A3 notation indicates that the chemical is a confirmed animal carcinogen with unknown relevance to humans (130). 4-Vinylcyclohexene is included on the TSCA list. A testing consent order is in effect for health effects and chemical fate testing (131).
C.2 Terpenes
Further side-chain substitution of cyclohexene, with a methyl, isopropenyl, ethenyl, or other group, forms a class of chemicals named terpenes. Limonene is a C10 cyclic olefin and a-pinenes are common monoterpenes.
15.0 Limonene
15.0.1 CAS Number: [*138-86-3*]

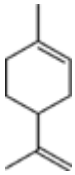
15.0.2 Synonyms: Carvene; cinene; cajeputene; eulimen; kautschin; a-limonene; *p*-mentha-1,8-diene; 1,8(9)-*p*-menthadiene; cyclohexene; 1-methyl-4-(1-methylethenyl)- or 1-methyl-4-isopropenyl-cyclohex-1-ene; 4-isopropenyl-1-methyl-1-cyclohexene; nesol; d-1,8-terpodiene; ciene; 1-methyl-4-(1-methylethenyl)cyclohexene; acintene DP dipentene; cyclil decene; 4-isopropenyl-1-methyl-; Dipenten; DL-*p*-mentha-1,8-diene; mentha-1,8-diene; mentha-1,8-diene, DL; menthadiene; methyl-4-(1-methylethenyl)cyclohexene; methyl-4-isopropenyl-1-cyclohexene; methyl-4-isopropenylcyclohexene; monocyclic terpene hydrocarbons; terpodiene; 4-(1-methylethenyl)-1-methyl-cyclohexene; dipentene, mixt. of limonene, 56–64%, and terpinolene, 20–25%; DL-Limonene

15.0.3 Trade Names: NA

15.0.4 Molecular weight: 136.24

15.0.5 Molecular Formula: $C_{10}H_{16}$

15.0.6 Molecular Structure:



15.1 Chemical and Physical Properties
15.1.1 General Selected physical properties are given in Table 50.2.

15.1.2 Odor and Warning Properties A highly fragrant, pleasant, lemon-like odor free from camphoraceous and turpentine-like notes has been noted.
15.2 Production and Use
Limonene occurs in the oil of many plants (132), and is the main constituent (≤86%) of the terpenoid fraction of fruit, flowers, leaves, bark, and pulp from shrubs, annuals, or trees including anise, mint, caraway, polystachya, pine, lime, and orange oil (118, 133). It occurs as a by-product in the manufacture of terpineol and in various synthetic products made from a-pinene or turpentine oil. It is found in the gas phase of tobacco smoke (134) and has been detected in urban atmospheres (135). It has antimicrobial, antiviral (136), antifungal (137), antilarval (138), and insect attractant (139) and repellent (140) properties. In Japan, it has been used to dissolve gallstones (141) and in wound healing (142). Used to add fragrance and taste to fruit and essence to flowers and leaves, as an odorant (143), a solvent (144), an aerosol stabilizer (145), and a wetting and dispersing agent (4). Polylimonene is used as a flavor fixative (12).
15.3 Exposure Assessment
GC or HPLC can be used with both microbore and standard columns in reversed and normal phase. Fractions are detected spectrophotometrically at 220 and 320 nm before and after evaporation of samples (146).
15.4 Toxic Effects
15.4.1 Experimental Studies 15.4.1.1 Acute Toxicity Acute toxicity is low; *d*-limonene solution injected as bolus into biliary tract of cats produced hepatobiliary tissue damage, depending on contact time, volume, and flow direction (147).

15.4.1.2 Chronic and Subchronic Toxicity Administration of 2-3.6 mL/kg per day to dogs for 1 for 6 months caused frequent vomiting, nausea, and decrease in body weight, blood sugar, and cholesterol. No significant change was observed in organs except in the kidney (148).

15.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The major metabolite in Sprague–Dawley rats is limonene 1,2-oxide. A metabolite isolated from rabbit urine was identified as *p*-mentha-1,8-dien-10-ol (149). After oral administration, the major metabolite in urine was perillic acid 8,9-diol in rats and rabbits, perillyl-b-*d*-glucopyranosiduronic acid in hamsters, *p*-menth-1-ene-8,9-diol in dogs, and 8-hydroxy-*p*-menth-1-en-9-yl-b-*d*-glucopyranosiduronic acid in guinea pigs and man (150).

15.4.1.3.1 Adsorption Monoterpenes are poorly resorbed in the GI tract. Exposure to limonene from in a foam bath led to a maximum blood level after 10 min of exposure and with a concentration proportional to the skin exposed (151). Limonene is absorbed 100 times more rapidly than water and 10,000 times faster than sodium and chloride ions (152).

15.4.1.3.2 Distribution The resorbed portion of agents of this type accumulates in the lipophilic body compartments and is then metabolized and excreted by the kidneys.

15.4.1.3.3 Excretion Metabolic studies in humans and animals demonstrated 75–95% of the material

to be excreted in the urine and ≤10% in the feces (153). In another study, 25% of the administered limonene was excreted in the bile within 48 h (154).

15.4.1.4 Reproductive and Developmental When dosed with 2869 mg/kg during days 9–15 of gestation, rats exhibited a decrease in body weight gain and the fetuses exhibited prolonged ossification of the metacarpal bone and proximal phalanx and slightly decreased spleen and ovarian weights (155). In mice given 2363 mg/kg orally on days 7–12 of gestation, fetuses exhibited a decrease in weight gain and increase in the incidence of abnormal bone formation (156). Rabbits showed decreased body weight gain and six deaths of 21 animals administered 1000 mg/kg during gestation. A dose of 250 mg/kg resulted in no teratogenic effects (157, 158).

15.4.1.5 Carcinogenesis Induction of kidney neoplasias has been observed in male rats of strains that have significant concentrations of the protein a2u-globulin (159). This protein is not expressed in females or species other than the rat; therefore limonene carcinogenicity appears to be limited to the male of specific strains of this species. Subcutaneous injection of the compound or its hydroperoxide into C57BL/6 mice decreased the incidence of dibenzopyrene-induced tumors appreciably (160). Given orally either 15 min or 1 h prior to nitrosodiethylamine, d-limonene reduced forestomach tumor formation by about 60% and pulmonary adenoma formation by about 35%.

15.4.1.6 Genetic and Related Cellular Effects Studies Limonene was found to be non-mutagenic in four strains of *Salmonella typhimurium* (TA98, TA100, TA1535, or TA1537) and not to significantly increase the number of trifluorothymidine resistant cells in the mouse L5178Y/TK + or–assay, and not to induce chromosomal aberrations or sister chromatid exchanges (SCEs) in cultured Chinese hamster ovary (CHO) cells. All assays were conducted in the presence and absence of exogenous metabolic activation (S9) (159).

15.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Activity as a dermal irritant and possible skin sensitizer has been reported (4). Dunkin–Hartley guinea pigs were induced by topical application of air oxidation products of limonene: (+)-limonene oxide, or (*R*)-(–)-carvone, (–)-carveal, or air-exposed *d*-limonene. Air oxidation of *d*-limonene is necessary for its sensitizing potential due to the production of potent allergens such as limonene oxide and carvone (161).

Administration of single oral doses of 0, 0.1, 0.3, 1, or 3 mmol in corn oil resulted in a dose–response relationship for the exacerbation of hyaline droplet formation in the kidneys of male Sprague–Dawley rats (27). The male rat hydrocarbon nephropathy should not be predictive of a normal human renal response. In a 24-h single-dose experiment on the renal toxicity of mercuric chloride, potassium dichromate, *d*-limonene, and hexachloro-1:3-butadiene administered simultaneously in 12-week-old male Wistar rats, absence of both dose additivity and potentiating interaction at subeffective levels of the individual nephrotoxicants was suggested (162).

15.4.2 Human Experience 15.4.2.1 General Information Toxicity is most likely low, although mild dermal irritation and skin sensitization may occur. Hematuria and albuminuria might occur if large amounts are ingested.

15.4.2.2 Clinical Cases 15.4.2.2.1 Acute Toxicity Liquid has been reported to irritate eyes and skin; ingestion causes irritation of GI tract (16).

15.4.2.2.2 Chronic and Subchronic Toxicity No information available; toxicity is most likely to be low. Mild dermal irritation and skin sensitization may occur. Hematuria and albuminuria might occur if large amounts are ingested.

15.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms In human volunteers exposed by inhalation (2 h, workload 50 W) in an exposure chamber on three different occasions to concentrations approximately 10, 225, and 450 mg/m^3 the relative pulmonary uptake was high,

approximately 70% of the amount supplied. A decrease in vital capacity was observed after exposure at a high exposure level. The subjects did not experience any irritative symptoms or symptoms related to the CNS (163). Metabolic studies in humans and animals demonstrated that 75–95% of the material was excreted in the urine and ≤10% in the feces (153). In another study, 25% of the administered dose was excreted in the bile within 48 h (154).

15.4.2.2.4 Reproductive and Developmental: NA

15.4.2.2.5 Carcinogenesis No data are available on carcinogenicity to humans. The overall evaluation is “Not classifiable as to its carcinogenicity to humans” (group 3). (164).

15.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

15.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* Allergic contact dermatitis from honing oil containing the compound was reported (165).

15.5 Standards, Regulations, or Guidelines of Exposure

The odor threshold in water is 10 ppb (165). It is quantified using gas chromatography. With proper handling precautions, this material presents no health hazard. On the EPS TSCA Chemical Inventory and Test Submission Data Base (41).

15.6 Studies on Environmental Impact

If limonene is released to soil, limited data indicate resistance to biodegradation under aerobic conditions and low to slight mobility in soil. Expected to rapidly volatilize from both dry and moist soil to the atmosphere, although adsorption to soil may attenuate the rate of this process. If limonene is released to water, limited data indicate resistance to biodegradation under aerobic conditions. It may bioconcentrate in fish and aquatic organisms and significantly adsorb to sediment and suspended organic matter. It is expected to rapidly volatilize from water to the atmosphere. The estimated half-life for volatilization from a model river is 3.4 h, although adsorption to sediment and suspended organic matter may attenuate the rate of this process. If released to the atmosphere, expected to rapidly undergo gas-phase oxidation reactions with photochemically produced hydroxyl radicals, ozone, and at night with nitrate radicals. Calculated lifetimes for these processes in a clean and moderately polluted atmosphere are 2.0 h and 30 min, 36 min and 11 min, and 9 min and 0.9 min, respectively. Limonene is readily degraded in soil (26).

Alicyclic Hydrocarbons
C. Stuart Baxter, Ph.D.

D. Cyclopolyenes

16.0 1,3-Cyclopentadiene

16.0.1 CAS Number: [*542-92-7*]

16.0.2 Synonyms: **R**-Pentine, pentole, pyropentylene or cyclopentdiene

16.0.3 Trade Names: NA

16.0.4 Molecular Weight: 66.10

16.0.5 Molecular Formula: C_5H_6

16.0.6 Molecular Structure:

16.1 Chemical and Physical Properties
16.1.1 General 1,3-Cyclopentadiene is a colorless liquid that dimerizes easily in the presence of peroxides and trichloroacetic acid to a colorless solid (4). Selected physical properties are given in Table 50.2.

16.1.2 Odor and Warning Properties It has a sweet odor resembling turpentine. Low odor threshold = 5.0 mg/m^3; high threshold = 5.0 mg/m^3. (154).
16.2 Production and Use
This compound occurs in the C6–C8 petroleum distillation fraction (1), and in coke-oven light oil fractions (4). It is produced by dehydrogenation of cyclopentadiene or monomerization of its dimer. It is used as an intermediate in resin manufacture and chemical syntheses, especially for Diels–Alder reactions (4).
16.3 Exposure Assessment
NIOSH method 2523. Matrix: air. Sampler: solid sorbent tube (maleic anhydride on Chromosorb 104, 100 mg/50 mg). Flow rate: 0.01–0.05 L/min. Sample size: 3 L (63a).
16.4 Toxic Effects
16.4.1 Experimental Studies 16.4.1.1 Acute Toxicity The 1-h LC_{50} is 39 mg/L in the rat and 15 mg/L in the mouse (41). The LD_{50} for the dimer in rats is 0.82 g/kg orally. When injected subcutaneously into the rabbit, 3.0 mL caused CNS depression with fatal convulsions. Signs and symptoms during CNS depression include primary motor unrest and decreased, intermittent respiration rate prior to death. Its vapors produce CNS depression in the frog in 10 min, but recovery is complete in 70 min (35).

16.4.1.2 Chronic and Subchronic Toxicity In a total of 35 exposures of 7 h/day over a period of 53 days at an average concentration of 500 ppm, mild centrolobular cloudy swelling of liver cells and cloudy vacuolization of renal tubular epithelium was noted in rats (167).

16.4.2 Human Experience 1,3-Cyclopentadiene is irritating to eyes and mucous membranes (118). It has caused contact dermatitis and sensitization (168). No other information is available.
16.5 Standards, Regulations, or Guidelines of Exposure
The OSHA (55) PEL is 75 ppm (200 mg/m^3), and the ACGIH (56) TLV is 75 ppm (203 mg/m^3). The NIOSH recommendation is 8-h TWA: 75 ppm (200 mg/cm^3) (87). Cyclopentadiene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (41).
16.6 Studies on Environmental Impact
1,3-Cyclopentadiene may be released to the environment in emissions from waste incineration, polymer manufacturing plants, combustion of polymers, biomass, gasoline, and cigarettes and also in wastewater from manufacturing plants. If concentrated solutions are spilled, this compound is expected to polymerize spontaneously to dicyclopentadiene. If released to soil in small amounts, it may undergo extensive leaching or rapid volatilization. If released to water in dilute amounts, cyclopentadiene is expected to undergo rapid volatilization (estimated half-life 2.4 h from a model river). The significance of biodegradation in either soil or water is unknown. Chemical hydrolysis, oxidation, bioaccumulation in aquatic organisms, and adsorption to suspended solids and sediments are not expected to be significant fate processes in water. If released to the atmosphere, cyclopentadiene is expected to exist almost entirely in the vapor phase. This compound is expected to rapidly react with ozone molecules, photochemically generated hydroxyl radicals, and possibly nitrate radicals. The atmospheric half-life for cyclopentadiene is estimated to be about 40 min.
17.0 Cyclooctadienes
17.0a **cis**, **cis**-1,3-Cyclooctadiene
17.0.1a CAS Number: [*3806-59-5*]

17.0.2a Synonyms: NA

17.0.3a Trade Names: NA

17.0.4a Molecular Weight: 108.18

17.0.5a Molecular Formula: C_8H_{12}

17.0.6a Molecular Structure:

17.0b Cycloocta-1,5-diene
17.0.1b CAS Number: [*111-78-4*]

17.0.2b Synonyms: 1,5-cyclooctadiene; COD

17.0.3b Trade Names: NA

17.0.4b Molecular Weight: 108.18

17.0.5b Molecular Formula: C_8H_{12}

17.0.6b Molecular Structure:

17.1 Chemical and Physical Properties
17.1.1 General Cyloocta-1,5-diene is a flammable, highly reactive liquid; selected physical properties are given in Table 50.2. Cycloocta-1,3-diene exhibits the same properties as the 1,5 isomer but is more reactive.

17.1.2 Odor and Warning Properties Aromatic odor. Threshold 10 ppb.
17.2 Production and Use
Cycloocta-1,5-diene is produced from petroleum distillation fractions and is used as an intermediate in the plastics industry, as a synthetic lubricant, and in numerous other applications.
17.3 Exposure Assessment
No information is available, but methods similar to those used for other cyclic alkenes are applicable.
17.4 Toxic Effects
17.4.1 Experimental Studies 17.4.1.1 Acute Toxicity: NA

17.4.1.2 Chronic and Subchronic Toxicity: NA

17.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 1,5-Cyclooctadiene has been shown to reduce glutathione concentration in the rat liver. In the rat and rabbit both the 1,3 and 1,5 isomers are metabolized to dihydroxycyclooctylmercapturic acids and to sulfate and glucuronide conjugates (169).

17.4.1.4 Reproductive and Developmental: NA

17.4.1.5 Carcinogenesis None of the components present in this material at concentrations of ≤0.1% are listed by IARC, NTP, OSHA, or ACGIH as a carcinogen.

17.4.1.6 Genetic and Related Cellular Effects Studies: NA

17.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Cyclooctadiene is corrosive to the skin, with necrosis of the epidermis and ulceration and marked inflammation of the dermis. Nonoccluded applications of cyclooctadiene to the skin of rabbits, guinea pigs, and hairless mice produced an immediate erythematous reaction. It is also a skin sensitizer (170). Cyclooctadiene applied to the guinea pig skin on 3 alternate days was irritating to the skin, causing erythema, dry appearance, slight dermal weight increase, and increased arginase activity (54).
17.5 Standards, Regulations, or Guidelines of Exposure:
NA
17.6 Studies on Environmental Impact
Aquatic toxicity:

24-h LC_{50}, goldfish: 14 mg/L

24-h LC_{50}, *Daphnia magna*: 0.9 mg/L

96-h LC_{50}, rainbow trout: 30–38 mg/L

18.0 1,3,5-Cycloheptatriene
18.0.1 CAS Number: [*544-25-2*]

18.0.2 Synonyms: Cyclohepta-1,3,5-triene, tropilidene

18.0.3 Trade Names: NA

18.0.4 Molecular Weight: 92.14

18.0.5 Molecular Formula: C_7H_8

18.0.6 Molecular Structure:

18.1 Chemical and Physical Properties
18.1.1 General 1,3,5-Cycloheptatriene is a flammable liquid. Selected physical properties for this compound triene are given in Table 50.2.

18.1.2 Odor and Warning Properties Aromatic odor.
18.2 Production and Use
This compound is found as an environmental air pollutant and is used in chemical synthesis.
18.3 Exposure Assessment
18.3.1 Air See Section 18.3.4.

18.3.2 Background Levels See Section 18.3.4.

18.3.3 Workplace Methods See Section 18.3.4.

18.3.4 Community Methods 1,3,5-Cycloheptatriene is identifiable and quantifiable by gas

chromatography. Gas chromatographic retention properties are applied to the identification of environmental contaminants (171).

18.3.5 Biomonitoring/Biomarkers Information is unavailable; methods have been reported for the detection of other cycloalkenes and their metabolites.
18.4 Toxic Effects
18.4.1 Experimental Studies 18.4.1.1 Acute Toxicity The oral LD_{50} of 1,3,5-cycloheptatriene is 57 mg/kg in the rat and 171 mg/kg in the mouse. The dermal LD_{50} in the rat is 442 mg/kg (172).

18.4.1.2 Chronic and Subchronic Toxicity: NA

18.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms

18.4.1.4 Reproductive and Developmental: NA

18.4.1.5 Carcinogenesis: NA

18.4.1.6 Genetic and Related Cellular Effects Studies: NA

18.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization This compound is a severe dermal irritant but not a sensitizer. When applied to the guinea pig skin on three alternate days, it causes erythema, thickening, and increased weight of the epidermal layer and increased dermal arginase activity. All dermal effects were less remarkable than for the cyclooctadienes (54). The compound was immediately irritant to the rabbit eye, producing mild conjunctivitis, which cleared within 48 h. The eyelids became swollen and exuded a discharge. Blephanitis resolved somewhat more slowly than for cyclododecatriene 1 week after the application.
18.5 Standards, Regulations, or Guidelines of Exposure
Analytical procedures are available for quantifying a number of the cycloalkenes. Protective garments should be worn to prevent contact with the skin and eyes. Cycloheptatriene is on the EPA TSCA Test Submission Data Base (41).
19.0 Cyclododecatriene
19.0a 1,5,9-Cyclododecatriene
19.0.1a CAS Number: [*2765-29-9*]

19.0.2a Synonyms: 1,5,9-Cyclododecatriene (mixed isomers); *cis,trans,trans*-1,5,9-cyclododecatriene; (*E,Z,Z*)-1,5,9-cyclododecatriene

19.0.3a Trade Names: NA

19.0.4a Molecular Weight: 162.27

19.0.5a Molecular Formula: $C_{12}H_{18}$

19.0.6a Molecular Structure:

19.0b **trans**, **trans**, **trans**-1,5,9-Cyclododecatriene
19.0.1b CAS Number: [*676-22-2*]

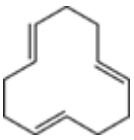
19.0.2b Synonyms: 1,5,9-Cyclododecatriene, (*E,E,E*)-

19.0.3b Trade Names: NA

19.0.4b Molecular Weight: 162.27

19.0.5b Molecular Formula: $C_{12}H_{18}$

19.0.6b Molecular Structure:



19.0.1 CAS Number: [*27070-59-3*]

19.0.2 Synonyms: 1,5,9-Cyclododecatriene, cyclododeca-1,5,9-triene

19.0.3 Trade Names: None known

19.0.4 Molecular Weight: 162.27

19.0.5 Molecular Formula: $C_{12}H_{18}$

19.1 Chemical and Physical Properties

19.1.1 General Cyclododeca-1,3,5-trienes are flammable, corrosive low-melting solids or liquids.

19.1.2 Odor and Warning Properties Oily aromatic odor.

19.2 Production and Use

These compounds are used in chemical synthesis.

19.3 Exposure Assessment

No information is available; methods used for other cycloalkenes are applicable.

19.4 Toxic Effects

19.4.1 Experimental Studies Application to guinea pig skin on 3 alternate days caused erythema, thickening, and increased weight of the epidermal layer and increased dermal arginase activity. All dermal effects were less remarkable than for the cyclooctadienes (54); however, cyclododecatriene is a more potent skin sensitizer (170). The compound is immediately irritant to the rabbit eye, producing mild conjunctivitis, which cleared within 48 h. The eyelids became swollen and exuded a discharge. Blephanitis resolved faster for cyclooctadiene, but was still apparent 1 week after application.

19.4.2 Human Experience 19.4.2.1 General Information: NA

19.4.2.2 Clinical Cases This compound was found to be an immediate irritant and corrosive agent toward the eyes and skin, and a skin sensitizer.

Alicyclic Hydrocarbons
C. Stuart Baxter, Ph.D.

E. Dicyclic Alkanes

20.0 Decalin
20.0a **cis**-Decalin
20.0.1a CAS Number: [*493-01-6*]

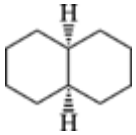
20.0.2a Synonyms: *cis*-Bicyclo[4.4.0]decane; *cis*-decahydronaphthalene

20.0.3a Trade Names: NA

20.0.4a Molecular Weight: 138.25

20.0.5a Molecular Formula: $C_{10}H_{18}$

20.0.6a Molecular Structure:



20.0b **trans**-Decalin
20.01b CAS Number: [*493-02-7*]

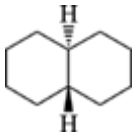
20.02b Synonyms: *trans*-Bicyclo[4.4.0]decane; *trans*-decahydronaphthalene; Decahydronapthalene-*trans*

20.03b Trade Names: NA

20.04b Molecular Weight: 138.25

20.05b Molecular Formula: $C_{10}H_{18}$

20.06b Molecular Structure:



20.0.1 CAS Number: [*91-17-8*]

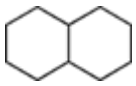
20.0.2 Synonyms: Bicyclo[4.4.0]decane, decahydronaphthalene, naphthalane, naphthane, perhydronaphthalene, Dec or DeKalin

20.0.3 Trade Names: NA

20.0.4 Molecular weight: 138.25

20.0.5 Molecular Formula: $C_{10}H_{18}$

20.0.6 Molecular Structure:



20.1 Chemical and Physical Properties
20.1.1 General Decalin is a flammable liquid. Selected physical properties are given in Table 50.2. On standing or storage, peroxides form that can cause explosions during distillation (4).

20.1.2 Odor and Warning Properties Slight odor resembling menthol.
20.2 Production and Use
Decalin occurs naturally in crude oil and is produced commercially by the catalytic hydrogenation of naphthalene. It is also a product of combustion and is released from natural fires (12). Of the dicyclic alkanes, decalin is the most important member industrially. It is widely used as a solvent for naphthalene, fats, oils, resins, and waxes, as an alternate for turpentine in lacquers, shoe polish, and floor waxes, as a component in motor fuels and lubricants, and as a fuel for stoves (4).
20.3 Exposure Assessment
20.3.1 Air: NA

20.3.2 Background Levels: NA

20.3.3 Workplace Methods: NA

20.3.4 Community Methods Decalin may be collected on charcoal, desorbed with carbon disulfide, and quantified by gas chromatography or mass spectroscopy.

20.3.5 Biomonitoring/Biomarkers Brownish green urine has been reported in workers exposed to a mixture of decalin and tetralin (68). Metabolites may be quantitated in the urine.
20.4 Toxic Effects
20.4.1 Experimental Studies 20.4.1.1 Acute Toxicity The oral LD_{50} is 4.17 g/kg in the rat, and the dermal LD_{50} is 5.9 g/kg in the rabbit. Exposure to the saturated vapor was lethal to rats in 2 h (180). The 4-h LC_{50} is 500 ppm for the rat and 993 ppm for the mouse (48). Exposure to 500 ppm for 4 h was lethal to four out of six rats (173).

20.4.1.2 Chronic and Subchronic Toxicity Of three guinea pigs exposed to 319 ppm (1.8 mg/L) for 8 h/day, one died on day 1, the second on day 21, and the third on day 23 (62). Gross and microscopic evaluation revealed lung congestion, kidney, and liver injury. Application to the skin of guinea pigs on 2 successive days resulted in death within 10 days of exposure. The systemic tissue injury was identical to injury from inhaled decalin (62).

20.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Both *cis*- and *trans*-decalin gave rise in the rabbit to racemic decanols (142, 174), which were excreted in the urine, conjugated with glucuronic acid. Guinea pigs dosed orally with decalin exhibited a brownish green urine, an occurrence also reported in workers exposed to a mixture of decalin and tetralin (62). This was not seen in inhalation or dermal studies.

20.4.1.4 Reproductive and Developmental Forty-eight pregnant CD-1 mice given 2700 mg/kg decalin daily in corn oil by gavage on days 6–13 of gestation and allowed to deliver experienced 14% maternal mortality associated with a significant increase in maternal weight gain. No effect in the offspring of treated mice for the parameters assayed was noted (175).

20.4.1.5 Carcinogenesis: NA

20.4.1.6 Genetic and Related Cellular Effects Studies: NA

20.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Decalin is irritating to the eyes, skin, and mucous membranes. Vapor exposures in guinea pigs and application of the liquid to rabbit eyes

caused cataracts (107).

20.4.2 Human Experience 20.4.2.1 General Information Systemic toxicity is not well defined, but no serious industrial poisonings are known (107).

20.4.2.2 Clinical Cases 20.4.2.2.1 Acute Toxicity Decalin induces dermatitis and conjunctival irritation.

20.4.2.2.2 Chronic and Subchronic Toxicity The lowest vapor concentration to affect humans was 100 ppm (10). Excessive exposure to high concentrations causes numbness, nausea, headache, and vomiting (149)

20.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms A brownish green urine was reported in workers exposed to a mixture of decalin and tetralin (68). This was not seen in inhalation or dermal studies.

20.4.2.2.4 Reproductive and Developmental: NA

20.4.2.2.5 Carcinogenesis: NA

20.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

20.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* Dermatitis without serious systemic poisoning has been reported in painters (68). When used as a cleaning agent, decalin has caused eczema, pruritis, and skin sensitization (93).
20.5 Standards, Regulations, or Guidelines of Exposure
Decalin is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (41).
20.6 Studies on Environmental Impact
Limited marine water and sediment grab sample data suggest that decalin will biodegrade in acclimated soils under the proper conditions. It is not expected to undergo hydrolysis or photolysis in soil, but to be slightly mobile to immobile. Volatilization from moist soils with a low organic matter content may be rapid. Limited data suggest biodegradation in acclimated aquatic systems under the proper conditions and little hydrolysis or photolysis in environmental waters. Decalin has the potential to bioconcentrate in aquatic systems, and may also partition from the water column to organic matter contained in sediments and suspended solids. Volatilization from environmental waters should be rapid. The volatilization half-life from a model river has been estimated to be 3.4 h. The volatilization half-life from a model pond, which considers the effect of adsorption, has been estimated to be about 28.1 days (48).

Decahydronaphthalene is expected to exist entirely in the vapor phase in ambient air. In the atmosphere, direct photolysis or hydrolysis is unlikely to occur. Reactions with photochemically produced hydroxyl radicals is likely to be an important fate processes in ambient air. An estimated rate constant at 25°C of $1.90 \times 10^{-11} cm^3 molecule^{-1} s^{-1}$ for the vapor-phase reaction with hydroxyl radicals corresponds to a half-life of 20.3 h at an atmospheric concentration of 5×10^5 hydroxyl radicals (48). The aquatic TLm96 was 10–100 ppm (60). Marine organisms can utilize decalin as their sole carbon source (176). *Pseudomonas fluorescens* and *Corynbacterium* degraded decalin more slowly than alkanes and alkenes (177).

Alicyclic Hydrocarbons
C. Stuart Baxter, Ph.D.

F. Dicyclic Alkenes
21.0 Tetralin
21.0.1 CAS Number: [*119-64-2*]

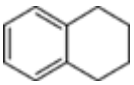
21.0.2 Synonyms: Naphthalene, 1,2,3,4-, tetrahydrobenzocyclohexane, naphthalene 1,2,3,4-tetrahydride, $d^{5,7,9}$-naphthantriene, tetrahydronaphthalene 1,2,3,4-, 1,2,3,4-tetrahydronaphthalin, tetraline, THN, bacticin

21.0.3 Trade Names: Tetranap

21.0.4 Molecular Weight: 132.20

21.0.5 Molecular Formula: $C_{10}H_{12}$

21.0.6 Molecular Structure:



21.1 Chemical and Physical Properties
21.1.1 General Tetralin or 1,2,3,4-tetrahydronaphthalene is a flammable liquid. Selected physical properties are given in Table 50.2.

21.1.2 Odor and Warning Properties These properties resemble those of benzene and menthol (4). Detection threshold 18 ppm in water; purity not specified (178).
21.2 Production and Use
Tetralin is prepared by the catalytic hydrogenation of naphthalene or during acidic, catalytic hydrocracking of phenanthrene (1). At 700°C, tetralin yields tars that contain appreciable quantities of 3,4-benzopyrene (179). Tetralin is used widely as a solvent for fats and oils, as an alternative to turpentine in polishes and paints (180), and as a pesticide (12).
21.3 Exposure Assessment
21.3.1 Air Tetralin is quantified by gas chromatography and mass spectrometry.

21.3.2 Background Levels In avian tissues pentane extraction followed by GLC and GLC-MS is used, and in fish samples by vacuum distillation and fused-silica capillary GC/MS (156).

21.3.3 Workplace Methods: NA

Alicyclic Hydrocarbons
C. Stuart Baxter, Ph.D.

G. Other Cyclic Olefins
25.0 Ethylidene Norbornene
25.0.1 CAS Number: [*16219-75-3*]

25.0.2 Synonyms: 5-Ethylidenebicyclo[2.2.1]hept-2-ene; bicyclo(2,2,1)hept-2-ene; 5-ethylidene-; ENB; 5-ethylidenebicyclo(2,2,1)hep-2-ene; 5-ethylidenebicyclo(2,2,1)hept-2-ene; ethylidenenorbornene, 2-norbornene, 5-ethylidene-; 5-ethylidene-2-norbornene; ethylidene-2-norbornene; 5-ethylidene-8,9,10-trinorborn-2-ene; 5-ethylidene-2-norbornene, mixture of endo and exo isomers, stabilized

25.0.3 Trade Names: NA

25.0.4 Molecular Weight: 120.19

25.0.5 Molecular Formula: C_9H_{12}

25.0.6 Molecular Structure:

25.1 Chemical and Physical Properties
25.1.1 General Colorless, mobile liquid.

25.1.2 Odor and Warning Properties Ethylidene norbornene has a pungent turpentine-like odor.
25.2 Production and Use
Ethylidene norbornene is the third monomer in EPDM (ethylene–propylene diene monomer) elastomers (13).
25.3 Exposure Assessment
Ethylene norbornene is quantitated by absorption in glacial acetic acid and determined by absorption at 536 nm (236). It can also be determined in air by absorption in toluene and subsequent chromatography of the solution on 60–80-mesh Chromosorb impregnated with 2,3-tris(cyanoethoxy) propane (237).
25.4 Toxic Effects
25.4.1 Experimental Studies 25.4.1.1 Acute Toxicity An oral LD_{50} of 3.2 g/kg was originally reported in rats (238). Slight toxicity by dermal route and moderate toxicity by oral route were reported in single-dose studies in rats, rabbits, mice, and dogs (238). On the basis of exposures of 7 h/day for 3 months in dogs, a TLV of 5 ppm for an 8-h workday has been suggested (239). In one study (240), peroral LD_{50} values of 2.54 and 5.66 mL/kg were reported for male and female rats, respectively. Percutaneous toxicity in the rabbit was low by 24 h occluded contact, with no mortalities below 8.0 mL/kg. Saturated vapor LT_{50} values in the rat were 75 (male) and 125 (female) min, and 4 h LC_{50} values were 2717 (male) and 3015 (female). Intravenously the LD_{50} ranged from 0.09 (male rabbit) to 0.11 ml/kg (female). The 4-h LD_{50} was 732 ppm for the female mouse and 3100 ppm for the male rabbit. Acute neurotoxic signs were seen by the intravenous and inhalation routes of exposure, including tremors, ataxia, and convulsions. Moderate skin irritation was observed with erythema and edema, but not necrosis, in rabbits. There was also slight conjunctival hyperemia and chemosis without corneal injury (240).

25.4.1.2 Chronic and Subchronic Toxicity Renal lesions occurred in rats at 90 or 237 ppm and at higher dose liver lesions. At concentrations of 61 or 93 ppm for 7 h/day for 89 days, hepatic lesions were observed in dogs. Inhalation of 61 ppm for 7 h daily for 88 days decreased weight gain in male, but not female, rats, whereas weght gains in dogs were not affected by 1.5 times this concentration (238). Repeated 7-h exposures to 237 ppm, days per week, were fatal to 21/24 rats. In a later study male and female rats were exposed for 6 h per day over an 11-day period to vapor concentrations of 52, 148, or 359 ppm, or 66–67 days over 4 weeks to 4.9, 44.8, and 149 ppm. Clinical signs were limited to periocular swelling and/or encrustation and urogenital area wetness. Body weight gain was decreased in the 359-ppm females and the subchronic 24.8- and 149-ppm males, and there was an increase in liver weight associated with minimal centrilobular hepatocytomegaly in the 9-day study. The principal effect noted was a hypertrophic and hyperplastic response of the follicular epithelium of the thyroid gland, for which there was a no-effect concentration of 4.9 ppm (241).

Necrosis was observed following application to rat skin. Inhalation of 0.11–0.43 mg/L by mice or rats 4 h/day for 7–12.5 weeks decreased the soporific effects of hexenal and caused morphological changes in heart, liver, and endocrine glands. Hormonal dysfunction of ovaries was observed in female rats (221).

25.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms: NA

25.4.1.4 Reproductive and Developmental: NA

25.4.1.5 Carcinogenesis: NA

25.4.1.6 Genitic and Related Cellular Effects Studies At doses of 0, 3, 10, 33, 100, and 333 mg/plate in four *Salmonella typhimurium* strains (TA98, TA100, TA1535, and TA1537) in the presence and absence of Aroclor-induced rat or hamster liver S9, no mutagenicity was observed. The highest ineffective dose level tested (without causing a slight clearing of the background lawn) in any *Salmonella* tester strain was 100 mg/plate (242). In a later study no activity was found again toward the *Salmonella strains*, nor in Chinese hamster ovary (CHO) cell HGPRT mutation, sister chromatid exchange (SCE), or cytogenetic assays, with or without metabolic activation (243).

25.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization At 90-ppm exposure of rats, kidney lesions were noted

25.4.2 Human Experience 25.4.2.1 General Information Human exposure data are very limited. Vapors are moderately irritating such that personnel seldom tolerate moderate or high concentrations. Odor threshold ranges between 0.007 and 0.014 ppm (244). No specific treatment is available.

25.4.2.2 Clinical Cases 25.4.2.2.1 Acute Toxicity Human volunteers noted some irritation of eyes and nose in 30-min exposures at 11 ppm, and transient eye irritation at 6 ppm (244). If swallowed, liquid will cause nausea and vomiting. Inhalation of vapors causes headache, confusion, and respiratory distress. Ingestion causes irritation of entire digestive system. Aspiration causes severe pneumonia. Contact with liquid causes irritation of eyes and skin. The vapor is irritating to the throat. If inhaled, it will cause coughing or difficult breathing. If spilled on clothing and allowed to remain, it may cause smarting and reddening of skin.

25.5 Standards, Regulations, or Guidelines of Exposure

Based on exposures of 7 h/day for 3 months in dogs, a exposure limit of 5 ppm for an 8-h workday was suggested (239). ACGIH and NIOSH have a ceiling value of 5 ppm as of 1983/84.

26.0 Vinylnorbornene

26.0.1 CAS Number: [*3048-64-4*]

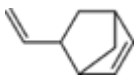
26.0.2 Synonyms: 5-ethenylbicyclo[2.2.1]hept-2-ene; vinylnorbornene; 5-vinylbicyclo[2.2.1]hept-2-ene; 5-vinyl-2-norbornene

26.0.3 Trade Names: NA

26.0.4 Molecular Weight: 120.19

26.0.5 Molecular Formula: C_9H_{12}

26.0.6 Molecular Structure:



26.1 Chemical and Physical Properties
26.1.1 General Vinylnorbornene is a colorless, mobile liquid.

26.1.2 Odor and Warning Properties Vinylnorbornene has an oily lachrymator-like odor.
26.2 Production and Use
Vinylnorbornene is the third monomer in EPDM (ethylene-propylene diene monomer) elastomers (13).
26.3 Exposure Assessment
Vinylnorbornene is quantitated by absorption in glacial acetic acid and determined by absorption at 536 nm (236). It can also be determined in air by absorption in toluene and subsequent chromatography of the solution on 60–80-mesh Chromosorb impregnated with 2,3-tris(cyanoethoxy) propane (237).
26.4 Toxic Effects
26.4.1 Experimental Studies 26.4.1.1 Acute Toxicity An oral LD_{50} of 5.9 mL/kg (male) and 11.9 mL/kg (female) was reported in rats (238). Percutaneous toxicity in the rabbit was low by 24 h occluded contact, with one mortality up to 16.0 mL/kg. Saturated vapor LT_{50} values in the rat were 28 (male) and 37 (female) min, and 4-h LC_{50} values were 2231 (male) and 2518 (female). Intravenously the LD_{50} ranged from 0.10 to 0.05. Acute neurotoxic signs were seen by the intravenous and inhalation routes of exposure, including tremors, ataxia, and convulsions. Moderate skin irritation was observed with erythema and edema, but not necrosis, in rabbits. There was also slight conjunctival hyperemia and chemosis without corneal injury (192). The inhalation mouse LC_{50} was 17700 mg/m^3 in 2 h; oral LD_{50} was 5667 mg/kg.

26.4.1.2 Chronic and Subchronic Toxicity: NA

26.4.1.3 Metabolism, and Mechanisms: NA

26.4.1.4 Reproductive and Developmental: NA

26.4.1.5 Carcinogenesis: NA

26.4.1.6 Carcinogenetic and Related Cellular Effects Studies No activity was found toward the Ames *Salmonella* strains, nor in CHO cell HGPRT mutation, SCE, or mouse bone marrow micronucleus assays, with or without metabolic activation (237).

26.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Necrosis was reported when applied to the skin of the mouse tail (221).
27.0 Camphene
27.0.1 CAS Number: [*79-92-5*]

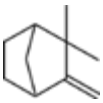
27.0.2 Synonyms: 3,3-Dimethyl-2-methylene norcamphone, bicyclo(2.2.1)heptane, 2,2-dimethyl-3-methylene-; 2,2-dimethyl-3-methylene-norbornane; 2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane; 2,2-dimethyl-3-methylenenorbornane; 3,3-dimethyl-2-methylenenorcamphane; (+/–)-camphene; camphene, remainder mainly a-fenchene

27.0.3 Trade Names: NA

27.0.4 Molecular Weight: 136.24

27.0.5 Molecular Formula: $C_{10}H_{16}$

27.0.6 Molecular Structure:



27.1 Chemical and Physical Properties
27.1.1 General Cubic crystals (4) form flammable vapors (7). Selected physical properties are given in Table 50.2.

27.1.2 Odor and Warning Properties Camphene has an insipid odor, with a camphoraceous taste.
27.2 Production and Use
Occurs naturally in the oils of several plants; can be prepared from a-pinene. Isolated as, and used in tablet form for mothproofing (245). Also used in the manufacture of camphor and in the cosmetic, perfume, and food flavoring industries (246).
27.3 Exposure Assessment
27.3.1 Air Camphene concentration is determined in ambient air by gas chromatographic method (247) and is analyzed by GC/MS (248).

27.3.5 Biomonitoring/Biomarkers Urinary conjugates of diol metabolites have been analyzed by gas chromatography or mass spectrometry following hydrolysis.
27.4 Toxic Effects
27.4.1 Experimental Studies 27.4.1.1 Acute Toxicity The oral LD_{50} value in the rat is >5 g/kg, and the dermal LD_{50} is >2.5 g/kg in the rabbit (190).

27.4.1.2 Chronic and Subchronic Toxicity: NA

27.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Camphene is metabolized in the rabbit to the glycol, conjugated, and excreted in the urine (249). Metabolites are analyzed by gas chromatography or mass spectrometry.

27.4.1.3.1 Adsorption Camphene is readily absorbed following inhalation, ingestion, or topical application.

27.4.1.3.2 Distribution: NA

27.4.1.3.3 Excretion In one study, 3.6% was eliminated unchanged in expired air within 3 h following dermal application or IV injection of 0.6 mg/kg body weight (0.05 mL in 2.5 mL of 1,2-propanediol) into a young pig. The major portion appeared within 5 minutes and 90% within 30 min.

27.4.1.3.4 Reproductive and Developmental: NA

27.4.1.3.5 Carcinogenesis: NA

27.4.1.3.6 Genetic and Related Cellular Effects Studies No mutagenic activity found toward Ames *Salmonella* tester strains in the presence or absence of S9 rat liver fraction (201).

27.4.2 Human Experience 27.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms In one study, 3.6% was eliminated unchanged in expired air within 3 h following dermal application or IV injection of 0.6 mg/kg body weight (0.05 mL in 2.5 mL 1,2-propanediol) into a human subject. The major portion appeared within 5 min and 90% within 30 min. The compound was absorbed through the skin and was also partially excreted in expired air, appearing within 20 min of the start of a 30-min full bath containing 150 mL pine bath oil in 450 L water, and was still detectable 1 day after the bath, although inhalation of volatiles from the bath was prevented. A maximal level was reached

after 75 min, with 60% exhaled within first 2 h and a total of 0.67 mL exhaled during the first 5 h. This study suggested a major route of elimination of unchanged compound in bile with excretion through intestinal tract, followed by glucuronide formation and excretion via the kidney (246).

27.4.2.2.4 Reproductive and Developmental: NA

27.4.2.2.5 Carcinogenesis: NA

27.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

27.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* Tests at 4% in petrolatum camphene produced no irritation after a 48-h closed-patch test on human subjects. Camphene was also found not to be a sensitizer for human skin (246).

27.5 Standards, Regulations, or Guidelines of Exposure

Limits in foods are nonalcoholic beverages, 40–90 ppm; ice cream, ices, and similar, 20 ppm; candy, 160 ppm; baked goods, 27 ppm. FDA requirement 121.1164 (250). Protective clothing including gloves and face shield are recommended when handling this agent (16). Camphene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (41)

27.6 Studies on Environmental Impact

The LC_{50} for sheepshead minnows is 1.9 ppm/96 h (95% confidence limit 1.6–2.2 ppm) (251).

Camphene is converted by *Aspergillus niger* into 2-nonene-2,3-dicarboxylic acid anhydride, with formation of diacetone alcohol as an artifact (246).

28.0 Caryophyllene

28.0.1 CAS Number: [*87-44-5*]

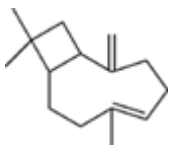
28.0.2 Synonyms: 4,11,11-Trimethyl methylenebicyclo[7.2.0]undec-4-ene; caryophylene; b-caryophyllene; tricyclo[8.2.0.0(4,6)]dodecane; 4,12,12-trimethyl-9-methylene-, (1*R*-(1*R**, 4*R**, 6*R**, 10*S**))-; tricyclo[8.20.0(4,6)]dodecane; 4,12,12-trimethyl-9-methylene-, (1*R*, 4*r*, 6*r*, 10*s*)-; humulene; b-caryophyllene; bicyclo[7.2.0]undec-4-ene; 4,11,11-trimethyl-8-methylene-, [1*R*-(1*R**, 4*E*, 9*S**)]-; bicyclo[7.2.0]undec-4-ene, 4,11,11,-trimethyl-8-methylene-, (*E*)-(1*R*, 9*S*)-(–)-; bicyclo [7.2.0]undec-4-ene, 8-methylene-4,11,11-trimethyl-, (*E*)-(1*R*, 9*S*)-(–)-; *trans*-caryophyllene; 1-caryophyllene; (–)-b-caryophyllene; (–)-caryophyllene; (–)-*trans*-caryophyllene; 8-methylene-4,11,11-(trimethyl)bicyclo[7.2.0]undec-4-ene; 2-methylene-6, 10,10-trimethyl bicyclo[7.2.0]undec-5-ene

28.0.3 Trade Names: NA

28.0.4 Molecular Weight: 204.35

28.0.5 Molecular Formula: $C_{15}H_{24}$

28.0.6 Molecular Structure:



28.1 Chemical and Physical Properties

Caryophyllene is a liquid with a boiling point of 129–130°C.

28.1.1 General Selected physical properties for a-caryophyllene are given in Table 50.2.

28.1.2 Odor and Warning Properties Fragrant cloves and turpentine odor are charactersitic.
28.2 Production and Use
This compound occurs naturally in many plants (4, 132) in the a, b, and iso forms (4). It is widely used in the perfume industry, and in the manufacture of its epoxide.
28.3 Exposure Assessment
Caryophyllene is quantifiable using thin-layer and gas chromatography.

28.3.1 Air: NA

28.3.2 Background Levels: NA

28.3.3 Workplace Methods: NA

28.3.4 Community Methods: NA

28.3.5 Biomonitoring/Biomarkers 14-Hydroxycaryophyllene oxide and other metabolites can be quantitated in the urine.
28.4 Toxic Effects
28.4.1 Experimental Studies 28.4.1.1 Acute Toxicity Caryophyllene is reported to be a skin irritant in the rabbit (41).

28.4.1.2 Chronic and Subchronic Toxicity: NA

28.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 14-Hydroxycaryophyllene oxide was isolated from the urine of rabbits treated with (–)-caryophyllene and the X-ray crystal structure reported. The metabolism was shown to progress through (–)-caryophyllene oxide since the latter compound also afforded 14-hydroxycaryophyllene as a metabolite (252).

Caryophyllene is expected to be readily absorbed and systemically distributed by inhalation or gastric or topical administration. It is excreted as 14-hydroxycaryophyllene oxide from the urine of rabbits treated with (–)-caryophyllene.

28.4.1.4 Reproductive and Developmental: NA

28.4.1.5 Carcinogenesis Caryophyllene showed significant activity as an inducer of the detoxifying enzyme glutathione *S*-transferase in the mouse liver and small intestine. The ability of natural anticarcinogens to induce detoxifying enzymes has been found to correlate with their activity in the inhibition of chemical carcinogenesis (251).
28.5 Standards, Regulations, or Guidelines of Exposure
Caryophyllene is on the EPA TSCA Chemical Inventory (48).

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Aromatic Hydrocarbons—Benzene and Other Alkylbenzenes

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A. Introduction

Benzene and its alkyl derivatives are monocyclic aromatic compounds (arenes). The compounds are of considerable economic importance as industrial raw materials, solvents, and components of innumerable commercial and consumer products. The aromatics differ vastly in chemical, physical, and biologic characteristics from the aliphatic and alicyclic hydrocarbons. The aromatics are more toxic to humans and other mammals; of prime importance are (*1*) the hematopoietic toxicity of benzene resulting in aplastic anemia in humans and other mammalian species, (*2*) benzene-induced leukemia in humans, and (*3*) the cerebellar lesions and loss of central nervous system (CNS) integrative functions in "glue sniffers" exposed to high levels of toluene.

The simplest single-ring aromatic hydrocarbon compound is benzene, the nonsubstituted ring system. When one methyl group is attached to the ring, toluene is formed, and with two attached methyl groups, xylene is formed. Xylene occurs in three isomeric forms. The hemimellitines and mesitylenes possess three methyl groups, durene four, and the penta- and hexamethylbenzenes, five and six methyl groups, respectively. Other industrially important compounds are ethylbenzene and isopropylbenzene or cumene.

1.0 Benzene and its Compounds in General

1.1 Physical and Chemical Properties

Benzene and its alkyl derivatives occur in liquid or vapor form. The lower molecular weight derivatives possess higher vapor pressures, volatility, absorbability, and solubility in aqueous media than do the comparable aliphatic or alicyclic compounds. Studies by Cometto-Muniz and Cain (1, 2) indicate that eye irritation thresholds were well above odor thresholds for a series of alkylbenzenes (toluene, ethylbenzene and propylbenzene) and that both sensory thresholds declined with carbon chain length. Selected physical data of benzene and its alkyl derivatives are given in Table 51.1 (3–23). These properties contribute to their biological activities. The compounds are characterized by miscibility or conversion to compounds soluble in aqueous body fluids, high lipid solubility, and donor–acceptor and polar interactions (24). Because of their low surface tension and viscosity, benzene and its alkyl derivatives may be aspirated into the lungs during ingestion, where they cause chemical pneumonitis.

Table 51.1. Physical Properties for Benzen

Compound	B P (° C)	CAS Registry No.	Density (at 20.4°C)	Empirical Formula	Flammability Limits[a] (%)	Flash point [°C (°F)]	Freezing point (° C)	MP (°C)	Mol W
Benzene	80.10	[*71-43-2*]	0.8787	C_6H_6	1.4–7.9	–11 (12)	5.53	5.5	78
Toluene	110.62	[*108-88-3*]	0.8869	C_7H_8	1.4–7.9	4.4 (40)	–94.99	95	92
o-Xylene	144.41	[*95-47-6*]	0.8802	C_8H_{11}	1.0–6.0	32 (90)		25.18	10
m-Xylene	139.10	[*108-38-3*]	0.8642	C_6H_{10}	1.1–7.0	29 (84)		47.87	10
p-Xylene	138.35	[*106-42-3*]	0.8611	C_8H_{11}	1.1–7.0	27 (81)		13.34	10
Xylenes, mixed Trimethylbenzene	138.3	[*1330-20-7*]	0.864	C_6H_{11}	1.0–7.0	37.6 (100)			10

1,2,3-	176.1	[*526-73-8*]	0.8944	C_9H_{12}	0.88[e]		–25.4	25.17	12
1,2,4-	169.35	[*96-63-6*]	0.8798	C_9H_{12}	0.88[e]	54.5 (130)	–42.2	43.8	12
1,3,5-	164.7	[*108-67-8*]	0.8652	C_9H_{12}	0.88 [e]			44.7	12
Tetramethylbenzene									
1,2,3,4-	205.0	[*488-23-3*]	0.9052	$C_{10}H_{14}$				–6.25	13
1,2,3,5-	198.0	[*527-53-7*]	0.8670	$C_{10}H_{14}$				–23.68	13
1,2,4,5-	196.0	[*95-93-2*]	0.8875	$C_{10}H_{14}$				79.24	13
Ethylbenzene	136.2	[*100-41-4*]	0.8670	C_9H_{10}	1.6–7	12.8 (55)		–94.97	10
Methylethylbenzene	161.3	[*620-24-4*]	0.8645	C_9H_{13}				–95.55	12
1,2-Diethylbenzene	183.4	[*135-01-3*]	0.8800	$C_{10}H_{14}$				–31.2	13
1,3-Diethylbenzene	181.0	[*141-93-5*]	0.8620	$C_{10}H_{14}$				–83.89	13
1,4-Diethylbenzene	183.8	[*105-05-5*]	0.8620	$C_{10}H_{15}$				–42.85	13
Diethylbenzene, mixed	183.8	[*25340-17-4*]	0.868	$C_{10}H_{14}$		55.6 (1.32)			13
n-Propylbenzene	159.2	[*103-65-1*]	0.8620	C_9H_{12}	0.8–6	30 (86)		–99.5	12
Cumene	152.4	[*98-82-8*]	0.8618	C_9H_{12}	0.9–6.5	36 (96)		–96	12
o-Cymene	178.15	[*527-84-4*]	0.8766	$C_{10}H_{14}$				–71.54	13
m-Cymene	175.14	[*535-77-3*]	0.8610	$C_{13}H_{12}$				–63.75	13
p-Cymene	177.1	[*99-87-6*]	0.8573	$C_{10}H_{14}$	0.7–5.6	47 (117) [d]		–67.94	13
n-Butylbenzene	183	[*104-51-8*]	0.8601	$C_{10}H_{14}$	0.8–5.8	71 (160)		–88.0	13
sec-Butylbenzene	173.0	[*135-98-8*]	0.8621	$C_{10}H_{14}$	0.8–6.9	52.2 (126)		–75	13
Isobutylbenzene	172.8	[*538-93-2*]	0.8532	$C_{10}H_{14}$	0.8–6.0	52.2 (126)		–51.5	13
tert-Butylbenzene	169	[*98-06-6*]	0.8655	$C_{10}H_{14}$	0.7–5.7[c]	60 (140)		–57.85	13
tert-Butyltoluene	192.8	[*98-51-1*]	0.8575	$C_{11}H_{14}$		68.3 (155)		–52.4	14
Dodecylbenzene	293-410	[*123-01-3*]	0.9	$C_{18}H_{30}$		140.6 (285)			24

[a] Lower limit (let) to upper.
[b] Solubility in water/alcohol/ether v = very soluble; s = soluble; d = slightly soluble; i = insoluble
[e] Open cup.
[d] Closed cup.
[c] –100°C.

1.2 Production and Use

Benzene and its alkyl derivatives are obtained as products or by-products in petroleum or coal refining, burning, or pyrolysis processes. From coke-oven operations, the aromatics are recovered from the gases and the coal tars. From crude oil distillation, they are produced by fractionated distillation, solvent extraction, naphthenic dehydrogenation, alkylation of benzene or alkenes, or from alkanes by catalytic cyclization or aromatization.

Benzene and its alkyl derivatives are used widely as chemical raw materials, intermediates, solvents, in oil and rosin extractions, as components of multipurpose additives, and extensively in the glue and veneer industries owing to their rapid drying characteristics. The compounds are also used in the dry-cleaning industry, in the printing and metal processing industries, and for many other similar applications. They can be found as constituents of aviation and automotive gasolines and represent important raw materials in the preparation of pharmaceutical products. The use of benzene as a solvent is decreasing because of its known leukemogenic properties (25, 26).

1.3 Exposure Assessment

Benzene and its alkyl derivatives are volatile enough to be monitored in air by adsorption on charcoal or resins, followed by desorption and analysis by gas chromatography. Methods for analysis in water and soil are also available. Benzene has been detected in cigarette smoke at concentrations of approximately 50 ppm (27, 28). Benzene and toluene have been detected in rainwater at concentrations of 0.1–0.5 mg/L, and ≤1.0 mg/L in the ambient air (29). Biomonitoring of exposures in occupational settings depends mainly on assessment of urinary metabolites.

1.4 Toxic Effects

Benzene is a known hematotoxin and leukemogen. The alkyl derivatives of benzene are not hematotoxic. The unique effects of benzene on bone marrow and blood-forming mechanisms are of major importance.

Benzene and its alkyl derivatives are primary skin irritants, and repeated or prolonged skin contact may cause dermatitis, dehydrating, and defatting of the skin. Eye contact with the liquids may cause lacrimation, irritation, and on prolonged contact, severe burns. Conjunctivitis and corneal burns have been reported for the C6–C8 members. The alkylbenzenes, with side chains C1–C4, are readily aspirated and can produce instant death, via cardiac arrest and respiratory paralysis. For example, in hexylbenzene exposure, death occurred in 18 min, during which time extensive pulmonary edema occurred (30), resulting in a considerable increase in lung weight. The higher alkylbenzenes showed few or no effects.

For the alkylbenzenes in general, the acute toxicity is greatest for toluene and decreases further with increasing chain length of the substituent, except for highly branched C8–C18 derivatives. The toxicity increases again for the vinyl derivatives. Pharmacologically, the alkylbenzenes are CNS depressants, and exhibit a particular affinity to nerve tissues.

1.4.1 Acute Toxicity The acute toxicities of benzene and its alkyl derivatives are CNS effects and irritancy. Benzene is more toxic than any of the substituted benzene derivatives, except for toluene and styrene. Benzene and alkylbenzenes cause local irritation and changes in endothelial cell permeability, and are absorbed rapidly. Secondary effects have been observed in the liver, kidney, spleen, bladder, thymus, brain, and spinal cord in animals (31). The aromatic hydrocarbons, even from a single dose, exhibit a special affinity to nerve tissue. Animals dosed with alkylbenzenes exhibit signs of CNS depression, sluggishness, stupor, anesthesia, and coma. A study of acute

behavioral effects of alkylbenzenes in mice (32) indicated that concentrations between 2000 and 8000 ppm for 20 min produced changes in posture, decreased arousal and rearing, increased ease of handling, disturbances of gait, mobility, and righting reflex, decreased forelimb grip strength, increased landing foot splay, and impaired psychomotor coordination. This is in sharp contrast with benzene, which is a neuroconvulsant, producing tremors and convulsions. The CNS depressant potency of the alkylbenzenes depends on branching or side-chain length. It diminishes with increasing numbers of substituents or side-chain carbon number up to dodecylbenzene, which has practically no CNS depressant activity (31).

1.4.2 Chronic Toxicity The hematotoxicity and leukemogenicity of benzene in humans have been established by a large body of epidemiological evidence (25, 26). Because of its affinity to blood-forming tissue and myelotoxic activity, chronic exposure to benzene is considered more serious than for all other alkylbenzenes. All substituted benzene derivatives tested are devoid of this myelotoxicity. This has been clearly demonstrated with toluene, which does not alter leukocyte count or bone marrow nucleation in the rat (31). In lifetime studies, benzene is carcinogenic in rodents (25, 26); benzene is a known human carcinogen (leukemogen) (25, 26).

1.4.3 Metabolism Benzene and its derivatives are readily hydroxylated, and their alkyl side chains are oxidized to carboxylic acids. Benzene may also be metabolized by ring opening. Benzene immediately increases the urinary excretion of organic sulfate. Of the alkylbenzenes, only m-xylene and mesitylene follow this trend. Metabolism is required for the expression of benzene toxicity (34).
1.5 Standards, Regulations or Guidelines of Exposure
From an industrial hygiene standpoint, benzene and its alkyl derivatives require close monitoring and evaluation, particularly benzene, toluene, xylene, ethylbenzene, cumene, and p-*tert*-butyltoluene. In the late 1990s, threshold limit values (TLVs) were lowered incrementally for some of the aromatic compounds. This was a consequence of the development of better sampling and analytic techniques and more extensive toxicity testing. Industrial monitoring programs should be continually evaluated. Where excursion values are found, biologic monitoring should be carried out in addition to regular medical surveillance programs.
1.6 Studies on Environmental Impact
Aromatic hydrocarbons appear to accumulate in marine animals to a greater extent and are retained longer than are alkanes (35). In all species tested, the accumulation of aromatic hydrocarbons depended primarily on the octanol/water partition coefficient. Once absorbed, higher molecular weight hydrocarbons are released more slowly (35). The concentration to produce deep CNS depression in barnacle larvae after immersion for 15 min was 3.1% for benzene and 4.5% for toluene (36). To some bacteria, as little as 0.01% of toluene, xylene, mesitylene, phenol, or cresol may be bacteristatic or bactericidal (37), whereas other microorganisms tolerate concentrations of ≤0.5% hydrocarbon. Benzene is the least susceptible to bacterial oxidation; increasing substitution and chain length, especially to even numbers, promotes the ease of oxidation (37).

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B. Specific Substances
2.0 Benzene
2.0.1 CAS Number: [*71-43-2*]

2.0.2 Synonyms: Phenyl hydride; coal naphtha; benzol; cyclohexatriene; benzine; benzolene; phene; (6)annulene; bicarburet of hydrogen; carbon oil; mineral naphtha; motor benzol; nitration benzene; pyrobenzol

2.0.3 Trade Name: NA

2.0.4 Molecular Weight: 78.113

2.0.5 Molecular Formula: C_6H_6

2.0.6 Molecular Structure:

2.1 Chemical and Physical Properties
Benzene, benzol, or phene is a clear, colorless liquid with a characteristic sweet odor at low concentrations, disagreeable and irritating at high levels. Selected physical data are summarized in Table 51.1. The odor threshold for benzene is 2.0 mg/L in water and is 1.5–4.5 ppm in air (38). The odor is irritating at 9000 ppm (39). The taste threshold is 0.5–4.5 mg/L in water (38). Its solubility in water is 1.78 g/L at 25°C. The octanol/water partition coefficient for benzene is 2.13–2.15, and the organic carbon partition coefficient is 1.8–1.9. Henry's law constant for benzene at 25°C is 5.5×10^{-3} atm·m^3/mol. Benzene forms a highly flammable (40) and explosive mixture with air at 1.4–8.0%. The autoignition temperature for benzene is 580°C. It is an excellent solvent. Chemically, it is fairly stable, but it readily undergoes substitution reactions to form halogen, nitrate sulfonate, and alkyl derivatives. Commercial benzene has three standard grades and usually contains varying concentrations of toluene, xylene, and phenol, and traces of carbon disulfide, thiophene, alkenes, naphthalene, and related compounds.

The photochemical formation of nitrobenzenes and nitrophenols from benzene has been observed in the presence of nitrogen oxides. Benzene also combines photochemically with halogens to produce eye and mucous membrane irritants (41). Ozone reacts 10–20 times more slowly with benzene than with toluene or other methyl-substituted derivatives (42).

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Polycyclic and Heterocyclic Aromatic Hydrocarbons
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Introduction to Class of Chemicals
Aromatic hydrocarbons are the class of chemicals that include multiring aromatic compounds. Smaller aromatic hydrocarbons, one to two rings, are of considerable economic importance as industrial raw materials, solvents, and components of innumerable commercial and consumer products. However, aromatics differ vastly in chemical, physical, and biological characteristics from the aliphatic and alicyclic hydrocarbons. In addition, aromatics are more toxic to humans and other mammals. Of prime importance are the carcinogenicity of styrene and the polycyclic aromatic hydrocarbons (1–11).

Chemically, aromatic hydrocarbons can be divided into three groups: (a) alkyl-, aryl-, and alicyclic-substituted benzene derivatives, (b) di- and polyphenyls, and (c) polycyclic compounds composed of two or more fused benzene ring systems. The basic chemical entity is the benzene nucleus, which occurs alone, substituted, joined, or fused.

Aromatics are moderately reactive and undergo photochemical degradation in the atmosphere. Aromatic compounds occur in liquid, vapor, or solid form. The lower molecular weight derivatives possess higher vapor pressures, volatility, absorbability, and solubility in aqueous media than the comparable aliphatic or alicyclic compounds. These properties contribute to their biological activities. They are characterized also by miscibility or conversion to compounds soluble in aqueous body fluids, high lipid solubility, and donor–acceptor and polar interaction. Because of their low surface tension and viscosity, aromatics may be aspirated into the lungs during ingestion, where they cause chemical pneumonitis.

Benzene and its alkyl derivatives, the polyphenyls, and polycyclic aromatics (PAHs) are obtained as products or by-products in petroleum or coal refining, burning, or pyrolysis. In coke-oven operations, the aromatics are recovered from the gases and the coal tars. In crude oil distillation, they are produced by fractionated distillation, solvent extraction, naphthenic dehydrogenation, alkylation of benzene or alkenes, or from alkanes by catalytic cyclization or aromatizations.

Aromatic hydrocarbons are used widely as chemical raw materials, intermediates, solvents, in oil and rosin extractions, as components of multipurpose additives, and extensively in the glue and veneer industries because of their rapid drying characteristics. Aromatics serve in the dry-cleaning industry, in the printing and metal processing industries, and for many other similar applications. They are important constituents of aviation and automotive gasolines and represent important raw materials in the preparation of pharmaceutical products.

Aromatics are primary skin irritants, and repeated or prolonged skin contact may cause dermatitis, dehydrating, and defatting of the skin. Eye contact with aromatic liquids may cause lacrimation, irritation, severe burns and from prolonged contact. Naphthalene causes cataracts in the eyes of experimental animals. Its vapors are respiratory and mucous membrane irritants and may cause severe systemic injury. Direct aerosol deposition or contact from ingestion and subsequent aspiration can cause severe pulmonary edema, pneumonitis, and hemorrhage (12, 13). Alkylbenzenes that have C_1 to C_4 side chains are readily aspirated and can produce instant death via cardiac arrest and respiratory paralysis.

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Phenol and Phenolics

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1.0 Phenol

1.0.1 CAS Number:

[*108-95-2*]

1.0.2 Synonyms:

Hydroxybenzene; carbolic acid; phenic acid; phenylic acid; phenyl hydroxide; Phenic; monohydroxy benzene; oxybenzene; benzenol; monophenol; phenyl hydrate; phenylic alcohol; phenyl hydroxide; baker's p and s; phenol alcohol; phenyl alcohol; phenol reagent

1.0.3 Trade Names:

Phenol

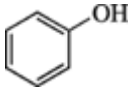
1.0.4 Molecular Weight:

94.11

1.0.5 Molecular Formula:

C_6H_6O

1.0.6 Molecular Structure:



1.1 Chemical and Physical Properties

Physical state	white crystalline mass of hygroscopic, translucent, needle-shaped crystals; pink or red when impurities are present; darkens on exposure to light.
Odor	Acrid odor, with threshold 0.04 ppm
Specific gravity	1.071
Melting point	43°C
Boiling point	182°C
Vapor density	3.24 (air = 1)
Vapor pressure	0.357 mmHg (20°C) 0.35 torr at 25°C
Refractive index	1.54 (45°C)
Concentration in "saturated" air	0.046% by volume (0.77g/m^3) (25°C)
Density of "saturated" air	1.00104 (air = 1)
Conversion	3.84 mg/m^3 = 1 ppm; 1 mg/m^3 = 0.26 mg/m^3
Flash point	Closed cup, 79°C; open cup, 85°C

Additional properties are as follows:

Flammability. Phenol presents a marked fire hazard. Phenol fires can be extinguished with water, carbon dioxide, or dry chemicals. Mixtures of air and 3–10% phenol are explosive (1).

Solubility. Phenol forms a true aqueous solution when present in concentrations of ≤8%, and also in concentrations ranging from about 71–97%, in terms of both weight and volume; it is miscible with water above 68°C. Phenol is soluble to >50% in ethyl alcohol, chloroform, ethyl ether, ethyl acetate, toluene, glycerol, and olive oil (2).

1.1.1 General: NA

1.1.2 Odor and Warning Properties Phenol has a distinct, aromatic, somewhat sickening sweet and acrid odor discernable at 0.5–5 ppm. It has a sharp and burning taste.

Phenol and Phenolics

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The authors thank Brendan Dunn of Allied Signal for his thorough review of the section on phenol.

Phenol and Phenolics
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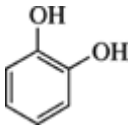
Larry E. Hammond, Ph.D., Marguerita L. Leng, Ph.D.

2.0 Pyrocatechol
2.0.1 CAS Number:
[*120-89-9*]
2.0.2 Synonyms:
Catechol; 1,2-benzenediol; *o*-dihydroxybenzene; pyrocatechin; 1,2-dihydroxybenzene; *o*-benzenediol; benzcatechin; Catechol–pyrocatechol; 1,2-dihydroxybenzene (Catechol)
2.0.3 Trade Names:
Catechol
2.0.4 Molecular Weight:
110.11
2.0.5 Molecular Formula:
$C_6H_6O_2$
2.0.6 Molecular Structure:



2.1 Chemical and Physical Properties
2.1.1 General

Physical state	Colorless to white crystalline solid that discolors in air and light; sublimes readily; volatile in steam
Specific gravity	1.344 (4°C)
Melting point	105°C
Boiling point	245.5°C (decomposes at 240 to 245°C)
Vapor density	3.79 (air = 1)
Solubility	Soluble in water, alcohol, ether
Flash point	137°C (closed cup)

2.1.2 Odor and Warning Properties There is a faint, characteristic odor.
2.2 Production and Use
Pyrocatechol may be obtained by the fusion of *o*-phenolsulfonic acid with alkali, by heating chorophenol with a solution of sodium hydroxide at 200°C in an autoclave, or by cleavage of the methyl ether group of guaiacol (obtained from beechwood tar) with hydroidic acid (107). Pyrocatechol is used for various purposes, but particularly as an antioxidant in the rubber, chemical, photographic, dye, fat, and oil industries. It is also employed in cosmetics as couplers in oxidative hair dyes (108, 109), but is no longer used as an antiseptic.
2.3 Exposure Assessment
2.3.1 Air: NA

2.3.2 Background Levels: NA

2.3.3 Workplace Methods: NA

2.3.4 Community Methods: NA

2.3.5 Biomonitoring/Biomarkers 2.3.5.1 Blood

2.3.5.2 Urine The methods of Baernstein or Tompsett can be used to determine pyrocatechol in urine and in other biologic materials (13). In another study, 24 h urine samples examined after 7–9 h of exposure to air polluted with pyrocatechol and phenol gave pyrocatechol levels of 24.2 mg, but control values of 19.2 mg, which were considered background (110). The 24-h urinary levels of pyrocatechol were 4.4 mg in nonsmokers, and 6.8 mg in smokers, indicating that diet is a major factor in determining pyrocatehcol intake (111).

2.4 Toxic Effects

2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity Pyrocatechol is moderately toxic in acute studies. Phenol-like signs of illness are induced in experimental animals given toxic or lethal doses. Unlike phenol, large doses of pyrocatechol can cause a predominant depression of the central nervous system (CNS) and a prolonged rise of blood pressure (13). Pyrocatechol is more toxic than phenol except by inhalation (111). The oral LD_{50} in rats is 0.3 g/kg. The dermal LD_{50} in rabbits is 0.8 g/kg. It is an irritant to eyes and skin, but less irritating to the skin than phenol. After 8h of inhalation at concentrations of 2 or 2.8 g/m^3 rats showed signs of intoxication (irritation and tremors) for ~24 h after exposure. At 1.5 g/m^3 no signs were observed (111). Flickinger (17) reported hyperemia of the stomach and intestines after lethal oral doses in rats, and loss of toes and tips of tails of rats after exposure to high concentrations (2 or 2.8 g/m^3) in a chamber. Dietering reported degenerative changes in the kidney tubules (13).

2.4.1.2 Chronic and Subchronic Toxicity The repeated absorption of sublethal doses by animals may also induce methemoglobinemia, leukopenia, and anemia.

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Pyrocatechol is readily absorbed from the GI tract and through the intact skin of mice, and probably through the lungs (13). Part of the catechol is oxidized with polyphenol oxidase to benzoquinone. Another fraction conjugates in the body with glucuronic, sulfuric, and other acids and is excreted in the urine, with a little “free” pyrocatechol. The conjugates hydrolyze easily in the urine with the liberation of the “free” catechol, which is oxidized by air with the formation of dark-colored substances that impart to the urine a “smokey” appearance (13).

Rabbits administered pyrocatechol orally excreted in the urine 18% as sulfate, 70% as monoglucuronide, and 2% as free pyrocatechol (112). When mice were exposed to cigarette smoke containing radiolabeled pyrocatechol, pyrocatechol was distributed readily into the blood and tissues; 90% of the radioactivity was excreted in the urine within 24 hrs (113).

2.4.1.4 Reproductive and Developmental Pyrocatechol was reported to be a moderately active maternal toxicant, and an active developmental toxicant in a preliminary screening assay (114). Sprague–Dawley rats were administered pyrocatechol at oral doses of 333, 667, or 1000 m g/kg on day 11 of gestation, and allowed to deliver normally. Both mid and high doses caused maternal lethality and weight gains. Litter size and weights were reduced at the maternally toxic doses. Malformations involving limbs, tail and urogenital systems were reported at all doses (114).

2.4.1.5 Carcinogenesis Pyrocatechol has been extensively studied for its role in carcinogenesis of the rat glandular stomach; it was concluded that pyrocatechol was carcinogenic (109). When rats and mice were administered 0.8% pyrocatechol in their feed for life, there was an increase in glandular stomach adenocarcinoma in both male and female rats. Pyrocatechol also caused hyperplasia of the glandular stomach in both rats and mice, a mechanism that could cause promotion of carcinogen-initiated cells (115); no effects on the esophagus or urinary bladder were reported. There were no cutaneous neoplasms when pyrocatechol was applied in dermal studies. Pyrocatechol may be classified as a cocarcinogen because it enhanced the number and/or incidence of lesions in the stomach induced by several carcinogenic nitrosamines, and cutaneous neoplasms when administered dermally together with several carcinogens (109).

2.4.1.6 Genetic and Related Cellular Effects Studies Pyrocatechol has been tested in a variety of bacterial and mammalian tests systems, and both positive and negative results were obtained (summarized in Ref. 109). For example, pyrocatechol was negative in the Ames assay, but induced SCEs (sister chromatid exchanges) in CHO (Chinese hamster ovary) V79 cells (116). In *in vivo* mouse micronucleus assays, in which the conjugation enzymes responsible for detoxication were present, both positive (117, 118) and negative results (119) were reported.

2.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Undiluted pyrocatechol was severely irritating to rabbit eyes, with permanent changes including corneal opacity (17). Pyrocatechol was a skin sensitizer in guinea pigs (120). In *in vitro* studies, pyrocatechol has been shown to affect several immunologic and other properties of murine bone marrow cells, both alone and when combined with hydroquinone (summarized in Ref. 108).

2.4.2 Human Experience 2.4.2.1 General Information: NA

2.4.2.2 Clinical Cases 2.4.2.2.1 Acute Toxicity Inhalation results in a burning sensation in the throat and lungs and, subsequently, a pronounced increase in the rate of breathing (13).

2.4.2.2.2 Chronic and Subchronic Toxicity Cases of industrial or accidental poisoning have been rare.

2.4.2.2.3 Pharmacokinics, Metabolism, and Mechanisms The calculated biological half-life of pyrocatechol in humans was 3–7h (110).

2.4.2.2.4 Reproductive and Developmental: NA

2.4.2.2.5 Carcinogenesis: NA

2.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

2.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* Contact with the skin has been known to cause an eczematous dermatitis. Absorption through the skin, in a few instances, has resulted in symptoms of illness resembling closely those induced by phenol, except for certain central effects (convulsions) that were more marked (13). Apparently pyrocatechol acts by mechanisms similar to those reported for phenol. The rise of blood pressure appears to be due to peripheral vasoconstriction. Death apparently is initiated by respiratory failure (13).

A woman developed acute contact dermatitis after using a permanent cream for eyelashes and eyebrows; when she was patch-tested, pyrocatechol evoked strong positive reactions (121). Another woman became allergic to pyrocatechol from her occupational exposure as a radiographer (122).

2.4.2.3 Epidemiology Studies 2.4.2.3.1 Acute Toxicity: NA

2.4.2.3.2 Chronic and Subchronic Toxicity: NA

2.4.2.3.3 Pharmacokinetics, Metabolism, and Mechanisms: NA

2.4.2.3.4 Reproductive and Developmental: NA

2.4.2.3.5 Carcinogenesis Between 35 and 45% of American women dye their hair, often at monthly intervals, over a period of years. A number of epidemiological studies have investigated the association between cancer and occupation as a hairdresser or barber, or personal use of hair dyes. IARC (123) concluded that there is inadequate evidence that personal use of hair colorants entails exposures that are carcinogenic. However, IARC concluded that “occupation as a hairdresser or barber entails exposures that are probably carcinogenic.”

2.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA for pyrocatechol is 5 ppm (23 m g/m^3) (124). The NIOSH REL is also 5 ppm (20 m g/m^3) (105). The "S" skin notation in the listing refers to the "potential significant contribution to the overall exposure by the cutaneous route, including mucous membrane and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance (124)".

2.6 Studies on Environmental Impact

The EC_{50} for *Pimephales promelas* (fathead minnow) was 9.00 mg/L for 96 h; the effect determined was loss of equilibrium. Similarly, the LC_{50} was reported to be 9.22 mg/L for 96 h (125).

Phenol and Phenolics

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3.0 Resorcinol

3.0.1 CAS Number:

[*108-46-3*]

3.0.2 Synonyms:

1,3-Benzenediol; *m*-dihydroxybenzene, resorcin, 1,3-dihydroxybenzene, 3-hydroxyphenol, CI 76505; *m*-hydroquinone

3.0.3 Trade Names:

Eskamel

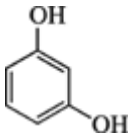
3.0.4 Molecular Weight:

110.11

3.0.5 Molecular Formula:

$C_6H_6O_2$

3.0.6 Molecular Structure:



3.1 Chemical and Physical Properties

White, needle-shaped crystals or rhombic tablets and pyramids, which turn pink on exposure to light and air. It is an acid with pK_a values of 9.51 and 11.32 in water at 30°C.

Specific gravity	1.2717
Melting point	109–111°C
Boiling point	280°C
Vapor density	3.79 (air = 1)
Percent in "saturated" air	2.64% by volume (25.1°C)
Density of "saturated" air	1.0739 (air = 1)
Solubility	Soluble in water, alcohol, glycerol, ether (1)

Flash point	127°C (closed cup)	127°C (closed cup)

3.1.1 General

3.1.2 Odor and Warning Properties Resorcinol has a faint, characteristic odor and a sweetish, followed by a bitter, taste.

3.2 Production and Use

Resorcinol is usually prepared by fusing sodium *m*-benzenedisulfonate with sodium hydroxide. The major use is in the production of resorcinol–formaldehyde adhesives used in tires, automobile belts and hoses, bonding wood products, and neoprene rubbers. It is also used in tanning, in photography, and in the manufacture of explosives, dyes, cosmetics, organic chemicals, antiseptics, resins, and adhesives (13). A minor use is as a bacteriocide in pharmaceuticals for the treatment of acne, psoriasis, eczema, seborrheic dermatitis etc. Resorcinol is used to remove warts, corns, and calluses. Resorcinol is most effective when delivered as an aerosol spray germicide (126).

3.3 Exposure Assessment

NIOSH (127) estimated that 100,000 workers are potentially exposed to resorcinol.

3.3.1 Air: NA

3.3.2 Background Levels: NA

3.3.3 Workplace Methods Air samples can be collected with impingers containing distilled water. If Millipore™ filters are used, about 50% may pass through the filter (17). Analysis can be performed with ultraviolet spectroscopy at 273.5 nm using a 10-cm cell.

3.3.4 Community Methods: NA

3.3.5 Biomonitoring/Biomarkers 3.3.5.1 Blood Detection of free resorcinol in plasma and urine requires the use of HPLC and a simple ethanol extraction. This method is useful to concentrations as low as 0.5%, at which it gives recoveries of greater than 90% with good reproducibility (13).

3.4 Toxic Effects

3.4.1 Experimental Studies 3.4.1.1 Acute Toxicity The primary signs of intoxication resemble those induced by phenol, and include initial stimulation of the CNS, followed by depression, renal glomerular and tubular degeneration, central hepatic necrosis, myocardial depression, pruitis and reddening of the skin. Resorcinol has been reported to be less toxic than phenol or pyrocatechol by oral and dermal routes.

The oral LD_{50} in rats is 0.98 g/kg, and the dermal LD_{50} in rabbits is 3.36 g/kg (17). It is irritating to the eyes and skin; eye irritation included corneal ulcerations that were not reversible. At high dermal doses, it causes irritation and necrosis in a dose-related response (17). Inhalation of aqueous aerosols by rats for 1h at 7.8 g/m^3 (1733 ppm) or 8 h at 2.8 g/m^3 (625 ppm) caused no deaths or gross lesions.

3.4.1.2 Chronic and Subchronic Toxicity Groups of 10 male and female F344 (Fischer 344) rats were given 0, 32, 65, 130, 260, or 520 m g/kg resorcinol by gavage 5 days/week for 13 weeks (126). Most animals at the top dose died. Daily doses of 65 m g/kg produced increased liver weights, but no other toxic effects were reported. When B6C3F1 mice were similarly treated, most mice at the high dose died, but only reduced adrenal weight was noted at other dose levels (126). In subacute inhalation studies rats, rabbits, and guinea pigs were exposed to 34 m g/m^3 (8 ppm) 6 h daily for 2 weeks without any gross toxic effects (17).

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Resorcinol was readily absorbed from the GI tract after oral administration to rats, rapidly metabolized and excreted in the urine (128). After an

oral dose of 122–225 m g/kg, >90% of the dose was excreted in the urine and 2% in the feces; 50% of the administered dose underwent enterohepatic circulation. The monoglucuronide conjugate accounted for 70% of the urinary metabolites, together with the monosulfate, diglucronide, and mixed sulfate/glucuronide. There was no evidence of bioaccumulation. Essentially identical results occurred after five pretreatment doses, indicating that conjugation was not saturated at these doses (128).

Similar results were obtained after subcutaneous (SC) administration of 50 or 100 m g/kg of resorcinol to rats (129). Resorcinol was distributed to all tissues but did not accumulate. After 1 h, 62% of the radiolabel appeared in the urine, and 98% within 24 h. Elimination was biphasic with half-lives of 20 min and 8–10hrs. Essentially the same results were obtained after a 30-day pretreatment of 100 m g/kg resorcinol (129).

3.4.1.4 Reproductive and Developmental Resorcinol is not a primary developmental toxicant. When pregnant rabbits were administered resorcinol orally at 40, 80, or 250 m g/kg per day on days 6–18 of gestation, there was no increase in embryonic or fetal deaths, or in congenital malformations (130). Oral administration to pregnant rats on days 6–15 of gestation at 125, 250, or 500 m g/kg per day caused maternal toxicity (reduced body weight) at the top dose, but there was no evidence of developmental toxicity. In a subsequent study rats were dosed with 80 m g/kg per day throughout gestation, producing overt maternal toxicity and some evidence of embryotoxicity; 40 m g/kg per day was a NOEL (130). In another study, daily doses of 125, 250 or 500 m g/kg were administered orally to Sprague–Dawley rats during days 6–15 of gestation (131). There was a slight reduction in maternal body weight gain at the top dose, but no effect on the number of litters, nor on the number of fetal anomalies or malformations.

3.4.1.5 Carcinogenesis Resorcinol was administered in water by gavage 5 days per week for 104 weeks to F344 rats and B6C3F1 mice at maximally tolerated doses; there was no evidence of carcinogenicity in any sex or species (126). Resorcinol at concentrations of 5, 10, or 50% in acetone was applied twice weekly to the ears of rabbits for 180 weeks; there were no local tumors or evidence of systemic toxicity (132).

Orally administered resorcinol did not induce proliferative lesions in hamster forestomach or bladder (133), and was not a promoter of carcinogenesis by other chemicals in these organs in rats (134). However, intraperitoneal (IP) injections of resorcinol did increase the incidence of esophageal tumors induced by a carcinogenic nitrosamine (135).

3.4.1.6 Genetic and Related Cellular Effects Studies Despite positive genotoxic findings in some *in vitro* genotoxicity assays, no positive findings have been reported in any *in vivo* studies in which the conjugation pathways are active (see see Table 53.2) (136–146).

Table 53.2. Genotoxicity of Resorcinol

Test System	Results	Ref.
In vitro Assays		
Salmonella typhimurium bacterial mutagenicity	Negative	14–19, 47, 60, 136–139
Drosophila melanogaster sex-linked recessive lethal	Negative	75
Mouse lymphoma mammalian mutagenicity	Positive	140
Chinese hamster ovary chromosomal	Positive	141

aberrations		
Human lymphocytes chromosomal aberrations	Positive	142
In vivo Assays		
Mouse bone marrow micronucleus	Negative	75, 143
Inhibition of rat DNA synthesis in rat testicular cells	Negative	144
Rat bone marrow micronucleus	Negative	145
Rat bone marrow sister chromatid exchange	Negative	146

3.4.2 Human Experience 3.4.2.1 General Information Few reports of the toxicity of resorcinol have been published. Oral ingestion in humans may cause methemoglobinemia, cyanosis, and convulsions, whereas dermal exposure has been reported to cause dermatitis, hyperemia, and pruritis (13). Industrial inhalation exposures are rather rare, but could occur in any industry if the compound is heated beyond 300°F.

3.4.2.2 Clinical Cases 3.4.2.2.1 Acute Toxicity Pathology reported for humans includes anemia, marked siderosis of the spleen and marked tubular injury in the kidney, fatty changes of the liver, degenerative changes in the kidney, fatty changes of the heart muscle, moderate enlargement and pigmentation of the spleen, and edema and emphysema of the lungs (13).

The cutaneous application of solutions or salves containing 3–5% resorcinol may result in local hyperemia, itching, dermatitis, edema, corrosion, and the loss of the superficial layers of the skin. The allergic/sensitization reactions also include eczematous reactions, erythema, edema, and the formation of vesicles. Burning sensations may also be noted (13). These changes, if they are severe, may be associated with some or all of the following effects: enlargement of regional lymph glands, restlessness, methemoglobinemia, cyanosis, convulsions, tachycardia, dyspnea, and death (13). Ingestion of resorcinol induces similar signs and symptoms. Thus a child, after accidentally swallowing 4 g, complained of dizziness and somnolence. The ingestion of 8 g, in another case, induced an almost immediate hypothermia, fall in blood pressure, and decrease in the rate of respiration, with tremors, icterus, and hemoglobinuria. Recovery was noted 2 h after the poisoning (13). Other cases are on record in which similar doses apparently had no ill effects (13).

3.4.2.2.2 Chronic and Subchronic Toxicity: NA

3.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Resorcinol is believed to be readily absorbed from the GI tract and, in a suitable solvent, is readily absorbed through the human skin. The compound is excreted in the urine, as are other phenols, in a free state and conjugated with glucuronic, sulfuric, or other acids (13).

3.4.2.3 Epidemiology Studies 3.4.2.3.1 Acute Toxicity In a study of 268 workers in a motorcycle tire manufacturing plant, the presence of dermatitis was directly correlated with exposure to the processes involving resorcinol use (147).

3.4.2.3.2 Chronic and Subchronic Toxicity Resorcinol in certain resins was reported to cause respiratory problems in the rubber industry (13). An epidemiologic study of rubber workers exposed to a hexamethylenetetramine–resorcinol rubber system revealed no specific symptoms caused by resorcinol. The concentrations of resorcinol in air were less than 0.3 m g/m^3 (148). In another study there were no reports of irritation or discomfort by workers when concentrations were 10 ppm or less for periods of 30 min (17).

3.4.2.3.3 Pharmacokinetics, Metabolism, and Mechanisms: NA

3.4.2.3.4 Reproduction and Developmental: NA

3.4.2.3.5 Carcinogenesis: NA

3.4.2.3.6 Genetic and Related Cellular Effects Studies: NA

3.4.2.3.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* Resorcinol has been reported to cause sensitization and cross-sensitization with other phenolic materials and to cause goiter (13).
3.5 Standards, Regulations, or Guidelines of Exposure
The TLV TWA is 10 ppm (45 m g/m^3). The STEL (short-term exposure limit) is 20 ppm (90 m g/m^3) (149). There is no proposed biological exposure index (BEI). NIOSH REL TWA 10 ppm (45 m g/m^3) STEL/CEIL(c) 20 ppm (90 m g/m^3).

Phenol and Phenolics
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4.0 Hydroquinone
4.0.1 CAS Number:
[*123-31-9*]
4.0.2 Synonyms:
1,4-Benzenediol, benzohydroquinone, 1,4-dihydroxy benzene, hydroquinol, a-hydroquinone, *p*-hydroxyphenol, b-quinol, *p*-benzenediol, benzoquinol, *p*-dihydroxybenzene, hydroquinole, *p*-hydroquinone, quinol
4.0.3 Trade Names:
The only trade name identified for hydroquinone was Tecquinol. This trade name is no longer used.
4.0.4 Molecular Weight:
110.11
4.0.5 Molecular Formula:
$C_6H_6O_2$
4.0.6 Molecular Structure:

Phenol and Phenolics

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5.0 Quinone
5.0.1 CAS Number:
[*106-51-4*]
5.0.2 Synonyms:
Benzoquinone, *p*-benzoquinone, 1,4-benzoquinone, 2,5-cyclohexadiene-1,4-dione, 1,4-dioxybenzene, 1,4-dione, quinone, cyclohexadienedione, 1,4-cyclohexadienedione, cyclohexadiene-1,4-dione
5.0.3 Trade Names:
Chinone, Steara PBQ
5.0.4 Molecular Weight:
108.10
5.0.5 Molecular Formula:
$C_6H_4O_2$
5.0.6 Molecular Structure:

5.1 Chemical and Physical Properties

Physical state	Large, yellow, monoclinic prisms
Specific gravity	1.318 (20°C)
Melting point	115.7°C
Boiling point	293°C
Vapor pressure	Considerable; sublimes readily on gentle heating
Flash point	38°C
Solubility	Soluble in alcohol and ether.
Solubility in water	2.5% at 38°C, 1.4% at 25°C, 1% at 12°C

5.1.1 General Quinone can decompose violently at elevated temperatures and has combustible vapors.

5.1.2 Odor and Warning Properties Quinone has an acrid odor similar to that of chlorine. The vapors are irritating enough to cause sneezing.
5.2 Production and Use
Quinone was produced as early as 1838 by oxidation of quinic acid with manganese dioxide (302). Quinone can be prepared by oxidation starting with aniline or by the oxidation of hydroquinone with bromic acid. More recently quinone has been made biosynthetically from D-glucose (302). The compound has been used in applications in the dye, textile, tanning, and cosmetic industries primarily because of its ability to transform certain nitrogen-containing compounds into a variety of colored substances. In the past, large amounts of quinone were produced as an intermediary for hydroquinone production. Newer production methods eliminate the need for quinone.

5.3 Exposure Assessment
Methods of controlling exposure during manufacture are largely a matter of reducing release by using containment systems and adequate ventilation. Severe local damage to the skin and mucous membranes may occur following contact with solid quinone, solutions of quinone, or quinone vapors condensing on exposed parts of the body (particularly moist surfaces) (303). Thus, skin contact is to be avoided and contaminated clothing should be removed immediately. Personal protection (full-face mask, air-supplied respirator) may be necessary in operations where other controls are not feasible (303). Quinone may be present in areas in which hydroquinone is used, as hydroquinone can be oxidized to quinone under moist or alkaline conditions.

5.3.1 Air Airborne quinone levels in a hydroquinone manufacturing operation have been reported to have declined from a high of 0.27 ppm to 1995 levels, which were <0.05 ppm (280).

5.3.2 Background Levels Quinone occurs naturally in a variety of arthropods that appear to use its irritating properties as a defense mechanism. Quinone containing *Tribolium* (order Coleoptera) beetles may result in contamination of food products, particularly flour (304, 305). Quinone is one of many constituents of tobacco smoke.

Quinone is chemically and photolytically extremely labile, and is assumed to be short-lived in the environment (306). A number of surveys and studies have failed to detect quinone in surfaces waters in the United States (301, 307, 308).

5.3.3 Workplace Methods See section 5.3.4.

5.3.4 Community Methods Air samples can be collected in a midget impinger containing isopropranol. A colored reaction product can be produced with phloroglucinol and read at 520nm (270). This method does not distinguish between quinone and hydroquinone.

5.3.5 Biomonitoring/Biomarkers Quinone forms adducts with cysteine residues of proteins such as hemoglobin and albumin. Background levels of these adducts in blood from people without occupational exposure to quinone are relatively high at >20 nm adducts/g protein (309). Quinone precursors from dietary and endogenous sources are proposed to explain high background levels. Quinone is a metabolite of benzene, phenol, hydroquinone, and acetaminophen; therefore, hemoglobin and albumin adducts do not represent biomarkers specific to quinone. Because of the high level of background adducts in blood, hemoglobin and albumin adducts are not likely to be useful biomarkers for occupational exposure to quinone.

Quinone and hydroquinone are closely related metabolically as quinone can be readily converted enzymatically and nonenzymatically to hydroquinone. Because of this close relationship, background levels of hydroquinone metabolites detected in the blood and urine of individuals without occupational exposure to either quinone or hydroquinone would include background levels of quinone (154).
5.4 Toxic Effects
5.4.1 Experimental Studies 5.4.1.1 Acute Toxicity Single dose oral LD_{50} values of 130 and 165 mg/kg have been reported for rats (4, 13, 14). Unlike hydroquinone, quinone does not produce tremors or convulsions, and death may be delayed for days after dosing (310, 311). Respiratory impairment was the primary effect observed as acute effects following quinone exposure (304). Parenteral exposure results in an LD_{50} value (IV LD_{50} – 25 mg/kg) that is significantly less than the oral LD_{50} (310, 311). No dermal toxicity studies were found in the literature. Woodard reported that quinone vapor was very irritating, causing coughing and sneezing (311). Solid quinone or relatively concentrated solutions are very irritating to the rabbit eye (312). Ocular sensory irritation is seen at a concentration of 0.0001% and acute conjunctivitis at 0.001%. A solution of 0.002% produced cloudiness of the cornea in 24 h and neovascularization in 4 days. The airborne concentration of

quinone that decreases the respiratory rate of mice by 50% (RD_{50}) is reported to be 22.5 m g/m^3 (313).

5.4.1.2 Chronic and Subchronic Toxicity Rats given 25 mg/kg quinone twice a week by SC injection for 2.5–5 months had anemia, methemoglobinemia, decreased serum albumin, and decreased serum cholinesterase (314).

Rats exposed to 2.7–3.6 m g/m^3 quinone 4 h/day for 4 months lost weight, showed easy tiredness, transient anemia, and thrombopenia (314). Two of eight rats exposed to 0.27–0.36 m g/m^3 quinone, 4 h/day for 4 months showed thrombopenia (314).

Mice given 2 mg/kg quinone IP, 6 days/week for 6 weeks manifested decreased red blood cells and lymphocytes, and increased polymorphonuclear leukocytes in their peripheral blood (184). Decreased bone marrow cellularity, decreased relative thymus weight, and increased relative spleen and lymph node weights were also observed in the quinone-dosed mice when compared to a control group.

The usefulness of these data is diminished by incomplete reporting of results. Parenteral administration of quinone is a confounding factor in interpreting these data as the hemogram can be expected to be altered in response to tissue inflammation and destruction caused by exposure to a highly irritating material.

5.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms There are no data available on the pharmacokinetics and metabolism of quinone using expected routes for occupational or environmental exposures. Much of the available mechanistic information has been collected using *in vitro* systems that attempt to model quinone interactions relevant to benzene toxicity.

Quinone vapor can be expected to be readily absorbed through the lungs, and quinone solutions should be readily absorbed from the GI tract. Absorption of solid quinone is likely to be slow because of its low water-solubility unless ingestion with an organic solvent occurs. Absorption of quinone through the skin can be expected; however, binding of quinone to epidermal proteins may reduce absorption when dilute solutions are encountered. Concentrated solutions of quinone may damage the barrier properties of the skin enhancing absorption.

Quinone can be expected to undergo transformations, including (*1*) enzymatic or nonenzymatic reduction and conjugation with glucuronide or sulfate resulting in detoxication and metabolites that are readily excreted in the urine; (*2*) covalent binding to proteins such as hemoglobin and albumin; (*3*) binding to glutathione, which may lead to detoxication or activation depending on the electrochemical state of the metabolite, and (*4*) one-electron reduction by reductases or diaphorases, which may produce a semiquinone and reactive oxygen species via redox cycling. Mean half-lives of 0.68 and 3.5 h have been reported following incubation of 50 mM quinone with fresh F344 rat or human blood at 37°C (309, 315). Hemoglobin and albumin have second-order rate constants of 18 and 76L mol^{-1} h^{-1} for human samples and 180 and 74L mol^{-1} h^{-1} for rat samples (309, 315).

Covalent binding of quinone to critical proteins is an expected mode of action *in vivo*. However, because of its reactive nature, it may not be possible to achieve a toxicologically significant internalized dose at systemic target sites when exposures occur via occupationally or environmentally relevant routes of exposure.

5.4.1.4 Reproductive and Developmental Studies Studies on reproductive and developmental effects for quinone have not been reported. However, these endpoints have been studied for hydroquinone, which is a precursor to quinone (228–230). On the basis of analogy with hydroquinone, quinone would not be expected to be a reproductive or developmental toxicant by common routes of occupational and environmental exposure. In an *in vitro* system, quinone was lethal to rat embryos at

100 mM and reportedly dysmorphogenic at 10 mM but not 50 mM (220).

5.4.1.5 Carcinogenesis Quinone has been tested for carcinogenicity in mice by skin application or inhalation and in rats by subcutaneous injection. None of these studies were considered sufficient to evaluate carcinogenicity (316, 317). A cancer bioassay of tribolium infested flour has been conducted but lack of quantification of quinone and methodological issues make the data difficult to interpret (305).

Quinone has produced negative results in studies designed to examine its ability to promote carcinogenicity. In a liver bioassay, quinone did not increase the formation of GGT-positive foci in the liver (241). Quinone did not promote induction of stomach or skin tumors in mice dosed with 7,12-dimethylbenzanthracene (318, 319).

5.4.1.6 Genetic and Related Cellular Effects Studies Genotoxicity assays with quinone have recently been reviewed by IARC (317). The results of several Ames/*Salmonella* assays were as a group inconclusive; however, mutations in *Neurospora* were increased. DNA strand breaks, mutations at the *hgprt* locus, and micronuclei were induced in mammalian cells *in vitro*. Weakly positive micronuclei responses were observed in mice dosed by gavage. A dominant lethal assay in mice given quinone IP was negative at a dose level of 6.25 mg/kg. These test results indicate that quinone is weakly positive for genotoxicity *in vivo*.

5.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Quinone produced an extreme skin sensitization response in the guinea pig maximization test (Magnusson–Kligman test) and positive response in the mouse local lymph node assay (261). Rajka and Blohm (256) found that quinone sensitized 19 of 20 guinea pigs given 10 daily injections of 0.001% quinone. Studies on cross sensitization with *p*-phenylenediamine are inconclusive (320, 321).

Numerous cytotoxicity tests have been conducted with quinone (314). Most of these studies have examined bone marrow cells in attempts to elucidate the mode of action of benzene, as quinone is one of the metabolites of benzene. These studies do not provide information that is readily applicable to common routes of quinone exposure.

5.4.2 Human Experience 5.4.2.1 General Information Skin contact with quinone can be expected to temporarily stain the skin a brownish color.

5.4.2.2 Clinical Cases 5.4.2.2.1 Acute Toxicity Reports of acute toxicity following exposure to quinone have not been published.

5.4.2.2.2 Chronic and Subchronic Toxicity Sterner et al. (270), Anderson (272), Anderson and Oglesby (275), and Oglesby et al. (271) reported that in a manufacturing process that produced hydroquinone by reduction of quinone, discoloration of the eyes and in some cases more serious ocular damages were seen among production workers. The changes occurred over a period of years, and no serious ocular cases were observed with less than 5 years of exposure.

Initially, there was brown staining of the conjunctiva. This pigment deposition in the conjunctiva did not impair vision; however, its presence was evidence of exposure, and its increase or decrease was used as an indication of the severity of exposure to hydroquinone dust and quinone vapor.

With continued eye exposure to high concentrations of hydroquinone and quinone, pigment deposition extended into the cornea, and structural alterations of the cornea occurred that impaired vision. One of the first complaints of individuals with corneal involvement was difficulty driving at night as light beams from oncoming automobiles were scattered and reflected by the corneal alterations.

The reports by Sterner et al. (270), Anderson (272), and Oglesby et al. (271) led to the establishment

of an ACGIH TLV of 0.1 ppm quinone vapor.

No evidence of systemic toxicity was seen in a group of hydroquinone production workers who were exposed to quinone vapor and hydroquinone dust (154, 280).

5.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Pharmacokinetics and metabolism studies with quinone have not been published.

5.4.2.2.4 Reproductive and Developmental Studies Case studies of reproductive or developmental toxicity following quinone exposure have not been reported.

5.4.2.2.5 Carcinogenesis Case studies of carcinogenicity following exposure to quinone have not been reported.

5.4.2.2.6 Genetic and Related Cellular Effects Studies Case studies of adverse genotoxic effects following exposure to quinone have not been reported.

5.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, etc Case studies of neurologic, pulmonary, sensitization or other adverse health effects following quinone exposure have not been reported.

5.4.2.3 Epidemiology Studies A cohort study of hydroquinone production workers who were also exposed to quinone reported significantly lower mortality due to a number of disease endpoints including cancer when compared to a general population control (279).

Pifer et al. (280) reported that a cohort of 879 men and women involved in manufacturing hydroquinone using a process that included production of quinone had significantly lower death rates for malignant and nonmalignant diseases when compared to general population and employed referent groups.

5.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV, OSHA PEL, NIOSH REL, and German MAK values for quinone are 0.1 ppm as an 8 h TWA. The NIOSH IDLH value was 100 mg/m^3.

5.6 Studies on Environmental Impact

In the past, large amounts of quinone were produced in the United States as an intermediary for hydroquinone production. Newer production methods eliminate the need for quinone. Therefore, releases of quinone from U.S. manufacturing sites to the environment have been decreasing steadily for several years according to Toxic Release Inventory (TRI) reports. TRI reports for the year 1997 included no releases of quinone to air, water, or land (322). In countries such as China, and India, where the aniline oxidation method continues to be used to produce hydroquinone, releases of quinone to the environment may occur. Environmental surveys of industrial sites in the United States have failed to detect quinone in surface waters (301, 307, 308).

Because of its low water solubility and vapor pressure, quinone is likely to partition into the atmosphere, if released. As a result of photolysis and chemical lability, quinone is expected to be short-lived in the environment following release (306). Since chemical structures such as quinone are readily metabolized by microorganisms, biodegradation is expected to be rapid. Polymeric forms of quinone are known as humic acids, which are common constituents of soil.

Phenol and Phenolics

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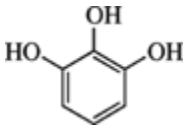
6.0 Pyrogallol
6.0.1 CAS Number:
[*87-66-1*]
6.0.2 Synonyms:
Pyrogallic acid; pyro; 1,2,3-trihydroxybenzene; 1,2,3-benzenetriol; fouramine base ap; Benzenetriol
6.0.3 Trade Names:
CI 76515; CI Oxidation Base 32; Fouramine Brown AP; Fourrine 85; Fourrine PG; Piral
6.0.4 Molecular Weight:
126.11
6.0.5 Molecular Formula:
$C_6H_6O_3$
6.0.6 Molecular Structure:



6.1 Chemical and Physical Properties

Physical state	White, or nearly white needle or leaf-shaped crystals or crystalline powder
Specific gravity	1.453 (4°C)
Melting point	131–134°C
Boiling point	309°C (decomposes at 293°C)
Solubility	Soluble in water (1–2), alcohol (1–1.5), and ether (1–2) at 25°C

6.1.2 Odor and Warning Properties Pyrogallol is practically odorless.
6.2 Production and Use
Pyrogallol is prepared by heating dried gallic acid at about 200°C with the loss of carbon dioxide (13) or by the chlorination of cyclohexanol to tetrachlorocyclohexanone, followed by hydrolysis (323). Pyrogallol's commercial use is based primarily on the fact that it is easily oxidized in alkaline solutions (even by atmospheric oxygen), so that such solutions become potent reducing agents. It is used specifically as a developer in photography and for maintaining anaerobic conditions for bacterial growth. It is additionally used in dyeing operations, the oxidized products being dark blue, process engraving, and as a topical antibacterial agent (13).
6.3 Exposure Assessment
6.3.1 Air: NA

6.3.2 Background Levels: NA

6.3.3 Workplace Methods: NA

6.3.4 Community Methods: NA

6.3.5 Biomonitoring/Biomarkers 6.3.5.1 Blood: NA

6.3.5.2 Urine The content of pyrogallol in the urine can be determined by various methods (324).
6.4 Toxic Effects

6.4.1 Experimental Studies 6.4.1.1 Acute Toxicity The oral LD_{50} for technical synthetic pyrogallol (92%, as a 500 mg/kg aqueous solution) in Sprague–Dawley rats was 1270 (males) and 800 (females) mg/kg (summarized in Ref. 323). Clinical observations included cyanosis, reduced activity, reduced muscle tone, body tremors, ataxia, lacrimation, salivation, piloerection, coolness to touch, hunched posture, pale extremities, and general soiling. General observations on gross necropsy included cyanosis, dark and/or enlarged spleen, dark kidneys, brown or pale liver and lungs, distension of the stomach and bladder, and fluid in the intestines.

Because of its marked reducing action, pyrogallol has a tremendous affinity for the oxygen of the blood. There was extensive destruction and fragmentation of the erythrocytes. Death is initiated by respiratory failure. The urine of poisoned animals may contain casts, glucose, hemoglobin, methemoglobin, urobilin, and other compounds that cause discoloration (323).

The dermal LD_{50} in rats administered pyrogallol in aqueous solution for 24 h under occlusion exceeded 2100 mg/kg (323). Clinical observations in females included cyanosis and pale extremities; the treated skin and surrounding fur of all animals was stained brown.

6.4.1.2 Chronic and Subchronic Toxicity Repeated absorption of toxic but sublethal concentrations into the tissues of animals has been found to cause severe anemia, icterus, nephritis, and uremia. The approximate lethal dosages of pyrogallol in aqueous solution for various animals species, under varying conditions of administration, was reported to be (324) rabbit, 1.1 g/kg (orally); rabbit or guinea pig, 10 g/kg (SC); dog or cat, 0.35 g/kg (SC); and dog, 0.09 g/kg (IV). Pathological changes in animals caused by pyrogallol include edema and hyperemia of the lungs, and moderate fatty degeneration, round cell infiltration, and necrosis of the liver. The kidneys may show hyperemia, necrosis of the epithelium, granular pigmentation, and glomerular nephritis (13). Changes of the bone marrow and myeloid changes in the spleen were noted after chronic administration of this compound (13).

6.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Pyrogallol is readily absorbed from the GI tract and from parenteral sites of injection. Little is absorbed through the intact skin. The bulk of absorbed pyrogallol is readily conjugated with glucuronic, sulfuric, or other acids and excreted within 24 h via the kidneys (13). When rats were administered 100 mg/kg pyrogallol, both pyrogallol and 2-*O*-methylpyrogallol were recovered in the urine as hydrolyzable conjugates; there was no unconjugated pyrogallol. Traces of resorcinol were detected in the feces suggesting that pyrogallol could be reduced (325).

6.4.1.4 Reproductive and Developmental A multigeneration rat reproduction study was conducted with a hair dye containing 0.4% pyrogallol applied to the skin twice per week during mating, gestation, and lactation through weaning (323). There were no treatment-related effects on reproduction, and only mild skin reactions at the application site noted intermittently.

Pyrogallol in propylene glycol was administered to pregnant Sprague–Dawley rats during days 6–15 of gestation at doses of 100, 200, or 300 mg/kg. There were no maternal mortalities, but at the top dose there was a decrease in maternal body weight gain, smaller fetuses, and an increase in the number of fetal resorptions. The numbers of fetal implants and abnormalities were not affected (326).

6.4.1.5 Carcinogenesis Pyrogallol was not carcinogenic in mouse and rabbit chronic dermal studies. Mice were treated twice weekly with pyrogallol in acetone (50%) on the shaved flank for life. There was no increase in dermal or systemic tumors (327). A similar study in rabbits also revealed no skin tumors, although positive controls showed an increase in tumors in both mice and rabbits (132).

Pyrogallol was considered to be cocarcinogenic when administered dermally three times a week together with the skin carcinogen benzo[a]pyrene for 440 days; pyrogallol administered alone caused

no increase in skin tumors (231).

6.4.1.6 Genetic and Related Cellular Effects Studies Pyrogallol was mutagenic in nearly all systems (323). Most of the assays were performed *in vitro*, but pyrogallol was also positive in *in vivo* assays. There was an increase in sex-linked recessive lethal mutations in *Drosophila melanogaster*, in mouse micronuclei (75), and in chromatid breaks in bone marrow cells of mice injected intraperitoneally with pyrogallol (323).

6.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Powdered pyrogallol was an ocular irritant, but not when tested at a concentration of 1% in propylene glycol (323). Powdered pyrogallol was slightly irritating when tested under dermal occlusion for 24 h in rabbits, and a 50% aqueous solution was slightly irritating in guinea pigs (323). Pyrogallol was reported to be a skin sensitizer when tested in guinea pigs by one unconventional procedure, but was negative in a second study using intradermal and dermal induction, and topical challenge applications (323).

6.4.2 Human Experience 6.4.2.1 General Information: NA

6.4.2.2 Clinical Cases 6.4.2.2.1 Acute Toxicity Cases of human poisoning have not been frequent. Cases reported in the older literature include one man who ingested an aqueous solution containing 8g of pyrogallol and who recovered after suffering an acute intoxication; another, who ingested 15 g of this compound, died despite prompt vomiting (13). Signs of acute intoxication include vomiting, hypothermia, fine tremors, muscular incoordination, diarrhea, loss of reflexes, coma, and asphyxia (13). When applied to the human skin in the form of a salve, it can cause local discoloration, irritation, eczema, and even death. Repeated contact with the skin has been reported to cause sensitization (13). The symptoms observed in acute intoxications in humans resemble closely the signs of illness displayed by experimental animals.

6.4.2.2.2 Chronic and subchronic Toxicity: NA

6.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Pyrogallol detected in human urine presumably results from intestinal bacterial decarboxylation of gallic acid, an ingredient in tea (324).

6.4.2.2.4 Reproductive and Developmental: NA

6.4.2.2.5 Carcinognesis: NA

6.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

6.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* Positive skin sensitization reactions to pyrogallol were reported in 25 patch-tested patients with leg ulcers (328). In contrast, there were no positive responses when 8230 patients with allergic contact dermatitis were patch tested with pyrogallol (1% in petrolatum) (329).

Phenol and Phenolics

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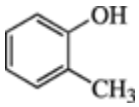
7.0 **o**-Cresol
7.0.1 CAS Number:

[*95-48-7*]
7.0.2 Synonyms:
2-Methylphenol; phenol, 2-methyl; 2-cresol; *o*-cresylic acid; 1-hydroxy-2-methylbenzene; 2-hydroxytoluene; *o*-hydroxytoluene; *o*-methylphenol; *o*-methylphenylol; *o*-oxytoluene; *o*-toluol
7.0.3 Trade Names:
NA
7.0.4 Molecular Weight:
108.14
7.0.5 Molecular Formula:
C_7H_8O
7.0.6 Molecular Structure:



7.1 Chemical and Physical Properties

Physical state	colorless, yellowish, or pinkish crystals, darkens with age and exposure to light and air (330, 331). *o*-Cresol can also appear as a liquid
Odor	Phenolic odor, with an odor threshold of 5 ppm; sometimes referred to as an *empyreumatic* odor
Specific gravity	1.030–1.038 (*o*-), (*m*-), (*p*-)
Melting point	11–35°C (mixture)/31°C (*o*-)/12°C (*m*-)/35°C (*p*-) (330, 332)
Boiling point	191–203°C (mixture)/191°C (*o*-)/202°C (*m*-)/202°C (*p*-) (330)
Vapor density	3.72 (air = 1) (332)
Vapor pressure	(25°C) 0.29torr (*o*-)/0.14torr (*m*-)/ 0.11torr (*p*-) at 25°C
Refractive index	1.537
Density of saturated air	1.00089 [air = 1]
Flash point	82°C (mixture)/81°C (*o*-)/86°C/*m*- *p*-) (all closed cup) (332)

Other characteristics are as follows:

Flammability. o-Cresol is combustible and presents a marked fire hazard. Fires can be extinguished with water, carbon dioxide, appropriate foam, or dry chemicals. Mixtures of air and 1.47% *o*-cresol are explosive (332).

Solubility. o-Cresol is soluble in organic solvents, vegetable oils, alcohol, ether, glycerin, chloroform, and dilute alkali; also in 40 parts water (330, 333).

7.1.1 General: NA

7.1.2 Odor and Warning Properties *o*-Cresol has a distinct phenolic odor discernible at 5 ppm. Taste has not been noted in the available literature.
7.2 Production and Use
The cresols (cresylic acids) are methyl phenols and generally appear as a mixture of isomers (330). *o*-Cresol is a 2-methyl derivative of phenol (335) and is prepared from *o*-toluic acid or obtained from coal tar or petroleum (333, 336). Crude cresol is obtained by distilling “gray phenic acid” at a temperature of ~180–201°C. *o*-Cresol may be separated from the crude or purified mixture by

repeated fractional distillation *in vacuo*. It can also be prepared synthetically by diazotization of the specific toluidine, or by fusion of the corresponding toluenesulfonic acid with sodium hydroxide.

o-Cresol is used as a disinfectant and solvent (330). Lysol™ disinfectant is a 50% v/v mixed-cresol isomer in a soap emsulion formed on mixing with water. Besides disinfection products at solutions of 1–5% (333), the cresols are used as degreasing compounds, paintbrush cleaners, and additives in lubricating oils (334). Cresols were previously widely used for disinfection of poultry houses, but this use was discontinued because of their toxicity; they cause respiratory problems and abdominal edema in young chicks (337). *o*-Cresol has been used in synthetic resins, explosives, petroleum, photographic, paint, and agricultural industries.

7.3 Exposure Assessment

With rare exceptions, human exposure in industry has been limited to accidental contact of *o*-cresol with the skin or inhalation of vapors (335).

7.3.1 Air: NA

7.3.2 Background Levels: NA

7.3.3 Workplace Methods Air sampling and analytical methods for personal monitoring are essentially the same manner as for phenol. Cresol is absorbed in dilute alkali and determined colorimetrically with diazotized *p*-nitroaniline reagent (339), absorbed in spectrograde alcohol with direct determination by ultraviolet spectrophotometry (340), or absorbed on silica and determined by gas–liquid chromatography (341). One sampling procedure consists of drawing a known volume of air through a silica gel tube consisting of two 20/40-mesh silica-gel sections, 150 and 75 mg, separated by a 2-mm portion of urethane foam. Acetone desorbed samples can be analyzed using gas chromatography with a flame ionization detector. The column is packed with 10% free fatty-acid polymer in 80/100 mesh, acid-washed DMCS Chromosorb W. The useful range of this method is 5–60 mg/m^3 (341).

7.3.4 Community Methods: NA

7.3.5 Biomonitorng/Biomarkers A sensitive method for the detection of cresol and metabolites in serum has been reported (342).

7.4 Toxic Effects

7.4.1 Experimental Studies 7.4.1.1 Acute Toxicity

Dermal. The dermal LD_{50} of *o*-cresol was 890 mg/kg in rabbits (18). Toxic symptoms are similar after oral and dermal routes.

Inhalation. No verifiable LC_{50} values have been reported, but rats survived a 1-h, exposure to 1220 mg/m^3 (340) and mice apparently survived a 2-h exposure [179 mg/m^3] to *o*-cresol (340).

Irritation and Sensitization. o-Cresol, undiluted and in solution, can cause severe local irritation and corrosion following dermal and ocular exposure. Irritant effects include severe skin lesions, edema, erythema, and necrosis. In a study using rabbits that were dosed with 524 mg *o*-cresol for 24 h under occlusion, severe skin effects were produced (340). Eye irritation can be severe and include corneal opacity.

7.4.1.2 Chronic and Subchronic Toxicity *o*-Cresol was tested for subchronic toxicity in animal studies of 28 and 90days' duration by dietary administration.

Ingestion by Diet In a 28-day study, F344/N rats and B6C3F$_1$ mice of both sexes (5/sex/group) were given *o*-cresol at concentrations of 300–30,000 ppm in the diet. All rats survived until study termination; some mice died at the 10,000- and 30,000-ppm dietary levels. Increased liver weights and kidney weights were noted in both species at doses as low as 3000 ppm. No microscopic

changes were associated with the organ weight changes. Bone marrow hyperplasia and atrophy of the uterus, ovary, and mammary gland were seen in the 10,000- and 30,000-ppm dietary groups (343).

In a 90-day study, F344/N rats (20/sex/dose) and $B6C3F_1$ mice (10/sex/dose) of both sexes received dietary administration of ≤30,000 ppm *o*-cresol (rats) and ≤20,000 ppm *o*-cresol (mice). No deaths in either species were related to administration of *o*-cresol. Hematology, clinical chemistry, and urinalysis were unremarkable; however, bile acid accumulation in the high dose rats was observed. Mild bone marrow hypocellularity in rats and forestomach hyperplasia in mice was revealed in animals with the higher doses (343).

7.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Cresol is absorbed through the skin, open wounds, and mucous membranes of the gastroenteric and respiratory tracts. The rate of absorption through the skin depends on the size of the area exposed rather than the concentration of the material applied (340). The metabolism and the rate of absorption, detoxification, and excretion of the cresols are much like those for phenol; they are oxidized and excreted as glucuronide and sulfate conjugates.

7.4.1.3.1 Absorption: NA

7.4.1.3.2 Distribution: NA

7.4.1.3.3 Excretion The major route of excretion of the cresols is in the urine. The *o*- and *m*- cresols are ring-hydroxylated to a small extent, whereas the *p*-cresol gives rise to the formation of some *p*-hydroxybenzoic acid. 2,5-Dihydroxytoluene has been isolated from the urine of rabbits fed *o*- and *m*-cresols, and *p*-hydroxybenzoic acid and *p*-cresylglucuronide from those administered *p*-cresol (340).

7.4.1.4 Reproductive and Developmental Although no reproductive or developmental toxicity studies were conducted on *o*-cresol, two subchronic assays did investigate the effect on the reproductive organs. In a 28-day subchronic study of *o*-cresol at doses of ≤30,000 ppm in the diet to both sexes of rats and mice, reproductive tissue evaluations showed no indication of adverse effects in the male reproductive system. The estrus cycle was, however, lengthened in rats and mice receiving 10,000 or 20,000 ppm *o*-cresol (343). In a 90-day study of *o*-cresol administered in the diet to rats and mice of both sexes, the reproductive organs were evaluated. Atrophy of the female reproductive organs was noted occasionally at 10,000 ppm, but more consistently at 30,000 ppm (343).

7.4.1.5 Carcinogenesis *o*-Cresol has been investigated for tumor promotion following induction by polycyclic aromatic hydrocarbons, but does not appear to be a tumorigen.

Skin Application Female Sutter mice (27–29/group) were dosed with a single application of dimethylbenzanthracene followed one week later by 25 mL of a 20% solution of *o*-cresol in benzene twice weekly for 12 weeks. Benzene-treated controls did not experience mortality, although many of the cresol mice died. *o*-Cresol produced 10/17 tumors (papillomas) on surviving mice (234). In another promotion study, mice were painted with a 20% solution of *o*-cresol for 11 weeks following initiation with dimethylbenzanthracene. No carcinomas were produced (344).

7.4.1.6 Genetic and Related Cellular Effects Studies In an unscheduled DNA synthesis assay, *o*-cresol was shown to be negative using rat hepatocytes (345). A cell transformation assay using BALB/3T3 cells showed *o*-cresol to be negative (346). *Salmonella* assays of various strains, both with and without liver homogenate, showed no mutagenic activity (59, 60, 347). In a mouse lymphoma forward mutation assay with liver homogenate, *o*-cresol was not mutagenic (345). Sister chromatid exchange (SCE) assays produced no evidence of mutagenicity in CHO (Chinese hamster ovary) cells (346). *o*-Cresol induced sister chromatid exchange in human lung fibroblasts (345, 348).

7.4.2 Human Experience 7.4.2.1 General Information Cresols can cause local and systemic toxicity in humans after exposure by oral or dermal exposure.

7.4.2.2 Clinical Cases Approximately 20 mL of a 90% solution of mixed cresol solution caused chemical burns, cyanosis, unconsciousness, and death within 4h when accidentally poured on an infant's head. Hepatic necrosis; cerebral edema; acute tubular necrosis of the kidneys; and hemorrhagic effusions from the peritoneum, pleura, and pericardium were observed postmortem. Blood cresol concentration was 120 mg/mL (349).

7.4.2.2.1 Acute Toxicity Oral lethality data from Lysol™ (which contains 50% mixed cresols) has been estimated to be between 60 and 120 mL (352). Ingestion is associated with corrosivity to body tissues and toxicity to the vascular system, liver, kidneys, and pancreas (344).

7.4.2.2.2 Chronic and Subchronic Toxicity Chronic cresol poisoning has been infrequently reported. About 10 subjects were exposed to *o*-cresol at 1.4 ppm and complained of respiratory tract irritation (350). Documentation was not confirmed. Seven workers who were exposed to mixed cresols vapor for 1.5–3 years experienced headaches, nausea, and vomiting. Some of those exposed also had elevated blood pressure, signs of impaired kidney function, blood calcium imbalance, and marked tremors (350).

7.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Cresols are normally present in human urine.
7.5 Standards, Regulations, or Guidelines of Exposure
The American Conference of Governmental Industrial Hygienists (ACGIH) TLV TWA for cresol is 5 ppm (22 mg/m^3) with a “skin” notation (351). The OSHA permissible exposure limit (PEL) is also 5 ppm (22 mg/m^3) with a skin notation (351). The “skin” notation in the listing refers to “the potential significant contribution to the overall exposure by the dermal route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance. The NIOSH REL TWA is 2.3 ppm (10 mg/m^3); the IDLH is 250 ppm.

Treatment of Cresol Ingestion Treatment should be supportive and symptomatic. There are no known antidotes (335).

Skin Decontamination Treatments after Accidental Exposure of Phenol Skin contact should be treated by washing with copious amounts of water, then bathing in glycerol, propylene glycol, or polyethylene glycol. Patients may require ventilatory support (335).

Phenol and Phenolics
Ralph Gingell, Ph.D., DABT, John O'Donoghue, Ph.D., DABT, Robert J. Staab, Ph.D., DABT, Ira W. Daly, Ph.D., DABT, Bruce K. Bernard, Ph.D., Anish Ranpuria, MS, E. John Wilkinson, Daniel Woltering, Ph.D., Phillip A. Johns, Ph.D., Stephen B. Montgomery, Ph.D., Larry E. Hammond, Ph.D., Marguerita L. Leng, Ph.D.

8.0 **m**-Cresol
8.0.1 CAS Number:
[*108-39-4*]
8.0.2 Synonyms:
3-Methylphenol; phenol, 3-methyl; 3-cresol; *m*-cresylic acid; 1-hydroxy-2-methylbenzene; 3-

hydroxytoluene; *m*-hydroxytoluene; *m*-methylphenol; *m*-methylphenylol; *m*-oxytoluene; *m*-toluol; *m*-cresylic; 3-methyl-1-hydroxybenzene; 1-hydroxy-3-methylbenzene; *m*-kresol; hydroxy-3-methylbenzene

8.0.3 Trade Names:

NA

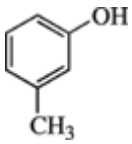
8.0.4 Molecular Weight:

108.14

8.0.5 Molecular Formula:

C_7H_8O

8.0.6 Molecular Structure:



8.1 Chemical and Physical Properties

Physical state	Colorless, yellowish, or pinkish liquid, darkens with age and exposure to light and air (330, 331)
Odor	Phenolic odor, with an odor threshold of 5 ppm; sometimes refered to as an *empyreumatic* odor
Specific gravity	1.030–1.038 (mixture)
Melting point	11–35°C (mixture)/31°C (*o*-)/12°C (*m*-)
Boiling point	191–203°C (mixture)/191°C (*o*-)/202°C (*m*-)
Vapor density	1.034 air = 1
Flash point	82°C (mixture)/81°C (*o*-)/86°C (*m*-, *p*-) (all closed cup)

Other properties are as follows:

Flammability. *m*-Cresol is combustible and presents a marked fire hazard. *m*-Cresol fires can be extinguished with water, carbon dioxide, appropriate foam, or dry chemicals. Mixtures of air and 1.47% *m*-cresol are explosive (332).

Solubility. *m*-Cresol is soluble in organic solvents, vegetable oils alcohol, ether, glycerin, chloroform, and dilute alkali; also in 40 parts water (330, 331).

8.1.1 General: NA

8.1.2 Odor and Warning Properties *m*-Cresol has a distinct phenolic odor discernable at 5 ppm.

8.2 Production and Use

The cresols (cresylic acids) are methyl phenols and generally appear as a mixture of isomers (334). *m*-Cresol is prepared from *m*-toluic acid or obtained from coal tar or petroleum (331, 335, 336). Crude cresol is obtained by distilling "gray phenic acid" at a temperature of ~180–201°C. The *m*-cresol may be separated from the crude or purified mixture by repeated fractional distillation *in vacuo*. It can also be prepared synthetically by diazotization of the specific toluidine, or by fusion of the corresponding toluenesulfonic acid with sodium hydroxide.

m-Cresol is used as a disinfectant and solvent (330). Lysol™ disinfectant is a 50% v/v mixed-cresol isomer in a soap emulsion formed on mixing with water. The isomer *m*-cresol is an oily liquid with

low volatility. Besides disinfection at solutions of 1–5% (331), the cresols are used in degreasing compounds, paintbrush cleaners, and additives in lubricating oils (334). Cresols were once widely used for disinfection of poultry houses but this use has been discontinued because they cause respiratory problems and abdominal edema in young chicks (337). *m*-Creosl has been used in synthetic resins, explosives, petroleum, photographic, paint, and agricultural industries.

8.3 Exposure Assessment

With rare exceptions, human exposure in industry has been limited to accidental contact of *m*-cresol with the skin or inhalation of vapors (335).

8.3.1 Air: NA

8.3.2 Background Levels: NA

8.3.3 Workplace Methods Air sampling and analytical methods for personal monitoring are essentially the same as for phenol. Cresol is absorbed in dilute alkali and determined colorimetrically with diazotized *p*-nitroaniline reagent (339), absorbed in spectrograde alcohol with direct determination by ultraviolet spectrophotometry, or absorbed on silica and determined by gas–liquid chromatography (340). One sampling procedure consists of drawing a known volume of air through a silica-gel tube consisting of two 20/40-mesh silica gel sections, 150 and 75 mg, separated by a 2-mm portion of urethane foam. Acetone-desorbed samples can be analyzed using gas chromatography with a flame ionization detector. The column is packed with 10% free fatty-acid polymer in 80/100-mesh, acid-washed DMCS Chromosorb W. The useful range of this method is 5–60 mg/m^3 (341).

8.3.4 Community Methods

8.3.5 Biomonitoring A sensitive method for the detection of cresol and metabolites in serum has been reported (342).

8.4 Toxic Effects

8.4.1 Experimental Studies 8.4.1.1 Acute Toxicity

Ingestion. Orally administered *m*-cresol is moderately to acutely toxic in animals. After oral administration to rats, the LD_{50} value was determined to be 2.02 g/kg body weight (340). It is considered to have about the same general degree of toxicity as phenol, but to be slightly less corrosive than phenol with slower absorption, which accounts for slightly milder systemic effects. *m*-Cresol is somewhat less toxic and less irritating than phenol (340). Corrosion to the GI tract and mouth is expected following cresol exposure with similar effects as phenol. Following oral administration, kidney tubule damage, nodular pneumonia, and congestion of the liver with pallor and necrosis of the hepatic cells is seen. Acute exposure can cause muscular weakness, GI disturbances, severe depression, collapse, and death.

Dermal. The dermal LD_{50} in rabbits of *m*-cresol was 2050 mg/kg (340). Toxic symptoms are similar after oral and dermal routes.

Inhalation. No verifiable LC_{50} values have been reported, but rats survived 1 h exposure to 710 mg/m^3 (340).

Irritation and Sensitization. m-Cresol, undiluted and in solution, can cause severe local irritation and corrosion following dermal and ocular exposure. Irritant effects include severe skin lesions, edema, erythema, and necrosis. In a study using rabbits that were dosed with 517 mg *m*-cresol for 24 h under occlusion, severe skin effects were produced (340). Eye irritation can be severe and include corneal opacity.

8.4.1.2 Chronic and Subchronic Toxicity *m*-Cresol was tested for subchronic toxicity in animal studies of 28 and 90 days duration by dietary administration.

Ingestion by Diet In a 28-day study, F344/N rats and B6C3F$_1$ mice of both sexes (5/sex/group) were given *m*-cresol at concentrations of from 300–30,000 ppm in the diet. All rats survived until study termination; some mice died at the 10,000 and 30,000 ppm dietary levels. Increased liver weights and kidney weights were noted in both species at doses as low as 3000 ppm. No microscopic changes were associated with the weight changes. Bone marrow hyperplasia and atrophy of the uterus, ovary, and mammary gland were seen occasionally in both the 10,000- and 30,000-ppm groups (343).

8.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Cresol is absorbed through the skin and open wounds and mucous membranes of the gastroenteric and respiratory tracts. The absorption rate through the skin depends on the size of the area exposed rather than the concentration of the material applied (340).

The metabolism and the rate of absorption, detoxification, and excretion of the cresol are much like those for phenol; they are oxidized and excreted as glucuronide and sulfate conjugates.

8.4.1.3.1 Absorption: NA

8.4.1.3.2 Distribution: NA

8.4.1.3.3 Excretion The major route of excretion of the cresols is in the urine. Both *o*- and *m*-cresols are ring-hydroxylated to a small extent, whereas *p*-cresol gives rise to the formation of some *p*-hydroxybenzioc acid. 2,5-Dihydroxytoluene has been isolated from the urine of rabbits fed *o*- and *m*-cresols, and *p*-hydroxybenzoic acid and *p*-cresylglucuronide from those administered *p*-cresol (340).

8.4.1.4 Reproductive and Developmental: NA

8.4.1.5 Carcinogenesis *m*-Cresol has induced a few papillomas but no carcinomas in tumor studies.

Skin Application Female Sutter mice (27–29/group) were dosed with a single application of dimethylbenzanthracene followed one week later by 25 mL of a 20% solution of *m*-cresol in benzene twice weekly for 12 weeks. Benzene-treated controls did not experience mortality, although many of the cresol-treated mice died. *m*-Cresol produced 7/17 tumors (papillomas) in surviving mice (234). In another promotion study, mice were painted with a 20% solution of *m*-cresol for 11 weeks following initiation with dimethylbenzanthracene; no carcinomas were produced (344).

8.4.1.6 Genetic and Related Cellular Effects studies *Salmonella* assays of various strains, both with and without liver homogenate, showed no mutagenic activity (57, 60, 345–348). Sister chromatid exchange assays produced no evidence of mutagenicity in CHO cells (346).

8.4.2 Human Experience 8.4.2.1 General Information Cresols can cause local and systemic toxicity in humans after exposure by oral or dermal routes.

8.4.2.2 Clinical Cases Approximately 20 mL of a 90% solution of mixed-cresol solution caused chemical burns, cyanosis, unconsciousness, and death within 4h when accidentally poured on an infant's head. Hepatic necrosis; cerebral edema; acute tubular necrosis of the kidneys; and hemorrhagic effusions from the peritoneum, pleura, and pericardium were observed postmortem. Blood cresol concentration was 120 mg/mL (349).

8.4.2.2.1 Acute Toxicity Oral lethality data from Lysol™, which is 50% mixed cresols, has been estimated to be between 60 and 120 mL (352). Ingestion is associated with corrosivity to body tissue and toxicity to the vascular system, liver, kidneys, and pancreas (344).

8.4.2.2.2 Chronic and Subchronic Toxicity Chronic cresol poisoning has been infrequently reported.

Seven workers who were exposed to mixed-cresol vapor for 1.5–3 years experienced headaches, nausea, and vomiting. Some of those exposed also had elevated blood pressure, signs of impaired kidney function, blood calcium imbalance, and marked tremors (344).

8.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Cresols are normally present in human urine.

8.4.2.2.4 Reproductive and Developmental: NA

8.4.2.2.5 Carcinogenesis: NA

8.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

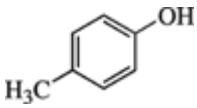
8.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* All isomers of cresol cause renal toxicity, hepatic toxicity, and CNS and cardiovascular disturbances (335).
8.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV TWA for cresol is 5 ppm (22 mg/m^3) with a "skin" notation (351). The OSHA PEL is also 5 ppm with a "skin" notation (350). The "skin" notation in the listing refers to "the potential significant contribution to the overall exposure by the dermal route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance." The NIOSH REL TWA is 2.3 ppm (10 mg/m^3); the IDLH value is 250 ppm.

Treatment of Cresol Ingestion Treatment should be supportive and symptomatic. There are no known antidotes (335).

Skin Decontamination Treatments after Accidental Exposure of Phenol Skin contact should be treated by washing with copious amounts of water, then bathing in glycerol, propylene glycol, or polyethylene glycol. Patients may require ventilatory support (335).

Phenol and Phenolics
Ralph Gingell, Ph.D., DABT, John O'Donoghue, Ph.D., DABT, Robert J. Staab, Ph.D., DABT, Ira W. Daly, Ph.D., DABT, Bruce K. Bernard, Ph.D., Anish Ranpuria, MS, E. John Wilkinson, Daniel Woltering, Ph.D., Phillip A. Johns, Ph.D., Stephen B. Montgomery, Ph.D., Larry E. Hammond, Ph.D., Marguerita L. Leng, Ph.D.

9.0 **p**-Cresol
9.0.1 CAS Number:
[*106-44-5*]
9.0.2 Synonyms:
4-Methylphenol; phenol, 4-methyl; 4-cresol; *p*-cresylic acid; 1-hydroxy-4-methylbenzene; 4-hydroxytoluene; *p*-hydroxytoluene; *p*-methylphenol; *p*-methylphenylol *p*-oxytoluene; *p*-toluol; 1-methyl-4-hydroxybenzene; *p*-methylhydroxybenzene; *p*-tolyl alcohol
9.0.3 Trade Names:
NA
9.0.4 Molecular Weight:
108.14
9.0.5 Molecular Formula:
C_7H_8O
9.0.6 Molecular Structure:



9.1 Chemical and Physical Properties

Physical state	Colorless, yellowish, or pinkish liquid, darkens with age and exposure to light and air (330, 331); *p*-cresol can also appear as a liquid
Odor	Phenolic odor, with an odor threshold of 5 ppm; sometimes refereed to as an *empyreumatic* odor
Specific gravity	1.034
Melting point	32–34°C
Boiling point	202°C (330)
Vapor density	3.7 (air = 1) (332)
Vapor pressure	0.11 torr (25°C)
Refractive index	1.537
Flash point	86°C (closed cup)

Other characteristics are as follows:

Flammability. *p*-Cresol is combustible and presents a marked fire hazard. Fires can be extinguished with water, carbon dioxide, appropriate foam, or dry chemicals. Mixtures of air and 1.47% *p*-cresol are explosive (332).

Solubility. *p*-Cresol is soluble in organic solvents, vegetable oils, alcohol, ether, glycerin, chloroform, and dilute alkali; also in 40 parts water (330, 333).

9.1.1 General: NA

9.1.2 Odor and Warning Properties *p*-Cresol has a distinct phenolic odor discernable at 5 ppm. Taste has not been noted in the available literature.

9.2 Production and Use

The cresols (cresylic acids) are methyl phenols and generally appear as a mixture of isomers (334). *p*-Cresol is a 4-methyl deriviative of phenol (335) and is prepared from *m*-toluic acid or obtained from coal tar or petroleum (333, 336). Crude cresol is obtained by distilling "gray phenic acid" at a temperature of ~180–201°C. *p*-Cresol may be separated from the crude or purified mixture by repeated fractional distillation *in vacuo*. It can also be prepared synthetically by diazotization of the specific toluene, or by fusion of the corresponding toluenesulfonic acid with sodium hydroxide.

p-Cresol is used as a disinfectant and solvent (330). Lysol™ disinfectant is a 50% v/v mixed-cresol isomer in a soap emulsion formed on mixing with water. Besides disinfection products at solutions of 1–5% (333), the cresols are used as degreasing compounds, paintbrush cleaners, and additives in lubricating oil (334). Cresols were previously widely used for disinfection of poultry houses, but this use was discontinued because they cause respiratory problems and abdominal edema in young chicks (337). *p*-Cresol has been used in synthetic resins, explosives, petroleum, paint, photographic and agricultural industries. *p*-Cresol is used safety in foods as a synthetic flavoring substance and adjuvant (338).

9.3 Exposure Assessment

With rare exceptions, human exposure in industry has been limited to accidental contact of *p*-cresol with the skin or to inhalation of vapors (335).

9.3.1 Air: NA

9.3.2 Background Levels: NA

9.3.3 Workplace Methods Air sampling and analytical methods for personal monitoring are essentially the same manner as for phenol. Cresol is absorbed in dilute alkali and determined colorimetrically with diazotized *p*-nitroaniline reagent (339), absorbed in spectrograde alcohol with direct determination by ultraviolet spectrophotometry, or absorbed on silica and deteremined by gas–liquid chromatography (340). One sampling procedure consists of drawing a known volume of air through a silica-gel tube consiting of two 20/40-mesh silica-gel sections, 150 and 75 mg, separated by a 2-mm portion of urethane foam. Acetone desorbed samples can be analyzed using a gas chromatography with a flame ionization detector. The column is packed with 10% free fatty-acid polymer in 80/100-mesh, acid washed DMCS Chromosorb W. The useful range of this method is 5 to 60 mg/m^3 (341).

9.3.4 Community Methods: NA

9.3.5 Biomonitoring/Biomarkers A sensitive method for the detection of cresol and metabolites in serum has been reported (342).

9.4 Toxic Effects

9.4.1 Experimental Studies 9.4.1.1 Acute Toxicity

Ingestion. Orally administered *p*-cresol is moderately acutely toxic in animals. After oral administration to rats, the LD_{50} value was 1.8 g/kg body weight (340). This is considered to have about the same degree of toxicity as phenol but to be slightly more corrosive than phenol with slower absorption, which accounts for slightly milder systemic effects (340). Corrosion of the GI tract and mouth is expected following oral cresol exposure similar to phenol. Following oral administration, kidney tubule damage, nodular pneumonia, and congestion of the liver with pallor and necrosis of the hepatic cells is seen. Acute exposure can cause muscular weakness, GI disturbances, severe depression, collapse, and death.

Dermal. The dermal LD_{50} in rats was 750 mg/kg (340). Toxic symptoms are similar after oral and dermal routes.

Inhalation. No verifiable LC_{50} values have been reported, but rats survived 1 h exposure to 710 mg/m^3 (340).

Irritation and Sensitization. p-Cresol, undiluted and in solution, can cause severe local irritation and corrosion following dermal and ocular exposure. Irritant effects include severe skin lesions, edema, erythema, and necrosis. Eye irritation can include severe irritation with corneal opacity.

9.4.1.2 Chronic and Subchronic Toxicity *p*-Cresol has been tested for subchronic toxicity in animal studies of 28 days' duration by dietary administration.

Ingestion by Diet In a 28-day study, F344/N rats and $B6C3F_1$ mice of both sexes (5/sex/group) were given *p*-cresol at concentrations of 300–30,000 ppm in the diet. All rats survived until study termination; some mice died at the 10,000 and 30,000 ppm dietary levels. Increased liver weights and kidney weights were noted in both species at doses as low as 3000 ppm, but no microscopic changes were associated with the organ weight changes. Bone marrow hyperplasia, and atrophy of the uterus, ovary, and mammary gland were seen in the 10,000- and 30,000-ppm dietary groups (343).

9.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 9.4.1.3.1 Absorption Cresol is absorbed through the skin, open wounds, and mucous membranes of the GI and respiratory tracts. The rate of absorption through the skin depends on the size of the area exposed rather than the concentration of the material applied (340).

The metabolism and the rate of absorption, detoxification, and excretion of the cresols are much like those of phenol; they are oxidized and excreted as glucuronide and sulfate conjugates.

9.4.1.3.2 Distribution: NA

9.4.1.3.3 Excretion The major route of excretion of the cresols is in the urine. Both *o*- and *m*-cresols are ring-hydroxylated to a small extent, whereas *p*-cresol gives rise to the formation of some *p*-hydroxybenzoic acid. 2,5-Dihydroxytoluene has been isolated from the urine of rabbits fed *o*- and *m*-cresols, and *p*-hydroxybenzoic acid and *p*-cresylglucuronide from those administered *p*-cresol (340).

9.4.1.4 Reproductive and Developmental Toxicity: NA

9.4.1.5 Carcinogenesis *o*-Cresol has been induced a few papilloma but no carcinomas in tumor studies.

Skin Application Female Sutter mice (27–29/group) were dosed with a single application of dimethylbenzanthracene followed one week later by 25 mL of a 20% solution of *p*-cresol in benzene twice weekly for 12 weeks. Benzene treated controls did not experience mortality, although many of the cresol mice did die. *p*-Cresol produced 7/20 tumors (papillomas) on surviving mice (234). In another promotion study, mice were painted with a 20% solution of *p*-cresol for 11 weeks following initiation with dimethylbenzanthracene. Four of fourteen mice treated with *p*-cresol produced papillomas; no carcinomas were produced (344).

9.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms: NA

9.4.1.4 Reproductive and Developmental: NA

9.4.1.5 Carcinogenesis: NA

9.4.1.6 Genetic and Related Cellular Effects Studies *In Vitro* Effects In an unscheduled DNA synthesis assay, *p*-cresol was shown to be negative using rat hepatocytes (345). A cell transformation assay using BALB/3T3 cells showed *o*-cresol to be negative (346). *Salmonella* assays of various strains, both with and without liver homogenate, showed no mutagenic activity (59, 60, 347). In a mouse lymphoma forward mutation assay with liver homogenates, *o*-cresol was not mutagenic (345). Sister chromatid exchange assays produced no evidence of mutagenicity in CHO cells (346). *o*-Cresol induced SCEs in human lung fibroblasts (345, 348).

9.4.1.7 Other: Neurological, Pulmonary, Sensitization Depigmentation occurred when CBA/J mice were treated topically with a laundry ink containing *p*-cresol (353).

9.4.2 Human Experience 9.4.2.1 General Information Cresols can cause local and systemic toxicity in humans after exposure by oral or dermal routes.

9.4.2.2 Clinical Cases Approximately 20 mL of a 90% solution of mixed-cresol solution caused chemical burns, cyanosis, unconsciousness, and death within 4h when accidentally poured on an infant's head. Heptaic necrosis; cerebral edema; acute tubular necrosis of the kidneys; and hemorrhagic effusions from the peritoneum, pleura, and pericardium were observed postmortem. Blood cresol concentration was 120 micrograms/ml (349).

9.4.2.2.1 Acute Toxicity Oral lethality data from Lysol™ (which contains 50% mixed cresols) has been estimated to be between 60 and 120 mL (352). Ingestion is associated with corrosivity to body tissue and toxicity to the vascular system, liver, kdineys, and pancreas [Proctor 88].

9.4.2.2.2 Chronic and Subchronic Toxicity Chronic cresol poisoning has been reported infrequently. About 10 subjects were exposed to *o*-cresol at 1.4 ppm and complained of respiratory tract irritation (350). Documentation was not confirmed. Seven workers who were exposed to mixed-cresol vapor for 1.5–3 years experienced headaches, nausea, and vomiting. Some of those exposed also had elevated blood pressure, signs of impaired kidney function, blood calcium imbalance, and marked tremors (344).

9.4.2.2.3 Pharmacokineics, Metabolis, and Mechanisms Cresols are normally present in human urine. The normal human excretes 16–39 mg *p*-cresol/day (340).

9.4.2.2.4 Reproductive and Developmental: NA

9.4.2.2.5 Carcinogenesis: NA

9.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

9.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* All isomers of cresol cause renal toxicity, hepatic toxicity, and CNS and cardiovascular disturbances (335).
9.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV TWA for cresol is 5 ppm (22 mg/m^3) with a "skin" notation (351). The OSHA PEL is also 5 ppm with a "skin" notation (351). The "skin" notation in the listing refers to "the potential significant contribution to the overall exposure by the dermal route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance." The NIOSH REL TWA is 2.3 ppm (10 mg/m^3); the IDLH value is 250ppm.

Treatment of Cresol Ingestion Treatment should be supportive and symptomatic. There are no known antidotes (335).

Skin Decontamination Treatments after Accidental Exposure of Phenol Skin contact should be treated by washing with copious amounts of water, then bathing in glycerol, propylene glycol, or polyethylene glycol. Patients may require ventilatory support (335).

Phenol and Phenolics
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10.0 Creosote
10.0a Coal-Tar Creosote
10.0.1a CAS Number: [*8001-58-9*]

10.0.2a Synonyms: Creosote oil; creosotes; coal-tar oil; naphthalene oil; heavy oil; cresylic creosote; AWPA #1; brick oil; creosote p1; creosotum; liquid pitch oil; Preserv-o-sote; tar oil; wash oil; dead oil; Smoplastic-F; Osmoplastic-D; original carbolineum

10.0.3a Trade Names: NA

10.0.4a Molecular Weight: varies with purity

10.0.5a Molecular Formula: NA

10.0.6a Molecular Structure: NA
10.0b Wood Creosote
10.0.1b CAS Number: [*8021-39-4*]

10.0.2b Synonyms: Beechwood creosote; creasote; *Fagus sylvatica* creosote

10.0.3b Trade Names: NA

10.0.4b Molecular Weight: Varies with purity

10.0.5b Molecular Formula: NA

10.0.6b Molecular Structure: NA
10.1 Chemical and Physical Properties
Coal-tar creosote is a translucent black or brown, oily liquid. It is heavier than water. Wood creosote is a colorless or yellowish oily liquid.

	Wood Creosote	Coal-Tar Creosote
Specific gravity	1.09	1.1
Melting point	–4°C	Not available
Boiling point	428°C at 0mmHg	203–220°C (decomposes)
Vapor pressure	39mmHg (51°C)	42mmHg (22°C)
Flash point		
Closed cup	74°C	73.9°C
Open cup	—	85°C

10.1.1 General: NA

10.1.2 Odor and Warning Properties Coal-tar creosote has a characteristic aromatic smoky odor. Wood creosote has a characteristic smoky odor and a caustic burning taste.
10.2 Production and Use
Wood creosote is obtained from wood tars, from beech and the resin from leaves of the creosote bush, and by distillation and is composed mainly of phenols, xylenols, guaiacol, and creosol. Coal-tar creosote is produced by high temperature carbonization and distillation of bituminous coal. Coal-tar creosote contains liquid and solid aromatic hydrocarbons, tar acids, and tar base (354). At least 75% of the coal-tar creosote mixture is polyaromatic hydrocarbons (355). Purification of the crude preparation is accomplished by distillation and extraction from suitable oils.

Coal-tar creosote has been used as a wood preservative pesticide in the United States since the late 1890s. This accounts for over 97% of coal tar creosote production (356). Coal-tar creosote prevents animal and plant growth on concrete marine pilings and is a component of roofing pitch. (355). Other uses include animal and bird repellent, insecticide, animal dip, fungicide, and pharmaceutical applications (357). Beechwood creosote has, in the past, been used for medicinal purposes. It is rarely used in the United States for medical purposes today (355).

10.3 Exposure Assesment

Workers most likely to be exposed are carpenters, railroad workers, farmers, tar distillers, glass- and steel-furnace attendants, and engineers. Injuries to the skin or eyes have occurred mainly among male workers engaged in dipping and handling mine timbers and woods for floors and other purposes. Recent studies indicate that dermal exposure to creosote contribute more significantly to total body burden than respiratory exposure (358). There is limited risk of exposure to wood creosote due to its limited commercial use.

10.3.1 Air According to the Toxic Release Inventory (TRI), coal-tar creosote manufacturing and processing facilities listed for 1993, the major portion of creosote released to the environment is released to the air. An estimated total of 1,152,129lb of coal-tar creosote, amounting to 99.2% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the Unites States in 1993. No major sources of wood creosote releases to the environment have been reported (355).

10.3.2 Background Levels No information was found on atmospheric ambient concentrations of wood or coal-tar creosote components. Results from 2 years of groundwater monitoring at a wood treatment facility in Conroe, Texas, where coal-tar creosote had been used for about 20 years showed that monitoring wells were contaminated with naphthalene, methylnaphthalene, dibenzofuran, and fluorene (359).

10.3.3 Workplace Methods GC/MS has been employed to determine creosote levels in workplace air from impregnated wood. Detection levels of $10–50 \times 10^{-6}$g creosote/m^3 sample, and recoveries of 82–102% were acheived (360).

10.3.4 Community Methods: NA

10.3.5 Biomonitoring/Biomarkers No biomarkers uniquely specific to wood creosote or coal-tar creosote have been identified (355). The levels of creosote in biological mateials can be estimated by measuring the polycyclic aromatic hydrocarbon (PAH) content in biological samples. Available methods include GC/FID, GC/MS, and HPLC. GC/MS and HPLC have been employed to detect creosote derived polyclyclic aromatic hydrocarbon complexes in human tissues, including adipose tissue, blood, and urine (361, 362).

10.3.5.1 Blood NA

10.3.5.2 Urine NA

10.3.5.3 Other NA

10.4 Toxic Effects

10.4.1 Experimental Studies 10.4.1.1 Acute Toxicity Ingestion The acute toxicity of wood creosote in both rats and mice was evaluated following single-gavage administration of a 10% aqueous solution (363). The oral LD_{50} of wood creosote was 885 mg/kg (males) and 870 mg/kg (females) in rats and 525 mg/kg (male) and 433 mg/kg (female) in mice. Most animals died within 24 h. The oral LD_{50} for coal tar creosote is reported to be 725 mg/kg in rats and 433 mg/kg in mice (355). A study by Pfitzer (364) reported a rat LD_{50} of 1700 mg/kg. The acute lethal dose of coal tar creosote in sheep and calves is 4 g/kg (365).

Dermal The dermal LD_{50} of coal-tar creosote is >7950 mg/kg following 24-h application to intact and abraided skin (364).

Inhalation Pfitzer (364) exposed rats by inhalation to near-saturated vapors generated from coal-tar creosote for one day. The animals exhibited dyspnea, slight nasal irritation, and eye irritation. The dose level was not determined.

10.4.1.2 Chronic and Subchronic Toxicity Ingestion No treatment related deaths were observed when rats were administered wood creosote in the feed at dose levels up to 1224 mg/kg/day in males or 768 mg/kg per day in females for 3 months (363). Male and female Wistar rats fed diets containing up to 313 or 394 mg/kg wood creosote per day for 96 weeks exhibited deaths in all groups. Treatment related deaths were observed in the males at the high dose only and were attributed to chronic progressive nephropathy (366).

10.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Generally, the PAH components of coal-tar creosote are metabolized by oxidative enzymes in the liver and lungs to generate active metabolites that can bind to macromolecules. The principal products include phenols, dihydrodiols, quinones, anhydrides, and conjugates of these products (355).

10.4.1.3.1 Absorption No studies specific to the absorption of wood creosote or coal tar creosote were found.

10.4.1.3.3 Distribution No studies specific to the distribution of wood creosote or coal tar creosote were found.

10.4.1.3.3 Excretion Creosote appears to be excreted in the urine mainly in conjugation with sulfuric, hexuronic, and other acids (367, 368). Oxidation also occurs with the formation of compounds that impart a “smoky” appearance to the urine. Traces are excreted by way of the lungs.

10.4.1.4 Reproductive and Developmental The only available study in animals reported dermal contact with coal-tar-creosote-treated wood by pregnant sows (369). Four sows were confined in wooden crates for 2–10 days before delivery. The crates were coated with three applications of 98.5% coal-tar creosote. Of 41 pigs delivered, 21 were dead at birth; 11 pigs died by day 3 post-farrowing. No toxic effects were evident in the sows. These findings were considered suggestive of developmental toxicity.

10.4.1.5 Carcinogenesis The carcinogenicity of creosote oils has been studied quite thoroughly using mice (370, 371). Studies indicate that coal-tar cresosote and several of its fractions can be carcinogenic when applied to the skin of mice and rabbits. Dermally applied coal-tar creosote can also act as a tumor-initiating agent when applied prior to croton-oil treatment (355).

10.4.1.6 Genetic and Related Cellular Effects Studies The genotoxic potential of coal-tar creosote has been investigated using *in vitro* assays of the material and of urine from exposed animals. The available genotoxicity data indicate that creosote is an indirect mutagen and induces gene mutation in bacteria and mouse lymphoma cells (355). Bos et al. (372) identified fluoranthene as one of the major volatile components of creosote responsible for the genotoxicity observed in *Salmonella typhimurium* strains.

10.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization

Neurological Effects. Rats and mice treated via gavage administration of a single high dose of beechwood creosote (300 mg/kg rats) exhibited muscle twitching followed by convulsions within 1–2 min. This was followed by asphyxiation, coma, and death (363).

Pulmonary Effects. Beechwood creosote failed to produce an adverse effect on lung weights when

fed to rats (1224 mg/kg per day males; 1570 mg/kg per day females) in the feed for 3 months (363). Thickening of tracheal mucous membrane was observed in mice who ingested feed (474 mg/kg males, 532 mg/kg females) containing beechwood creosote for 52 weeks. This was attributed by the author to inhalation of volatile components rather than to oral toxicity (363).

Immunological and Lymphoreticular Effects. Daily exposures to beechwood creosote at 805 or 1224 mg/kg in the diet for 3 months resulted in increased relative spleen weight of male rats. Similar effects were not seen in mice (363).

10.4.2 Human Experience 10.4.2.1 General Information: NA

10.4.2.2 Clinical Cases 10.4.2.2.1 Acute Toxicity Ingestion Fatalities have occurred 14–36 h after the ingestion of about 7g of coal-tar creosote by adults or 1–2 g by children (373). The symptoms of systemic illness included salivation, vomiting, respiratory difficulties, thready pulse, vertigo, headache, and loss of pupillary reflexes, hypothermia, cyanosis, and mild convulsions. The repeated absorption of therapeutic doses from the GI tract may induce signs of chronic intoxication, characterized by disturbances of vision and digestion (increased peristalsis and excretion of bloody feces). In isolated cases of "self-medication," hypertension, and general cardiovascular collapse have been described (374). Acute toxic hepatitis has been attributed to the ingestion of chaparral, an herbal supplement derived from the leaves of the creosote bush (375). Icterus and jaundice were observed in a 42-year-old male who consumed 500 mg of chaparral a day for 6 weeks. Elevated bilirubin, g-glutamyltranspeptidase, AST, and LDH were observed. Recovery occurred in approximately 3 weeks.

Dermal Creosote burns were observed in construction workers who handled creosote-treated wood (376). The majority of these cases were mild and were characterized by erythema of the face. Coal-tar creosote is capable of inducing phototoxicity of the skin (355).

10.4.2.2.2 Chronic and Subchronic Toxicity: NA

10.4.2.2.5 Pharmacokinetics, Metabolism, and Mechanisms: NA

10.4.2.2.4 Reproductive and Developmental No studies on reproductive or developmental effects of wood creosote or coal-tar creosote were identified. A site-surveillance program was conducted by the Texas Department of Health in 1990 at a housing development that was built on an abandoned creosote wood treatment plant. No reproductive or developmental findings were evident (355).

10.4.2.2.5 Carcinogenesis Cookson (377) described a 66-year-old coal-tar creosote factory worker who developed a squamous-cell carcinoma of the right hand after 33 years of heavy exposure. Autopsy revealed metastases to the lungs, liver, kidneys, heart, and lymph nodes. A similar case was reported in which a worker developed squamous-cell papillomas of the hands, nose, and thighs after several years of employment in the creosote impregnation of logs (378). Lenson (379) reported on a 64-year-old creosote shipyard worker who developed several primary carcinomas of the face.

10.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

10.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* Contact of creosote with the skin or condensation of vapors of creosote on the skin or mucous membranes may induce an intense burning and itching with local erythema, grayish yellow to bronze pigmentation (376), papular and vesicular eruptions, gangrene, and cancer (380–382). Heinz bodies were noted in the blood of a patient 1 year after his exposure to creosote (379). Jonas (376) made similar observations following percutaneous absorption. On contact with the eyes, creosote caused protracted keratoconjunctivitis. This involves loss of corneal epithelium, clouding of the cornea, miosis, irritability, and photophobia. Subsequently, both blurring of vision and superficial keratitis can occur (334).

10.4.2.3 Epidemiology Studies Most of the available information on the effects of coal-tar creosote in humans comes from cases of acute poisoning following accidental or intentional exposure to coal-tar creosote and from occupational exposures in the wood preserving and construction industries. These studies are limited by lack of exposure concentrations and duration and by exposure to other potentially toxic substances. The few available studies are limited by small sample size, short follow-up periods, and brief exposure periods. These studies suggest that coal-tar creosote is a dermal irritant and a carcinogen following dermal exposure. Additional well-controlled epidemiological studies are needed (355).

10.4.2.3.1 Acute Toxicity: NA

10.4.2.3.2 Chronic and Subchronic Toxicity: NA

10.4.2.3.3 Pharmacokinetics, Metabolism, and Mechanisms: NA

10.4.2.3.4 Reproductive and Developmental A site-surveillance program was conducted by the Texas Department of Health in 1990 at a housing development that was built on an abandoned creosote wood treatment plant. No reproductive or developmental findings were evident (355).

10.4.2.3.5 Carcinogenesis Case reports and occupational surveys associate occupational creosote exposure with the development of skin cancer (355). These reports outline a similar disease etiology for different groups of workers exposed to creosote that include the development of dermatoses that progressed to carcinoma, usually squamous-cell carcinoma. Cancer of the scrotum in chimney sweeps has been associated with prolonged exposure to coal-tar creosote. The latency period for the development of dermatoses was usually 20–25 years (377, 383, 384). More recent studies suggest that prolonged exposure to coal-tar creosote and other coal-tar products may cause cancer of the skin and other organs (385–387).

10.4.2.3.6 Genetic and Related Cellular Effects Studies: NA

10.4.2.3.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* Leonforte (388) reported several cases of acute allergic dermatitis subsequent to contact with a creosote bush and confirmed by a patch test.

10.5 Standards, Regulations, or Guidelines of Exposure

The USEPA has classified coal-tar creosote as a class B1 carcinogen (Probable human carcinogen) (389). IARC classifies creosote as a human carcinogen (class 2A) (390). Creosotes are listed by the California Environmenal Protection Agency under Proposition 65 as chemicals known to cause cancer (391). The Occupational Safety and Health Administration (OSHA) has set an exposure limit of 0.2 mg/m^3 of coal-tar pitch volatiles in the workplace during an 8 h workday, 40 h workweek. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends the same level for coal tar pitch volatiles. The National Institute for Occupational Safety and Health (NIOSH) recommends a maximum level of 0.1 mg/m^3 of coal-tar pitch volatiles for a 10 h workday, 40 h workweek (392).

10.6 Studies on Environmental Impact

Coal-tar creosote materials encountered in old production facilities or waste-disposal sites within the top several feet of soil have become weathered, as virtually all of the phenolic and heterocyclic fractions have volatilized, oxidized, or biodegraded (355, 393). The lighter fractions of PAH will have degraded, and the remaining material shows limited ability to migrate. Johnston et al. (394) concluded that aqueous partitioning and volatilization are probably the main processes that control modification of coal-tar at gasworks sites. Spills of newly produced creosote may pose a more serious toxicity concern.

Phenol and Phenolics
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11.0 Pentachlorophenol and Sodium Pentachlorophenate
11.0a Pentachlorophenol
11.0.1a CAS Number:
[*87-86-5*]
11.0.2a Synonyms:
Pentachlorophenate; 2,3,4,5,6-pentachlorophenol; pentachlorofenolo; pentachlorphenol; penta; Dowicide 7; Dowicide EC-7; penchlorol; Santophen 20; Chlorophen; Pentacon; Penwar; Sinituho; PCP; pentachlorofenol; pentachlorophenol, dp-2; Dow pentachlorophenol dp-2 antimicrobial; chem-tol; cryptogil oil; Dowicide 7; durotox; EP 30; fungifen; grundier arbezol; lauxtol; lauxtol a; liroprem; term-i-trol; Thompson's wood fix; penta-kil; peratox; permacide; permagard; permasan; permatox dp-2; permatox penta; permite; priltox; santobrite; Pol-NU; Oz-88; Osmoplastic; Forepen; Dura-Treet (395)
11.0.3a Trade Names:
Block Penta, Forpen-50, GlazD Penta, K-Ban, Osmose, Penta Concentrate, Penta OL, Pentacon, Pentacon-5, Pentacon-7, Pentacon-10, Pentacon-40, Pentasol, Penta-WR, Penwar, Penwar 1-5, Pol-Nu, Pol-Nu-Pak, Treet II, Vulcan Premium Four # Penta (PCP2) Concentrate, Woodtreat (396–398)
11.0.4a Molecular Weight:
266.35 (395)
11.0.5a Molecular Formula:
C_6HCl_5O
11.0.6a Molecular Structure:

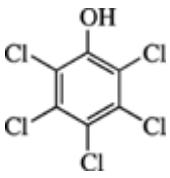

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Table 53.6. Physicochemical Properties of Various Chlorophenols

Name	CAS Number	Appearance	Odor Threshold (mg/mL)	Specific Gravity (g/mL)	MP (°C)	BP (°C)	Vapor Density (mmHg)	Vapor Pressure (mmHg)	D (g

2,3,4,5-Tetrachlorophenol	[*4901-51-3*]	Beige solid	N/A	1.6	116	Sublimes	N/A	N/A	N/
2,3,4,6-Tetrachlorophenol	[*58-90-2*]	Beige solid	N/A	1.839	70	150	N/A	1–60	N/
2,3,5,6-Tetrachlorophenol	[*935-95-5*]	Beige solid	N/A	1.6	114–116	164	N/A	N/A	N/
2,3,4-Trichlorophenol	[*15950-66-0*]	Light peach solid	N/A	N/A	77–79	Sublimes	N/A	N/A	N/
2,3,5-Trichlorophenol	[*933-78-8*]	White chalky solid	N/A	N/A	57–59	248–249	N/A	N/A	N/
2,3,6-Trichlorophenol	[*933-75-5*]	Purple crystals	300	N/A	56	253	N/A	N/A	N/
2,4,5-Trichlorophenol	[*95-95-4*]	Off-white-solid	N/A		68	253	>1	1–5	1.
2,4,6-Trichlorophenol	[*88-06-2*]	Orange-and-white-solid	N/A		69.5	244.5	N/A	1–5	N/
3,4,5-Trichlorophenol	[*609-19-8*]	Off-white solid	N/A	N/A	101	271–277	N/A	N/A	N/
2,3-Dichlorophenol	[*576-24-9*]	Brown crystals	30	N/A	59	206	N/A	N/A	N/
2,4-Dichlorophenol	[*120-83-2*]	White solid	210		45	210	5.62	1	N/
2,5-Dichlorophenol	[*583-78-8*]	White crystals	30	N/A	57	211	N/A	N/A	N/
2,6-Dichlorophenol	[*87-65-0*]	Purple crystals	3–200	N/A	67	219	1–10	N/A	N/
3,4-Dichlorophenol	[*95-77-2*]	Brown and yellow crystals	100	N/A	67		N/A	N/A	N/
3,5-Dichlorophenol	[*591-35-5*]	Pink crystals	N/A	N/A	68	233	N/A	N/A	N/
2-Chlorophenol	[*95-57-8*]	Yellow liquid	20			175.6	N/A	1–22	1.
3-Chlorophenol	[*108-43-0*]	White crystals	1–5			214	N/A	1–5	1.
4-Chlorophenol	[*106-48-9*]	White crystals	N/A		43.2–43.7	220	4.4	0.1	1.

M.P = Melting Point; B.P. = Boiling Point; V.D. = Vapor Density; V.P. = Vapor pressure; Sub. = Sublimes.

Table 53.7. Solubilites of Various Chloro-phenols

Name	DMSO (mg/mL)	CH_3OH	Ethanol (mg/mL)	Ethyl ether	Acetone (mg/mL)	Benzene	CCl_4	Water (mg/ml)

2-Chlorophenol	100	N/A	100	N/A	100	N/A	N/A	10–50
3-Chlorophenol	100	N/A	100	N/A	100	N/A	N/A	10–50
4-Chlorophenol	100	N/A	100	N/A	100	N/A	N/A	10–50
3,5-Dichlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
3,4-Dichlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
2,3-Dichlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
2,6-Dichlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
2,5-Dichlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
2,4-Dichlorophenol	100	N/A	100	N/A	100	N/A	N/A	<0.1
3,4,5-Trichlorophenol	100	N/A	100	>10%	100	N/A	N/A	<1
2,4,6-Trichlorophenol	100	525%	100	354%	100	113%	37%	<0.1
2,4,5-Trichlorophenol	100	615%	100	525%	100	163%	51%	<1
2,3,6-Trichlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
2,3,5,6-Tetrachlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
2,3,5-Trichlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
2,3,4,6-Tetrachlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
2,3,4,5-Tetrachlorophenol	100	N/A	100	N/A	100	N/A	N/A	<1
2,3,4-Trichlorophenol	100	N/A	100	>10%	100	>10%	N/A	<1

Table 53.8. Uses of Various Chlorophenols

Compound	Use
2,3,4,5-Tetrachlorophenol	Fungicide
2,3,4,6-Tetrachlorophenol	Pesticide; wood preservative; slimicide for paper mills
2,4,5,6-Tetrachlorophenol	Fungicide

2,4,5-Trichlorophenol	Chemical intermediate for herbicides, insecticides, preservative for adhesives, textiles, rubber, wood, paints, in paper manufacture; cooling towers, on swimming-pool surface, veterinary medication
2,4-Dichlorophenol	In synthesis of anthelmintic bithionol sulfoxide; chemical intermediate
2,5-Dichlorophenol	Chemical intermediate for 3,6-dichloro-*O*-anisic acid, the herbicide dicamba
2,6-Dichlorophenol	This compound is used as a starting material for the manufacture of trichlorophenol, tetrachlorophenols and pentachlorophenol; used as sex pheromone with pesticide control
3,5-Dichlorophenol	Known uses: used in veterinary medicine as an anthelmintic
3,4-Dichlorophenol	Chemical intermediate for 2-chloro-1,4-dihydroxyanthraquinone and 2,3,4-Trichlo
o-Chlorophenol	Component of disinfectant, soil sterilant, organic synthesis of dyes
m-Chlorophenol	Intermediate in organic synthesis and phenolformaldehyde resins, catalyst for a polymers, vet antiseptic
p-Chlorophenol	In synthesis of dyes, pharmaceuticals, solvent in refining mineral oils, intermediate for use in dental practice, bacterial agent, topical antiseptic ointment, soil sterilant

Table 53.9. Acute Toxicity of Various Chlorophenols

Compound	Mouse	Rat	Rabbit
a. LD_{50} of the isomers by oral administration (8)			
p-chlorophenol	367	500	
o-chlorophenol	345	670	
m-chlorophenol	521	570	
2,3-dichlorophenol	2376		
2,4-dichlorophenol	1276	580	
2,5-dichlorophenol	946		
2,6-dichlorophenol	2120		
3,4-dichlorophenol	1685		
3,5-dichlorophenol	2389		
2,4,5-trichlorophenol	600	820	1000
2,4,6-trichlorophenol		820	
2,4,5,6-tetrachlorophenol		140	250
2,3,4,5-tetrachlorophenol	400		
2,3,5,6-tetrachlorophenol	109		

b. LD_{50} (mg/m^3) of the isomers by the inhalation route (8)

Compound	Rat	Hamster
p-chlorophenol	11	10,000

c. LD_{50} (mg/m^3) values for administration of the isomers by the subcutaneous (or dermal (sk)) route (8)

Compound	Rat	Rabbit	Guinea Pig
p-chlorophenol	1030;1500(sk)		
o-chlorophenol	950	950	800
m-chlorophenol	1390		
2,6-dichlorophenol	1730		
2,4-dichlorophenol	1730		
2,4,5-trichlorophenol	2260		
2,4,5,6-tetrachlorophenol	210	250(sk)	
2,4,5,6-tetrachlorophenol			

d. LD_{50} Values for administration of the isomer by the intraperitoneal route (or the intravenous (iv) route) (8)

Compound	Mouse	Rat	Rabbit
p-chlorophenol	332	281	
o-chlorophenol	235	230	120
m-chlorophenol		355	
2,4-Dichlorophenol	153	430	
2,6-Dichlorophenol		390	
2,3,6-Trichlorophenol		308	
2,4,6-Trichlorophenol		276	
2,4,5-trichlorophenol	56(iv)	355	
2,3,4,5-tetrachlorophenol	97		
2,3,5,6-tetrachlorophenol	500		
2,4,5,6-tetrachlorophenol	250	130	

Table 53.10. Genotoxicity of Various Chlorophenols

Isomer	Ames Test	Mouse Lymphoma	Chromosome Aberrations	Sister Chromatid Exchanges	Ref.
m-Chlorophenol	Negative				60

p-Chlorophenol	Negative				60
o-Chlorophenol	Negative				60
2,3-Dichlorophenol	Negative	Positive	Negative	Positive	599, 600
2,4-Dichlorophenol	Negative	Positive	Negative	Positive	60, 599, 600
2,5-Dichlorophenol	Negative				60
2,6-Dichlorophenol	Negative				60
3,4-Dichlorophenol	Negative				60
3,5-Dichlorophenol	Inconclusive				60
2,3,4-Trichlorophenol	Negative		Positive	Positive	596, 601
2,3,5-Trichlorophenol	Negative				60
2,3,6-Trichlorophenol	Negative		Positive	Negative	60, 596
2,4,5-Trichlorophenol	Negative				60
2,4,6-Trichlorophenol	Negative	Positive	Negative	Negative	65, 596, 601
3,4,5-Trichlorophenol	Negative		Negative	Negative	596
2,3,4,5-Tetrachlorophenol	Negative		Positive	Inconclusive	60, 596

Table 53.11. Some Ecotoxicological Properties of 2,4,6-Trichlorophenol

Log octanol/water partition coefficient	3.87
Bioconcentration factor	310 in golden orfe (*Leucisens idus melanotus*)
Half-life	
Air	<1 day (estimated)
Water	<1–19 days (estimated)
Soil	5 days for complete biodegradation

Phenol and Phenolics

Ralph Gingell, Ph.D., DABT, John O'Donoghue, Ph.D., DABT, Robert J. Staab, Ph.D., DABT, Ira W. Daly, Ph.D., DABT, Bruce K. Bernard, Ph.D., Anish Ranpuria, MS, E. John Wilkinson, Daniel Woltering, Ph.D., Phillip A. Johns, Ph.D., Stephen B. Montgomery, Ph.D., Larry E. Hammond, Ph.D., Marguerita L. Leng, Ph.D.

13.0 2,4-Dichlorophenoxyacetic Acid

13.0.1 CAS Number:

[*94-75-7*]

13.0.2 Synonyms:

Dichlorophenoxyacetic acid; phenoxy herbicide; 2,4-D; 2,4-D acid; phenoxyacetic acid herbicide.

13.0.3 Trade Names:

Formula 40*, Esteron* 99* Concentrate, HiDep, Weedar 64, Weedone, Aqua-Kleen, LV400 2,4-D Weed Killer, Salvo, Savage, Weed Rhap A-4D, Weedestroy AM-40, DMA* 4

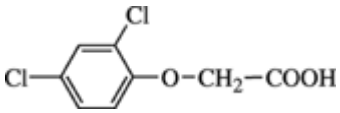
13.0.4 Molecular Weight:

221.01

13.0.5 Molecular Formula:

$C_8H_6Cl_2O_3$

13.0.6 Molecular Structure:



13.1 Chemical and Physical Properties

13.1.1 General

Color	White to light tan
Physical state	Crystalline solid or flake
Density	1.565
Boiling point	160°C at 0.4 mm Hg
Melting point	140–141°C
Hydrolysis (per day)	Stable in water at 25°C at pH 5 Stable in water at 25°C at pH 7 Stable in water at 25°C at pH 9
Photolysis (per day)	Aqueous: $t_{½}$ 13 days in water at 25°C, pH 7.0 Soil: $t_{½}$ 68 days in loam soil at 25°C, pH 7.8
Vapor pressure (mPa)	1.4×10^{-7}mmHg at 25°C
Water solubility (ppm)	311 ppm in water at 25°C and pH 1 20,031 ppm in water at 25°C and pH 5 23,180 ppm in water at 25°C and pH 7 34,196 ppm in water at 25°C and pH 9
Henry's law ($Pa \cdot m^3/mol$)	1.3×10^{-10} in water at 25°C, pH 1 5.7×10^{-11} in water at 25°C, pH 3 1.0×10^{-12} in water at 25°C, pH 5

Octanol/water partitioning (log K_{ow})	385 in water at 25°C, pH 1
	1.10 in water at 25°C, pH 5
	0.12 in water at 25°C, pH 7
	0.09 in water at 25°C, pH 9
Acid dissociation (pK_a)	2.87 in water at 25°C

13.1.2 Odor and Warning Properties Phenolic odor (odorless when pure).

13.2 Production and Use

2,4-Dichlorophenoxyacetic acid (2,4-D) is an organic herbicide that has provided economical, selective, postemergence control of broadleaf weeds in grass crops and non-cropland since the late 1940s and it is still the most widely used herbicide throughout the world. The Environmental Protection Agency (EPA) has approved 2,4-D registered products for weed control in farming, forestry, powerline maintenance, roadside brush control, aquatics, on home lawns, and for other end uses. The various forms of 2,4-D are absorbed through both the roots and leaves of most plants, especially broadleaf species (606).

The structure of 2,4-D is similar to that of the plant-specific hormone indole acetic acid and thus acts as a plant growth regulator. The acid is the parent compound, but many of the 2,4-D formulations in use contain the amine salts, which are more water-soluble than the acid, or the ester derivatives, which are readily dissolved in an organic solvent.

Phenoxy herbicides play a major role in weed management when used either alone or in combination with other herbicides. Applied as a foliar spray at 10–24 ppm in water, it acts as a fruit-drop-prevention agent in citrus. In contrast, 2,4-D is used at higher concentrations (0.25–4lb acid equivalent per acre) to control weeds in the crop and non-cropland areas. The herbicide 2,4-D is registered for use on over 65 crops in the United States: raw agricultural commodity (RAC) residue tolerances have been established (607). Also, 2,4-D is registered for numerous non-cropland and aquatic uses. The first year of sales and testing in the United States was 1945, and 917,000lb were produced. Production rose to 5.5 million lb in 1946 and 14, 36, 54, 52–67 million lb in 1950, 1960, 1964, and 1990, respectively. At the time of writing, the annual production of 2,4-D for use of the United States is approximately 47 million lb and greater than 100 million lb worldwide (608, 609). The major manufacturers are Dow AgroSciences (United States), Nufarm (Australia), Atanor (Argentina), A. H. Marks (England) UFA (Russia), Rokita (Poland), and Polaquimia (Mexico).

13.3 Exposure Assessment

13.3.1 Air Based on *EPA Toxicology Endpoint Selection Document*, 1996, exposure via inhalation (acute, short-term, or long-term) is not a concern based on the LC_{50} = >1.79 mg/L; acute inhalation tox category III (610).

13.3.2 Background Levels: NA

13.3.3 Workplace Methods NIOSH/OSHA Occupational Health Guideline for 2,4-D is 10 mg 2,4-D per m^3 exposure averaged over an 8 h shift (611).

13.3.4 Community Methods The EPA drinking-water maximum contaminant level goal (MCLG) for 2,4-D is 0.070 mg/L (ppm) (612).

13.3.5 Biomonitoring/Biomarkers 13.3.5.1 Blood In rats ^{14}C-2,4-D was rapidly and almost completely absorbed, as peak plasma levels were attained about 4 h after treatment, and 85–94% of the dose was excreted in the urine. The feces are a minor excretory pathway (2–11%). Rapid excretion of radiolabeled 2,4-D is also corroborated by the approximate half-life of 5 h for urinary excretion after oral administration (163). The rapid clearance of 2,4-D from plasma and its rapid excretion in the urine indicate that it has little potential to accumulate in mammals. Analysis of all

major tissues and organs for residual ^{14}C activity indicated that only a small fraction of the dose was still present 48 h after treatment. Tissues and organs from animals at the low dose contained <0.7% of the administered dose (613). These results indicate that the fate of 2,4-D in the rat is independent of dose and sex, that the compound is rapidly and almost completely eliminated, essentially by the urinary route, and that it has little potential to accumulate.

13.3.5.2 Urine See section 13.3.5.1.
13.4 Toxic Effects
13.4.1 Experimental Studies 13.4.1.1 Acute Toxicity The acute toxicity of 2,4-D is summarized in Table 53.12 (614–620). After oral administration, the clinical signs of toxicity observed consistently were ataxia, myotonia, and decreased limb tone. No dermal or systemic toxicity was seen in rabbits treated dermally, and no deaths were seen after inhalation. Clinical signs of toxicity seen during eye exposure were decreased activity and closed eyes. Signs seen at the end of and during the week after exposure were salivation, lacrimation, mucoid nasal discharge, labored breathing, dried red or brown material around the eyes and nose, matted fur, and staining of the fur in the anogenital region. None of these signs was seen within 3–7 days of treatment. There was no significant finding postmortem (614).

Table 53.12. Acute Toxicity of 2,4-D

Route	LD_{50} (mg/kg bw) or LC_{50} (mg/L)	Ref.
Oral—rat	699	614, 615
Dermal—rabbit	>2000	614, 616
Inhalation—rat	>1.8	614, 617
Eye irritation—rabbit	Irritation >21 days	618, 619
Dermal irritation—rabbit	Nonirritant	619, 620
Dermal sensitization	Negative/nonsensitizing	619

13.4.1.2 Chronic and Subchronic Toxicity Subchronic rat and dog toxicity studies were conducted on all three forms of 2.4-D: 2,4-D acid, dimethylamine salt [DMA], and 2-ethylhexyl ester [2-EHE]. Toxicity was comparable for the three forms in both species, and suport a rat subchronic NOEL of 15 mg/kg per day, and a dog subchronic NOEL of 1 mg/kg per day (629, 630). A one year chronic study in the dog with 2,4-D acid at doses of 0, 1.0, 5.0 and 7.5 mg/kg per day showed no indication of immunotoxic or oncogenic effects; the chronic dog NOEL was 1.0 mg/kg per day (629). Doses in the 2-year chronic/oncogenicity rat study were 0, 5, 75, and 150 mg/kg per day. The chronic toxicity NOEL of 5 mg/kg per day was established. A slight increase in astrocytomas observed (in males only) at 45 mg/kg per day in a previously conducted chronic rat study was not confirmed in the Jeffries 1995 study (621) at daily doses as high as 150 mg/kg the MTD. Daily doses in the 2-year mouse oncogenicity studies were 0, 5, 62.5, and 125 mg/kg for males. No oncogenic effect was noted in the study. In summary, the finding of these studies indicate low chronic toxicity of 2,4-D and the lack of oncogenic response to 2,4-D following chronic dietary exposure of 2,4-D in the rat and the mouse (622). EPA states in its review of the chronic rat and mouse studies, “2,4-D acid was not carcinogenic in male or female rats or mice” (623).

13.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 13.4.1.3.1 Absorption 2,4-D was rapidly absorbed, distributed, and excreted after oral administration to mice, rats, and goats. At least 86–94% of an oral dose was absorbed from the gastrointestinal tract in rats. 2,4-D was excreted rapidly and

almost exclusively (85–94%) in urine by 48 h after treatment, primarily as unchanged 2,4-D. In rats no metabolites have been reported apart from conjugates (613). In goats minor metabolites were free and conjugated 2,4-dichlorophenol (2,4-DCP). Pharmacokinetic studies with salts and esters of 2,4-D have shown that the salts dissociate and the esters are rapidly hydrolyzed to 2,4-D. The similarity in the fate of 2,4-D and its salts and esters explains their similar toxicities (614, 619).

Absorption of 2,4-D appears to be rapid and complete from the GI tracts of humans and experimental animals (624, 625). Although ingestion is usually a relatively minor route of exposure, most toxicity testing of 2,4-D has been conducted by oral exposure. Because 2,4-D is absorbed more efficiently through the GI tract than through the skin, 2,4-D should be more toxic when ingested than when applied to the skin. Therefore, using oral studies of 2,4-D to test toxicity may add some margin of safety when these data are used to predict risk from exposure to 2,4-D through skin contact.

13.4.1.3.2 Distribution Once absorbed, 2,4-D was widely distributed throughout the body, but did not accumulate because of its rapid clearance from the plasma and rapid urinary excretion (614, 626). The excretion, tissue residues, and metabolism of ^{14}C-2,4-D were investigated in a lactating goat given an oral dose of 483 ppm for three consecutive days in a capsule. About 90% of the dose was recovered in the urine and feces. Milk, liver, kidneys, composite fat, and composite muscle accounted for <0.1% of the total dose received. The residues in the milk were 0.22–0.34 ppm at the morning milking and 0.04–0.06 ppm in the evening. Kidneys accounted for the highest residue concentration, 1.4 ppm; liver contained 0.22 ppm, fat contained 0.09 ppm, and muscle contained 0.04 ppm (614, 627). Binding of 2,4-D to plasma proteins can occur and may affect distribution (625). When 2,4-D is bound to the plasma proteins, it cannot reach tissues where it might cause damage. High doses of 2,4-D can saturate or use up all the plasma protein binding sites, which could result in a dramatic rise in the concentration of "free" 2,4-D. Free 2,4-D may be excreted; however, at very high doses of 2,4-D, the rate of excretion may slow down, and therefore the concentration of 2,4-D that can reach tissues in the body may increase and cause toxicity.

13.4.1.3.3 Excretion In animals and humans who have ingested 2,4-D, it was quickly absorbed and excreted rapidly in the urine; about 84–94% of the administered dose was found in the urine within 48h. No metabolites were detected (613, 614, 626). Also refer to Sections 13.4.1.3.1, 13.4.3.2, and 13.4.2.2.3.

13.4.1.4 Reproductive and Developmental Reproductive The reproductive toxicity of 2,4-D has been studied at dietary doses of 0, 5, 20, and 80 mg/kg/day in a two-generation reproductive study in Fischer 344 rats (628). The parental F_0 group was treated with 2,4-D for 15 weeks prior to mating. No adverse effects on fertility were observed in the 5- and 20-mg/kg daily dose groups, although reduced pup weights were noted in the 20-mg/kg F_{2a} litters. A daily NOAEL of 5 mg/kg for reproductive toxicity was established from this study. In addition to this reproduction study, recent subchronic and chronic studies in rats, mice and dogs produced no evidence of treatment-related histopathological changes in the testes at any of the dose levels tested (622, 629, 630).

Developmental The teratogenic potential of 2,4-D acid and a variety of its salt and ester derivatives have been evaluated in a series of studies in both rats and rabbits. In rats, the lowest daily no-observed-effect-level (NOEL) doses were 25 mg/kg for 2,4-D acid and 50 mg/kg (acid-equivalent dose) for the various 2,4-D derivatives. Observations of embryo or fetal toxicity, which were observed only in the presence of maternal toxicity, were limited to decreased fetal body weights and increased incidences of minor-skeletal variations. In rabbits, no gross, soft-tissue, or skeletal malformations or variations were observed up to a top daily dose of 90 mg/kg of 2,4-D acid, or at top daily doses equal to or greater than 90 mg/kg of 2,4-D derivatives (acid-equivalent doses). The NOAEL daily doses for rabbit maternal toxicity were 30 mg/kg for 2,4-D and 10 mg/kg for the derivative acid-equivalents. Thus, these extensive series of studies support the conclusion that 2,4-D has a very minimal potential for inducing developmental toxicity, and that such toxicity only occurs in the presence of maternal toxicity. Importantly, the minimal developmental toxicity of 2,4-D in rats

was reported only at daily doses equal to or above 50 mg/kg, the dose level at which 2,4-D has been shown to exhibit nonlinear pharmacokinetic behavior in rats due to saturation of renal 2,4-D clearance (631).

13.4.1.5 Carcinogenesis The carcinogenicity of 2,4-D has been assessed in two recent rat studies conducted according to good laboratory practice (GLP) requirements (621, 632). In the 1986 study conducted in Fischer 344 rats, the kidney was the primary organ affected by 2,4-D treatment (632). The minor kidney lesions constituted the basis for establishment of an overall rat NOEL of 5 mg/kg per day. A low incidence of astrocytomas was observed only in high dose males of this study. However, a follow-up analysis of the astrocytoma findings led to the conclusion that the brain tumors were not likely treatment-related for several reasons, including (*1*) no earlier tumor appearance in treated versus nontreated rats, (*2*) no evidence of tumor multiplicity, (*3*) similar tumor size and anaplastic characteristics of astrocytomas in control and treated rats, and (*4*) no evidence of brain lesions or brain toxicity in treated rats not exhibiting tumors (624). Astrocytomas were not confirmed in the Jeffries 1995 study at the threefold higher daily dose of 150 mg/kg (621, 622).

The EPA Carcinogenicity Peer Review Committee (CPRC) met in 1996 to discuss and evaluate the weight of the evidence on 2,4-D with particular reference to its carcinogenic potential. The CPRC concluded that 2,4-D should remain classified as a Group D—Not classifiable as to human carcinogenicity. That is, the evidence is inadequate or no human and animal evidence of carcinogenicity (623).

13.4.1.6 Genetic and Related Cellular Effects Studies The genotoxic potential of 2,4-D has been adequately evaluated in a range of assays *in vivo* and *in vitro*. Overall, the responses observed indicate that 2,4-D is not genotoxic, although conflicting results were obtained for mutation in *Drosophila*. In a more extensive range of assays, several amine and ester formulations of 2,4-D were evaluated and were not genotoxic *in vivo* or *in vitro*. The World Health Organization concluded that 2,4-D and its salts and esters are not genotoxic (614, 626).

13.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Neurological Single-dose acute and 1-year chronic neurotoxicity screening studies in rats were conducted on 2,4-D according to the USEPA guidelines in 1991. The studies emphasized a functional observation battery, automated motor activity testing, and comprehensive neurohistopathology of perfused tissues. Daily doses were ≤250 mg/kg by gavage for the single-dose study and ≤150 mg/kg in the diet for 52 weeks in the repeated-dose study. In the acute study, slight transient gait and coordination changes were observed along with decreased motor activity at the time of maximal effect on the day of treatment (day 1). No gait, coordination, or motor activity effects were noted by day 8. In the chronic study, the only finding of neurotoxicologic significance was retinal degeneration in females in the high dose group. In summary, the findings of these studies indicated a mild, transient locomotor effect from high level chronic exposure. The results from these two studies, indicated that the NOAEL for acute neurotoxicity was 67 mg/kg per day and for chronic neurotoxicity was 75 mg/kg per day (610, 614, 626, 633). The mechanism by which the effects occur at high doses appears to be dependent on the inhibition of the organic acid transport system and/or damage to the blood–brain barrier. Exposures to 2,4-D below the threshold for inhibition of the organic acid transportation pathway (approximately 40–100 mg/kg body weight) are not associated with increased concentrations of 2,4-D in the brain, alterations to brain neurochemistry, behavioral effects, or CNS pathology. This provides a very large margin of safety (>20,000-fold) when compared to estimation of bystander exposures (0.0005 mg/kgbw per/day) following commercial aerial application of 2,4-D (634). Therefore, when application of 2,4-D is conducted in compliance with recommended uses and rates, it is not expected to result in detrimental impacts on the nervous system (624).

Pulmonary The pulmonary effects reported in case studies of extreme human exposure cannot be associated with 2,4-D exposures that would be expected to occur following routine and recommended use of this herbicide. Assessment of the potential impact of 2,4-D on human pulmonary system is based mainly on anecdotal and uncontrolled case studies in which pulmonary

effects as a result of exposure to very high levels of 2,4-D have been reported. Some pulmonary effects such as labored breathing and respiratory tract irritation have been reported in herbicide sprayers who were exposed to extremely high levels of 2,4-D. However, these workers were exposed to a number of different chemical formulations, including other herbicides and solvents, at undetermined concentrations. Thus, these pulmonary effects cannot be attributed, directly or indirectly, to 2,4-D exposure. Animal studies indicate that pulmonary effects can be considered to be secondary to other impacts, such as kidney toxicity. A comparison of the NOEL to estimated bystander exposures following commercial aerial application of 2,4-D (0.0005 mg/kgbw/day) (634) yields a margin of safety of over 10,000-fold (624).

Dermal Dermal exposure data support the conclusion that exposure to 2,4-D under recommended conditions and application rates would not be expected to cause adverse dermal effects. Several studies have quantified typical bystander exposure to (634, 635). On the basis of these studies, bystander exposure to 2,4-D from various sources, including home and garden use and commercial aerial application, was estimated to range from less than the detection limit to 0.0005 mg/kgbw/day. These bystander exposures to 2,4-D are >20,000-fold lower than the most conservative daily NOAEL of 10 mg/kgbw for dermal toxicity determined from subchronic animal studies (624).

Immunotoxicity The available animal and human studies do not provide evidence that 2,4-D adversely affects the immune system nor does it act as a dermal sensitizer (624).

Thyroid The reported effects of 2,4-D on the rodent thyroid following administration at high doses in the subchronic and chronic studies are considered to be of no relevance to humans. This conclusion was based on the known differences between rodents and humans with respect to thyroid hormone carrier proteins, thyroid hormone turnover, TSH levels, and responsiveness to goitrogens and/or anti-thyroid substances. Also supporting this conclusion were data indicating that thyroid effects in rodents occur only at doses that are at, or exceed, the capabilities of clearance mechanisms (624).

Testes and Ovaries No definitive human studies are available describing potential effects of 2,4-D exposure on the testes or ovaries (624). An exhaustive series of animal studies provide strong evidence that 2,4-D does not adversely affect the testes or ovaries under recommended conditions of use.

13.4.2 Human Experience 13.4.2.1 General Information The phenoxy herbicides are low in toxicity to humans and animals (636, 637). No scientifically documented human health risks, either acute or chronic, exist from the approved uses of phenoxy herbicides, including 2,4-D. Acute toxicity to humans, based on oral, dermal, ocular, or inhalation administration, may vary with the 2,4-D formulation. However, phenoxy herbicides have been used widely by numerous individuals (637) from homeowners to farmers and ranchers, and even with significant exposure, humans have shown essentially no acute toxicity (624).

13.4.2.2 Clinical Cases See section 13.4.2.1

13.4.2.2.1 Acute Toxicity: See section 13.4.2.1

13.4.2.2.2 Chronic and Subchronic Toxicity: NA

13.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Absorption After dermal application of ^{14}C-2,4-D to the forearm of five male volunteers, 5.8% of the dose was absorbed within 120h (610, 638). When the acid and its dimethylamine salt (DMA) were applied to the back of the hand, 4.5% of the acid and 1.8% of the salt were absorbed, and of this 85% of the acid and 77% of the salt were recovered in the urine within 96 hours after application (639). The rate of excretion depends on the dose. Excretion of 2,4-D is through the organic acid transport system in the kidney (624). Low doses of 2,4-D are excreted more rapidly than high doses, which can saturate this active kidney transport

system. Munro et al. (624) point out that the doses of 2,4-D that most humans are exposed to should be below doses that saturate active kidney transport. Therefore, they suggested the toxicologic results from animals treated with high doses of 2,4-D that saturate renal transport should be interpreted with caution because they may not be relevant to typical human exposures (624). Studies conducted in a variety of species show that, after oral dosing, 2,4-D is found in the liver, kidney, lung, and to a lesser extent in the brain (624). The distribution of 2,4-D through the human body appears to be similar to that in test species. When organs were examined following fatal poisonings (suicides), the highest levels of 2,4-D were found in kidney and liver, and lower levels are found in brain, muscle, and heart (625).

13.4.2.2.4 Reproductive and Developmental: NA

13.4.2.2.5 Carcinogenesis Collectively, the epidemiological and toxicological data show that 2,4-D is not likely to be carcinogenic in humans unless it is acting through an unknown mechanism that is not evident in animals. According to the calculated RfD and data from exposure studies, the general public should not experience toxic effects from exposure to 2,4-D. Because workers involved in the manufacture or application of 2,4-D may be exposed to levels above the RfD, appropriate protective equipment should be used (640).

13.4.2.2.6 Genetic and Related Cellular Effects Studies: NA

13.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, *etc* Neurotoxicity Some case reports have suggested an association between exposure to 2,4-D and the development of nervous system effects ranging from peripheral polyneuropathy and reduced nerve conduction velocity to depression, anxiety, and other symptoms of post-traumatic stress syndrome in Vietnam veterans (624). In test animals, doses of 2,4-D above 100 mg/kg can cause myotonia of the skeletal muscle (624), and oral doses above 150 mg/kg of 2,4-D can damage the blood–brain barrier (641). Toxicologic studies in rats and rabbits indicate, however, that neurotoxic effects of 2,4-D do not occur at doses below those that saturate the kidney transport system. Therefore, neurotoxic effects would only be expected to occur at high doses of 2,4-D.

13.4.2.3 Epidemiology Studies 13.4.2.3.1 Acute Toxicity See section 13.4.1.1.

13.4.2.3.2 Chronic and Subchronic Toxicity See section 13.4.1.2.

13.4.2.3.3 Pharmacokinetics, Metabolism, and Mechanisms See section 13.4.1.3.

13.4.2.3.4 Reproductive and Developmental See section 13.4.1.4.

13.4.2.3.5 Carcinogenesis: See section 13.4.1.5. The following observations are also germane.

Epidemiological studies have suggested an association between the development of non-Hodgkin's lymphoma and exposure to chlorophenoxy herbicides, including 2,4-D. The results of these studies are not consistent; the associations found are weak, and conflicting conclusions have been reached by the investigators. Most of the studies did not provide information on exposure specifically to 2,4-D, and the risk was related to the general category of herbicides. Case-control studies provide little evidence of an association between the use of 2,4-D and non-Hodgkin's lymphoma. Cohort studies of exposed manufacturing workers have not confirmed the hypothesis that 2,4-D causes this neoplasm (642). Findings of three agencies are as follows:

IARC. A working group convened by the International Agency for Research on Cancer (643) concluded that there was limited evidence that chlorophenoxy herbicides are carcinogenic to humans. 2,4-D could not be clearly distinguished from the chlorophenoxy herbicides.

Canada. The Ontario Pesticide Advisory Committee of the Ontario Ministry of the Environment

(644) concluded that “there is limited evidence of carcinogenicity in man from exposure to phenoxyacetic acid herbicides. In terms of exposure to 2,4-D specifically, the evidence must still be regarded as inadequate to classify it as a carcinogen.”

Harvard School of Public Health. A panel at the Harvard School of Public Health (645, 646) concluded: “Although a cause-effect relationship is far from being established, the epidemiological evidence for an association between exposure to 2,4-D and non-Hodgkin's lymphoma is suggestive and requires further investigation. There is little evidence of an association between 2,4-D use and any other form of cancer.”

13.4.2.3.6 Genetic and Related Cellular Studies. See section 13.4.1.6.

13.4.2.3.7 Other: Neurological, Pulmonary, Skin Sensitization, etc See section 13.4.1.7. The following findings are also relevant.

Dermal There are no studies reported in the epidemiological literature directly linking 2,4-D with dermal effects in humans. One report (647) provides evidence of a possible association, but the effect reported may be attributable to other factors. Caution must be exercised in the interpretation of epidemiological data because exposure cannot be quantified, and exposures to mixtures of herbicides or solvents cannot be excluded. The only evidence for dermal sensitization to 2,4-D is based on a group of 30 farmers, all of which were already diagnosed with contact dermatitis (648). Although three of this group reported positive patch test results for 2,4-D, the interpretation of this study is confounded by preexisting dermal conditions of unknown origin.

Immunotoxicity Current epidemiology studies do not provide evidence that 2,4-D affects the immune system of humans (624). A study conducted in farm workers applying a mixture of 2,4-D and 4-chloro-2-methylphenoxyacetic acid (MCPA) suggested that phenoxy herbicides may exert short-term immunosuppressive effects (649). Since this study did not include a control group matched to the same work conditions (*i.e.*, normal variations in immune system parameters were not characterized), and also did not provide any information on actual worker exposure to 2,4-D, the results are uninterpretable.

13.5 Standards, Regulations, or Guidelines of Exposure:

Absorption. Based on dermal absorption data from a ^{14}C-labeled 2,4-D acid human study (638) EPA set maximum absorption at 5.8% (610).

Acute Dietary Endpoint (1-day exposure). Dose and endpoint for use in risk assessment: NOEL = 67 mg/kg per day (610).

Short-Term Occupational or Residential Exposure (1–7 days). Dose and endpoint for use in risk assessment: NOEL = 30 mg/kg per day (610).

Intermediate-Term Occupational or Residential Exposure (1 week to several months). Dose and endpoint for risk assessment: NOEL = 1 mg/kg per day (610).

Chronic Occupational or Residential Exposure (several months to lifetime). Dose and endpoint for risk assessment: NOEL = 1 mg/kg per day (610, 614).

Inhalation Exposure (any time period). Exposure via inhalation is not a concern based on the LC_{50} = >1.79 mg/L. This risk assessment will not be required by EPA (610).

Air. NIOSH/OSHA Occupational Health Guideline for 2,4-D is 10 mg 2,4-D/m^3 air averaged over an 8-h shift (611). (ACGIH TLV TWA = 10 mg/m^3; NIOSH REL IDLH value = 100 mg/m^3).

Water. EPA drinking-water regulations and health advisory lifetime standard for 2,4-D: 0.070 mg/L (ppm) (612).

13.6 Studies on Environmental Impact
Terrestrial Environment

Soil. As part of the 2,4-D EPA reregistration process in the Unites States, 30 soil dissipation studies were conducted with 2,4-D dimethylamine salt (2,4-D DMA) and 2,4-D 2-ethylhexyl ester (2,4-D 2-EHE) over a 2-year period. The data from the current and former studies show that ester and amine forms have little effect on the rate of dissipation of 2,4-D *per se* because they are converted rapidly to the same anionic form. The average half-life ($t_{½}$) in the soil is 4.4 days for 2,4-D DMA and 5.1 days for 2,4-D 2-EHE (650).

Groundwater. The rapid dissipation of 2,4-D in soil and its affinity to attach to soil colloids significantly reduce the potential for downward movement. 2,4-D is not expected to be a concern for groundwater contamination (607).

Microorganisms. The most significant routes of exposure of soil microorganisms to 2,4-D are likely to be from its use by ground or aerial applications. Data from laboratory studies indicate that the risk to soil microorganisms should be low even at excessive application rates of 7.4 and 18.75 kg 2,4-D/ha (651, 652).

Bees. Honeybees may be exposed to 2,4-D by foraging flowering weeds present in treated crops. Oral and contact LD_{50} study values for 2,4-D DMA and 2,4-D 2-EHE were all >100 mg/bee, which is considered low bee toxicity (651, 652).

Earthworms. Earthworms may be exposed from either single or multiple applications of 2,4-D to a wide variety of crops but in particular from its use on grass, fallowland, and stubble. A 14-day LC_{50} study exposed earthworms to 2,4-D DMA at 350 mg/kg soil, with no mortality noted at concentrations less than or equal to 100 mg a.e./kg. The risk to earthworms from the use of 2,4-D is low (651, 652).

Birds. The risk to birds based on foraging on grass or insects is considered low. The acute avian LD_{50} values range from 200 to >2000 mg/kgbw for mallards, bobwhite quail, Japanese quail, pheasants, partridges, and doves. Dietary LC_{50} values exceed 4640 mg/kg diet for mallards, bobwite quail, Japanese quail, and pheasants. At doses greater than recommended application rate, 2,4-D did not adversely affect the reproductive performance of pheasants, quail, partridges, or chickens (651, 652).

Aquatic Environment

Bioaccumulation. There was no evidence of bioaccumulation of 2,4-D in aquatic organisms (651, 652).

Fish. The main risk to aquatic organisms from the use of 2,4-D is from overspray during aerial use, spray drift from ground-based applications, or use to control aquatic weeds. Because of the very rapid degradation of the salts and esters of 2,4-D in water, the long-term risk to aquatic organisms is considered to be low. Embryos and larvae of fathead minnow, were exposed to up to 416.1 mg/L of 2,4-D ester for 32 days; the NOEC was 80.5 mg/L. Generally, 2,4-D and its salts are less toxic to fish than are the esters. Typical 96 h LC_{50} values for adult fish were 5–10 mg acid equivalentsa.e./L for the ester, 200–400mga.e./L for 2,4-D, and from 250–500 mg a.e./L for 2,4-D salts (651, 652). Highest applications in water are expected to be approximately 2 ppm for weed control. Significant safety margins exist between maximum water concentration and toxic levels to fish.

Amphibians. Frog and toad tadpole 96 h LC_{50} values ranged from 8 mg/L for 2,4-D 2-EHE (maximum solubility of ester) to 477 mg/L for the 2,4-D DMA salt. No effects were noted, indicating that 2,4-D is considered low toxicity to amphibians (651, 652).

Phenol and Phenolics

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14.0 Pentabromophenol
14.0.1 CAS Number:
[*608-71-9*]
14.0.2 Synonyms:
Pentabromohydroxybenzene
14.0.3 Trade Names:
NA
14.0.4 Molecular Weight:
488.59
14.0.5 Molecular Formula:
C_6HBr_5O
14.0.6 Molecular Structure:

14.1 Chemical and Physical Properties
14.1.1 General

Physical	Light brown powder; monoclinic prisms or needles
Melting point	229.5°C
Solubility	Insoluble in water; miscible in ether, hot alcohol, benzene (653).

14.2 Production and Use
Flame retardant, molluscicide, and chemical intermediate.
14.3 Exposure Assessment:
NA
14.4 Toxic Effects
14.4.1 Experimental Studies 14.4.1.1 Acute Toxicity The approximate (oral) LD_{50} in the rat of pentabromophenol is slightly more than 200 mg/kg when administered as the sodium salt in aqueous solution. The signs and symptoms from pentabromophenol included increased respiratory rate and amplitude with general body tremors, occasional convulsions, and death (13).

14.4.1.2 Chronic and Subchroic Toxicity Sodium and copper pentachlorophenate were given in drinking water to three young bulls at a daily dosage of 7.6 mg/kgbw for 5 weeks. No significant signs of intoxication and no micropathological changes were noted (13).

14.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms These compounds are rapidly absorbed from the gastroenteric tract (13).
14.5 Standards, Regulations, or Guidelines of Exposure:
NA
14.6 Studies on Environmental Impact
The EC_{50} for *Pimephales promelas* (fathead minnow) was 93.0 mg/L for 96 h. The effect was loss of

equilibrium; the LC_{50} for *P. promelas* was 93.0 mg/L for 96 h (654).

Phenol and Phenolics

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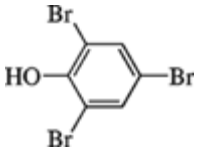
15.0 2,4,6-Tribromophenol
15.0.1 CAS Number:
[*118-79-6*]
15.0.2 Synonyms:
Bromol; tribromophenol
15.0.3 Trade Names:
Bromol
15.0.4 Molecular Weight:
330.82
15.0.5 Molecular Formula:
$C_6H_3Br_3O$
15.0.6 Molecular Structure:



15.1 Chemical and Physical Properties

Appearance	Long, soft white crystals
Specific gravity	2.55 at 20°C
Density	2.55 g/mL
Boiling Point	244°C
Melting point	95–96°C

Additional parameters were as follows:

Solubility. Water—excess amounts of ^{14}C-labeled 2,4-6-tribromophenol were shaken in a water bath at 35°C overnight. Samples were centrifuged at 15°C, 25°C or 35°C at 12,000g for 1 h. Solubility was determined by radioassay. Solubility (ppm): 996 (15°C), 969 (25°C), and 884 (35° C) (655).

Partition Coefficient. The *n*-octanol/water coefficient of radiolabeled 2,4,6-tribromophenol was 2198 (log 10 = 3.342) (655).

Photolysis. A photolysis study using ^{14}C-labeled 2,4,6-tribromophenol was conducted on silica-gel TLC plates under UV light. The half-life was estimated to be 4.6h. The disappearance of 2,4,6-tribromophenol followed apparent first-order kinetics. A degradation product was tentatively identified as 2,6-dibromo-3,5-dihydroxy-*p*-quinoimine (655).

15.1.1 General: NA

15.1.2 Odor and Warning Properties 2,4,6-Tribromophenol has a penetrating bromine odor.
15.2 Production and Use
2,4,6-Tribromophenol is produced by the controlled bromination of phenol (655).
15.3 Exposure Assessment:
NA
15.4 Toxic Effects
15.4.1 Experimental Studies 15.4.1.1 Acute Toxicity Ingestion Single doses of 2,4,6-tribromophenol in 0.5% Methocel (hydroxypropylmethylcellulose) were administered by intubation to groups of five male and five female rats each at levels of 1585, 2512, 3980, 6308, 10,000, and 15,848 mg/kg. Reactions noted between 0 and 4 h after dosing at ≥6308 mg/kg included decreased motor activity, tachypnea, tachycardia, ataxia, and tremors. There were no effects on body weight. Death occurred between 0 and 4 h on the day of the dosing. The oral LD_{50} values (with 95% confidence limits) in mg/kg were 5012 (4034–6227) in males and females and 5012 (4178–6013) for males and females combined (655).

Three groups of five male rats each received single oral doses of 2,4,6-tribromophenol suspended in corn oil at levels of 50, 500, and 5000 mg/kg. All rats died at 5000 mg/kg within 24 h of treatment. 2,4,6-Tribromophenol was considered toxic but not highly toxic by the oral route of administration (655).

Groups of five male and five female rats received single oral doses by gavage of 2,4,6-tribromophenol suspended in corn oil. Levels tested were 631, 1000, 1585, 2512, 3980, and 6308 mg/kg. Deaths occurred on the day of dosing (0–4h) and on day 1. The oral LD_{50} values (with 95% confidence limits) in mg/kg were 1995 (1728–2304) in males and 1819 (1513–2187) in females. The combined male–female value was 1905 (1738–2089) (655).

Dermal Administration A single topical application of 8000 mg/kg of 2,4,6-tribromophenol to the shaved backs of two male and two female New Zealand white rabbits was used to evaluate dermal toxicity. The skin of one rabbit of each sex was abraded while the skin of the other remained intact. Afer application of 2,4,6-tribromophenol, the sites were wrapped with occlusive dressings for 24 h. Following the exposure period, the wrappings were removed and the area washed with tepid tap water. There were no effects on body weights or survival during the 14-day observation period. The dermal LD_{50} for 2,4,6-tribromophenol in rabbits is >8000 mg/kg (655).

A single topical application of either 200 or 2000 mg/kg of 2,4,6-tribromophenol was administered to two groups of four New Zealand white rabbits each. The trunks of the animals were then wrapped for a 24 h exposure. There were no deaths. 2,4,6-Tribromophenol was not considered to be toxic by the dermal route of administration (655).

Inhalation A single group of five male and five female rats was exposed to a dust atmosphere of 2,4,6-tribromophenol at an analytical concentration of 1.63 mg/L for 4h. Reactions noted during exposure were ptosis and red nasal discharge. All rats survived the 14-day observation period. The inhalation LC_{50} was reported as >1.63 mg/L (655).

One group of five rats per sex was exposed to a dust atmosphere of 2,4,6-tribromophenol at 50 mg/L (highest attainable concentration). During exposure, reactions noted included decreased motor activity, eye squint, slight dyspnea, erythema, and ocular porphyrin discharge. At 24 h, diarrhea, ocular porphyrin discharge, and slight dyspnea were noted. Some of the observations continued for most of the 14-day observation period. The inhalation LC_{50} was calculated as >50 mg/L (655).

Groups of 10 male rats each were exposed to dust atmospheres of 2,4,6-tribromophenol at either 2 or 200 mg/L for 1 h. Reactions noted during exposure were eye squint, increased followed by decreased respiration, prostration, nasal discharge, lacrimation, erythema, decreased motor activity, and salivation. No deaths occurred. 2,4,6-Tribromophenol was not considered to be toxic by the inhalation route of administration (655).

Eye Irritation The potential of 2,4,6-tribromophenol to produce eye irritation was evaluated in rabbits in accordance with regulations of the Federal Hazardous Substances Act (FHSA). A single application of 100 mg of 2,4,6-tribromophenol was placed into the conjunctival sac of the right eye of each of three male and three female New Zealand white rabbits. Eyes were scored for irritation at 24, 48, and 72 h and at 7 days post-instillation according to the method of Draize. Instillation elicited slight to moderate conjunctival redness in four of six rabbits at 24 h, six of six rabbits at 48h, and slight redness in one of six rabbits at day 7. Very slight to slight chemosis and very slight to marked discharge were observed in four of six rabbits at 48h. Dulling of the cornea was observed in one of six rabbits at 48 and 72h. Examination with fluorescein and UV light at 72 h indicated slight corneal damage in five of six rabbits. 2,4,6-Tribromophenol was considered an eye irritant (655).

Additionally, 100 mg of 2,4,6-tribromophenol was instilled into the conjunctival sac of three male and three female New Zealand white rabbits. Conjunctival and iridal irritation was observed. Very slight opacity was noted at 24 h, and dulling of the cornea at 48 h was noted in one rabbit. Fluorescein examination under UV light revealed corneal damage in one rabbit at the 72 h examination. 2,4,6-Tribromophenol was considered a moderate eye irritant (655).

Primary Skin Irritation 2,4,6-Tribromophenol was evaluated for primary skin irritation in rabbits in accordance with the regulations of the Federal Hazardous Substances Act (FHSA). A single application of 500 mg of 2,4,6-tribromophenol was made to the shaved backs of three male and three female New Zealand white rabbits (skin was abraded on three rabbits) and the sites occluded for 24 h. Sites were scored for irritation at 24 and 72 h post-application. The primary irritation score was 0.3. 2,4,6-Tribromophenol was not considered a primary irritant, nor was it expected to pose a corrosive hazard (655).

15.4.1.2 Chronic and Subchronic Toxicity 28-Day Dermal Toxicity 2,4,6-Tribromophenol was evaluated for toxicity in a 28-day dermal study with New Zealand white rabbits. The material was ground to a fine powder and prepared as a suspension in 1.0% (w/v) aqueous methylcellulose. The material suspensions and control (1000 mg/kg aqueous methylcellulose) were applied topically to the clipped unoccluded skin. Groups consisted of four rabbits each (2/sex/group with the skin of two males and two females/group abraded). Doses were applied 5 days/week for 4 weeks (20 applications) at levels of 100, 300, and 1000 mg/kg. One rabbit died after 15 applications. The cause of death could not be determined. There were no pharmacotoxic signs, but 2,4,6-tribromophenol was slightly irritating to the skin following repeated exposure. No effects on body weight, hematology, clinical chemistry, urinalysis, and organ weights and ratios were produced. Microscopically, dose-related lesions were noted at the treated skin sites. The lesions consisted of epidermal acanthosis and hyperkeratosis, and were accompanied by multifocal to diffuse inflammatory infiltrates (655).

21-Day Dust Inhalation Toxicity 2,4,6-Tribromophenol was evaluated for toxicity in a 21-day dust inhalation study. Two groups of five male and five female rats were exposed to dust atmospheres of 2,4,6-tribromophenol for 6 h/day, 5 days/week (15 exposures). A concurrent control received no dust exposures. Test concentrations were 0.1 and 0.92 mg/L. One male and one female at 0.92 mg/L died after 10 and 11 exposures, respectively. Reactions noted in treated groups included hypoactivity, salivation, lacrimation, and red nasal discharge. Body weight gain of high level males and females were lower than that of the controls. No effects were noted in hematology, clinical chemistries, and urinalysis evaluations. At necropsy, four of five males and all females from the high exposure group were emaciated. In the high test concentration, tan discoloration was observed on the kidney of one male and an area described as fibrotic was observed in the liver of one female. Histopathologic evaluation revealed dilation of the renal tubules in three of five animals of each sex and a solitary

area of hepatic necrosis in one female. The changes were considered to be related to treatment (655).

15.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The rates of absorption, distribution, and excretion of 2,4,6-tribromophenol were determined in rats. Single oral doses of radiolabeled 2,4,6-tribromophenol were administered and animals sacrificed at various intervals post-treatment. 2,4,6-Tribromophenol was rapidly absorbed. The bulk of radioactivity (77.0%) was readily excreted in the urine and 2–14% eliminated in the feces within 48h. Blood concentrations peaked at 4.57 ppm after 1 h and plunged to 0.002 ppm by 24 h. The only detectable residues after 48 h were in the kidneys, liver, and lungs. The pharmacokinetics appeared to follow a one-compartment open-model system. 2,4,6-Tribromophenol was rapidly distributed in the body, and the rate of elimination in urine was proportional to the concentration in the blood. The rate constant for elimination (K_e) was 0.3 and the $t_{½}$ in the blood was 2.03h. The results indicate that 2,4,6-tribromophenol should be neither persistent nor accumulative in mammalian systems (655).

Bioaccumulation in Fat Tissue Six test groups of five rats each and six control groups of three rats each were used. In all test groups 2,4,6-tribromophenol was fed at 1000 ppm. Increases in fat residue content were noted after 7 days of feeding. Small quantities of residue were found in fat tissue of animals allowed a 7-day recovery after 7 days of feeding. Animals fed 21 days showed similar increases in fat residues as animals fed for 7 days. However, no detectable residues were noted in animals allowed recovery of 14 days or longer (655).

15.4.1.4 Reproductive and Developmental 2,4,6-Tribromophenol was ground with a mortar and pestle, suspended in corn oil, and administered via gavage to groups of five female rats each. Test concentrations of 0 (corn oil), 10, 30, 100, 300, 1000, and 3000 mg/kg were administered on days 6–15 of gestation. All animals were sacrificed on day 20 of gestation. All females died after 1 day of treatment at 3000 mg/kg. Slight decreases in body weight gains between days 6 and 12 of gestation, an increase in post-implantation loss, and slight decrease in the number of viable fetuses were noted at 1000 mg/kg. The maximum dose suggested for a teratology study was 1000 mg/kg (655).

Lyubimov et al. (656) exposed Wistar rats to 2,4,6-tribromophenol by whole-body inhalation at concentrations of 0.03, 0.1, 0.3, and 1.0 mg/m^3, 24 h/day, 7 days/week from day 1 to 21 of gestation. Significant decreases were observed in orientation reactions at a concentration of 1.0 mg/m^3. Nonsignificant trends toward decreased horizontal movement and emotionality in the open field and increased electrical impulse skin pain threshold were observed. Preimplantation and postimplantation embryo losses were significantly increased in a dose-dependent manner and were seen at all concentrations except the lowest (0.03 mg/m^3). Significant effects were found for lower incisor eruption and ear unfolding at 0.3 mg/m^3. Grooming behavior was decreased in males at all concentrations and in females at 0.3 mg/m^3. The NOEL for developmental neurotoxicity in this study was >0.03 mg/m^3. The results of this study suggest that 2,4,6-tribromophenol may cause developmental neurotoxicity, embryotoxicity and fetal toxicity.

15.4.1.5 Carcinogenesis: NA

15.4.1.6 Genetic and Related Cellular Effects Studies 2,4,6-Tribromophenol was evaluated for mutagenicity in the *Salmonella*/microsome assay using *S. typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *Saccharomyces cerevisiae*, strain D4 with and without metabolic activation. 2,4,6-Tribromophenol was not mutagenic in any strain tested (657).

15.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization The potential of 2,4,6-tribromophenol to produce dermal sensitization was evaluated in guinea pigs. Doses were administered by intradermal injections in the right flank of 8 guinea pigs every other day 3 days/week, until 10 induction doses were given. 2,4,6-Tribromophenol was administered as a 1% solution in 0.9%

sodium chloride (NaCl). a concurrent positive control, DNCB (dinitrochlorobenzene), was administered to a group of four guinea pigs using the same regimen, and 0.9% NaCl solution was administered in a like manner to the left flank of each animal. The first sensitizing dose was administered at a volume of 0.05 and 0.1 mL for the remaining nine doses. The challenge dose (0.05 mL) was administered 2 weeks after the last dose. Four of eight 2,4,6-tribromophenol-treated animals exhibited a flare response that was slightly greater than that seen during the induction phase. 2,4,6-Tribromophenol was considered to be potentially sensitizing in humans, producing slight sensitization in the occasionally susceptible individual (655).

15.5 Standards, Regulations, or Guidelines of Exposure:

NA

15.6 Studies on Environmental Impact

First-instar (24-h-old) daphnids were exposed to 2,4,6-tribromophenol at concentrations of 1.8, 3.2, 5.6, 10.0, and 18 ppm for 48 h under dynamic conditions. A solvent control (acetone) and untreated control were run concurrently. Four vessels containing five *Daphnia* each were used for each test and control group. The 48 h median tolerance limit (TL_{50}) was 5.5 (4.4–7.0) ppm (655).

2,4,6-Tribromophenol was tested in two species of fish (trout—0.18, 0.21, 0.24, 0.28, 0.32 ppm; bluegill—0.18, 0.24, 0.32, 0.42, 0.56 ppm). Static bioassays were conducted at 10°C for trout and 18°C for bluegill. Each group (control untreated and acetone solvent control) consisted of 10 fish each. Rapid or shallow respiration was noted in trout at all concentrations; quiescence was noted at concentrations of ≥0.21 ppm; and loss of equilibrium, lying on bottom of the vessel, and dark discoloration were noted at concentrations of 0.24 ppm and above. The median tolerance limit [TL_{50}] value for trout was 0.24 ppm. At concentrations of ≥0.24 ppm, bluegills exhibited quiescence and flaccid and dark discoloration. Fish at 0.42 and 0.56 ppm displayed loss of equilibrium, shallow respiration, and lying on the bottom of the vessel. The median tolerance limit [TL_{50}] value for bluegills was 0.28 ppm.

Bluegills were exposed to radiolabeled 2,4,6-tribromophenol in a flow-through bioassay. The fish were exposed to a concentration of 0.0092 ppm for 28 days followed by a 28-day withdrawal period. Samples of water and edible tissue and viscera were taken and analyzed periodically. Bioaccumulation in the edible tissue was 20-fold and viscera 140-fold over the concentration in the water. The plateau levels in the edible tissue and viscera were reached in 3–7 days of exposure. The half-life for radiolabeled carbon residue (withdrawal phase) was <24 h in both the edible tissue and viscera (655).

Oxygen uptake by microorganisms was measured in the presence of 2,4,6-tribromophenol using the Warburg respirometer. The biological seed culture was prepared from fresh sewage and topsoil. Nine concentrations were tested: 1, 10, and 100 ppb; 1, 10, and 100 ppm; and 0.1, 1.0, and 10%. Incubation was at ambient temperatures (water bath at 23°C) with constant shaking for 96h. Test concentrations of 100 ppm, 0.1, 1.0, and 10% exhibited slight inhibition of microbial respiration. After 96h, the average oxygen uptake in samples with concentrations ranging from 1 ppb to 10 ppm was 26.5 mg O_2/L media. Amount O_2 utilized in control (seeded dilution water) was 21.1 mg/L. The highest volume of absorbed oxygen was 75.9 mg/L with 1 ppm glucose (PC). Concentrations of oxygen at 100 ppm, 0.1, 1.0, and 10% TBP were decreased, indicating inhibited endogenous respiration (655).

Phenol and Phenolics

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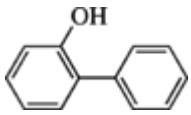
16.0a **o**-Phenylphenol (OPP)
16.0.1a CAS Number:
[*90-43-7*]
16.0.2a Synonyms:
2-Phenylphenol; 2-hydroxybiphenyl; orthoxenol; 2-biphenylol; 1,1'-biphenyl-2-ol; (1,1'-biphenyl)-2-ol; orthohydroxydiphenyl; biphenyl-2-ol; biphenylol; hydroxydiphenyl; hydroxy-2-phenylbenzene; hydroxybiphenyl; OPP; phenylphenol; *o*-biphenylol; *o*-hydroxybiphenyl
16.0.3a Trade Names:
Dowicide 1, Preventol O Extra
16.0.4a Molecular Weight:
170.21
16.0.5a Molecular Formula:
$C_{12}H_{10}O$
16.0.6a Molecular Structure:



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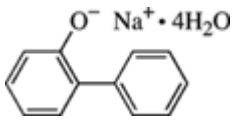
16.0b Sodium **o**-Phenylphenate (SOPP) and its tetrahydrate (SOPP · $4H_2O$)
16.0.1b CAS Number:
[*132-27-4*] and [*6152-33-6*] respectively.
16.0.2b Synonyms:
2-Biphenylol, sodium salt; 2-phenylphenol sodium salt; sodium *o*-phenylphenoxide; [1,1'-biphenyl]-2-ol, sodium salt; OPP-NA; 2-hydroxybiphenyl sodium salt; orphenol; *o*-phenylphenol, sodium derivative; Preventolon; (2-biphenylyloxy)sodium; sodium *o*-phenylphenolate; SOPP; biphenylol, sodium salt; hydroxydiphenyl, sodium salt; phenylphenol, sodium salt
16.0.3b Trade Names:
Dowicide A, Preventol ON Extra
16.0.4b Molecular Weight:
192.19
16.0.5b Molecular Formula:
$C_{12}H_9NaO$
16.0.6b Molecular Structure:



16.1 Chemical and Physical Properties
16.1.1 General 16.1.1.1 Melting Points OPP: 57°C; SOPP · $4H_2O$: 298°C (loss of water at 120°C)

16.1.1.2 Solubility (g/kg solvent at 20°C):

	OPP	SOPP·$4H_2O$
Water	0.76 (pH 5.67)	534 (pH 13.61)
Methanol	500	526
Acetone	479	543
Acetonitrile	532	531
Octanol	529	439
Toluene	466	0.53
Hexane	48.6	0.047

16.1.1.3 Vapor pressure (at 25°C)

OPP: 1.62×10^{-3}mmHg or 2.16×10^{-4}kPa
SOPP: 1.8×10^{-9}mmHg or 2.4×10^{-10}kPA

16.1.1.4 Partition Coefficient (Octanol/Water)

OPP: $\log_{10}K_{ow} = 3.0$ at pH 7

16.1.1.5 Dissociation Constant

SOPP: $pK_a = 9.84$ (20°C), pH of 1% solution = 11.2–11.6

16.1.1.6 Appearance

OPP: White to pink solid or crystals
SOPP: Available only as the tetrahydrate
SOPP · $4H_2O$: White to buff solid or flakes

16.1.1.7 Stability

OPP: Stable to hydrolysis and photolysis
SOPP · $4H_2O$: Dissociates in water to OPP^- and Na^+

16.1.2 Odor and Warning Properties

OPP: Phenolic odor
SOPP · $4H_2O$: Strongly alkaline solution in water

16.2 Production and Use
OPP is produced as a by-product in the manufacture of diphenyloxide or by aldol condensation of hexazinone. Current global production is estimated to be less than 10 millionlb per year. Chief uses of products containing OPP are as disinfectants, antimicrobials, preservatives, antioxidants, and sanitizing solutions in various industries.

SOPP is produced as its tetrahydrate by reaction of OPP with NaOH, followed by flaking. This water-soluble form is used primarily for sanitation of equipment and for postharvest treatment of fresh fruits and vegetables to control microbial and fungal infections during prolonged storage and distribution worldwide.
16.3 Exposure Assessment
16.3.1 Air No exposure limits established by OSHA, ACGIH, or NIOSH

16.3.2 Background Levels: NA

16.3.3 Workplace Methods: NA

16.3.4 Community Methods: NA

16.3.5 Biomonitoring/Biomarkers 16.3.5.1 Blood: NA

16.3.5.2 Urine OPP is rapidly and almost completely excreted in urine as water-soluble conjugates that can be quantitated using any of several chromatographic methods (658, 659). In an occupational exposure study, 11 volunteers were treated with 10 consecutive 3- mL applications of an undiluted hand disinfectant containing 2% OPP. Each time, the formulation was rubbed on the hands for 1 min, then water was added and the hands were rinsed under running water for 30s before drying on a paper towel. Total 24-h urine samples were collected over a 4-day period after treatment and were analyzed by steam distillation followed by gas chromatography. The total OPP excreted by the 11 subjects ranged from 2.95 to 7.22 mg, with an average of 4.45 mg on the first day, 1.08 mg on the second day and only traces on the third and fourth days. Since the total OPP applied was ~600 mg, most was washed off and only about 1% was absorbed through the skin under the conditions of this study (660).
16.4 Toxic Effect
16.4.1 Experimental Studies 16.4.1.1 Acute Toxicity OPP is slightly toxic, with reported oral LD_{50} values of 1100–3500 mg/kg in male and female mice, and 2600–2800 mg/kg in male and female rats. It is essentially nonirritating to skin but may cause moderate eye irritation and corneal injury. The dermal LD_{50} of OPP is >5 g/kg in rabbits. Repeated applications did not cause delayed hypersensitivity in guinea pigs (658, 659).

The sodium salt (SOPP) is slightly more toxic, with LD_{50} values of 800–900 mg/kg bw in male and female mice, and 850–1700 mg/kgbw in male and female rats. It can cause severe skin burns and severe eye irritation with corneal injury due to its high alkalinity; a 1% solution of SOPP has a pH of 11.2–11.6 (658, 659).

16.4.1.2 Chronic and Subchronic Toxicity OPP and its sodium salt (SOPP) have been studied extensively in Japan, Germany, and the United States as required for pesticide registration and reregistration. Only subchronic and chronic studies with OPP are reviewed here; humans are not exposed to SOPP in the diet, such as on washed fruit, because it readily hydrolyses to OPP during the fungicidal treatment. The many feeding studies conducted with SOPP at high levels in the diet of rats are considered to be of little relevance for the assessment of potential toxicity in humans

exposed to low levels of OPP (658, 659).

16.4.1.2.1 Subchronic Toxicity Two similar short-term studies were conducted in Japan in which groups of 10–12 rats of each sex were fed OPP at dietary levels of 0.125 or 0.156, 0.313, 0.625, 1.25, and 2.5% for 12 or 13 weeks. The dietary NOEL was 0.625% in each study, reported to be equivalent to a dose level of ~780 mg/kgbw per day in one study (661) and to ~420 mg/kgbw per day in the other (662). Body weights and body weight gains were severely depressed in males and females fed 2.5% OPP in the diet. Only 73% of males survived compared to 92% of females at this high dietary level equivalent to a dose level of ~2500 mg/kgbw per day, and all rats in lower dose groups lived to the end of these short-term studies. Absolute and relative weights of many organs were depressed in male rats fed 2.5% OPP, and proliferative lesions of the urinary bladder and slight nephrotoxic lesions were noted (662).

In a U.S. study, 30 male rats were fed a diet containing 2% OPP (~1250 mg/kgbw daily) and were sacrificed at intervals for ≤90 days. Food consumption was greatly reduced with consequent weight loss during the first week, which improved but remained somewhat depressed throughout the study. Seven of the rats died of apparent malnutrition. Observations included small amounts of blood in the urine, significantly decreased urine specific gravity at 65 and 90 days, increased sizes of liver and kidneys, and discolored focal areas of the kidneys at the end of the study. On microscopic examination slightly swollen liver cells were seen, as well as signs of kidney pathology that were not considered severe enough to seriously impair renal function and did not increase in severity on days 30–90 of treatment. No treatment-related urinary bladder lesions were seen in this study (663).

16.4.1.2.2 Chronic Toxicity Groups of 50 mice of each sex were fed diets to provide dose levels of 0, 250, 500, and 1000 mg/kgbw daily for 2 years. Satellite groups of 10 mice/sex/dose level were sacrificed at 1 year for evaluation of general chronic toxicity. In-life observations, mortality, hematology, clinical chemistry, and urinalyses were not affected. Significantly decreased body weights and body weight gains were noted in all groups except low dose males. The primary target organ was the liver, based on increased absolute and/or relative weights at all dose levels, and on gross and histopathology. Microscopic changes in the liver suggested adaptation to OPP metabolism, associated with a statistically significant increased incidence of liver cell adenomas in middle and high dose males. No oncogenic effects were observed in low dose males or in females at any dose level. The minor effects observed in the low dose groups suggest that a long-term NOEL would likely be 100 mg/kgbw OPP daily in mice (664).

To confirm the adverse findings in male rats in short-term studies, several longer-term studies were conducted with OPP in Japan using small groups of male rats. In a 91-week study at dietary levels of 0.63, 1.25 and 2.5% OPP, survival rates and mean body weights were significantly lower in mid-dose and high-dose groups. Bladder tumors were seen in 23/24 males in the mid-dose group, but in only 4/23 of high dose group. Moderate to severe nephrotic lesions were found in 3/24 of the group fed 1.25% OPP and in all 23 of the male rats fed 2.5% OPP for 91 weeks (662). In another study, no tumors were induced when male rats were fed 2% OPP for 36 or 64 weeks, or 1.25% for 96 weeks followed by 8 weeks on untreated diet. In the latter 104-week study, only papillary or nodular hyperplasia of the bladder was seen in 3/27 male rats fed 1.25% OPP (665).

In a recent study conducted according to U.S. pesticide guidelines, groups of 70–75 rats of each sex per dose level were fed OPP at constant nominal dietary concentrations of 0, 0.08, 0.4, and 0.8% (males) or 1.0% (females). These levels were equivalent to average daily dose levels of 39/49, 200/248, and 402/647 mg/kgbw in male and female rats, respectively. Satellite groups of 20 rats/sex/dose level were sacrificed at 1 year to evaluate interim toxicity; remaining rats were sacrificed at 2 years to evaluate long-term toxicity and carcinogenicity. Food consumption remained unchanged, but mean body weights were decreased in mid-dose and high dose males and females. Increased mortality was noted in highdose males fed 0.8% but not in females fed 1.0% OPP. Clinical observations included abnormal urine color and various staining, and an increased incidence of blood in the urine of high dose males. Postmortem findings included wet/stained ventrum, urinary bladder

masses, and pitted zones and abnormal texture in the kidney. No effect on organ weights was noted. Histopathological findings in mid-dose and high dose males were characterized as structural alterations in the kidney and urinary bladder, including evidence of urothelial hyperplasia and/or neoplasia (papilloma and transitional-cell carcinoma). Neoplastic changes were not observed in high-dose females at a dose level ~60% higher than in males. The NOEL for systemic chronic toxicity was 0.08% OPP in the diet, equivalent to daily dose levels of 39 and 49 mg/kgbw in male and female rats, respectively (666).

16.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Extensive studies have been conducted in the United States and Japan on the metabolism of OPP in mice, rats, cats, and dogs given relatively high single or multiple oral doses. The results are compared in a recent publication, which also reports a metabolism study in human male volunteers exposed to a low dermal dose of radiolabeled OPP (667).

16.4.1.3.1 Absorption When single oral doses of 500 mg/kg of ^{14}C-OPP or ^{14}C-SOPP were given to male rats, both compounds were absorbed rapidly as demonstrated by recovery of ~90–95% of the radioactivity in urine and 5–6% in feces, chiefly in the first 24 h. The disposition of the radioactivity was not greatly affected by preconditioning the rats by feeding equimolar amounts of unlabeled OPP (1.3%) or SOPP · $4H_2O$ (2.0%) in the diet for 2 weeks before administration of the labeled compounds. SOPP appeared to be eliminated somewhat more rapidly than OPP (663).

16.4.1.3.2 Distribution OPP is distributed rapidly via enterohepatic circulation and does not bioaccumulate in tissues after either oral or dermal exposure in experimental animals (658, 659).

16.4.1.3.3 Excretion Absorbed OPP is excreted rapidly in urine primarily as the sulfate and glucuronide conjugates. Administration of high doses results in saturation of the sulfation pathway and some conversion of OPP to 2,5-dihydroxybiphenyl (phenylhydroquinone), which is also excreted as sulfate and glucuronide conjugates (663, 667).

16.4.1.4 Reproductive and Developmental In a reproduction study, groups of 30 rats of each sex were fed OPP at dietary concentrations to provide dose levels of 0, 20, 100 or 500 mg/kgbw daily over two generations. Animals in the high dose groups exhibited parental toxicity consisting of reduction in male and female body weights, urine staining in males, bladder calculi in males, and histological changes in the kidneys, bladder, and ureter of males. No reproductive effects were observed at any dose level. The parental and neonatal NOEL was 100 mg/kgbw per day, and the NOEL for reproductive effects was 500 mg/kgbw per day (659, 668).

A teratogenicity study was conducted in which groups of 25–27 female rats were bred and given daily doses of 100, 300, or 700 mg OPP/kgbw by gavage on days 6–15 of gestation. No evidence of maternal or fetal toxicity was produced by administration of the two lower dose levels. The high dose did not cause embryotoxic or teratogenic effects, but was slightly toxic to the dams as evidenced by decreased body weight gain and food consumption during the treatment period (659, 669).

Another teratogenicity study was conducted in groups of 16–24 artificially inseminated female New Zealand white rabbits by oral gavage of OPP in corn oil at targeted daily dose levels of 0, 25, 100, or 250 mg/kgbw on days 7–19 of gestation. The high dose caused increased mortality (13%), gross pathological alterations of the GI tract, and histopathological alterations of the kidneys. The NOEL for maternal toxicity was 100 mg/kgbw per day and the embryonal/fetal NOEL was 250 mg/kgbw per day, the highest dose level tested in rabbits (659, 670).

16.4.1.5 Carcinogenesis IARC classified SOPP as a B2 carcinogen in 1983, based on reports from Japan that high dietary levels of this sodium salt caused bladder tumors in male rats (671, 672). Both sodium saccharin and sodium cyclamate also cause bladder tumors at high doses in male rats, but

classification of these food additives as B2 carcinogens was recently rescinded by IARC at a meeting in 1998.

OPP was not classified by IARC because little published data were available when this form was evaluated in 1983 (671, 672). Since then, several conventional long-term studies have been conducted with OPP in both sexes of mice and rats. Groups of 50 mice/sex were fed dietary levels of OPP to provide dose levels of 0, 250, 500, or 1000 mg/kgbw daily for 2 years. The liver was identified as the target organ, with microscopic changes suggestive of adaptation to OPP metabolism. No oncogenic effects were observed in females at any dose level or in low dose males, but a statistically significant increased incidence of liver cell adenomas was seen in male mice given 500 or 1000 mg/kgbw daily for 2 years. These dose levels also caused significantly decreased body weights and body weight gains, indicating that the MTD had been exceeded (664). OPP was also administered to groups of 50 rats/sex/dose level at nominal dietary concentrations of 0, 800, 4000, and 8000 ppm in males and at 0, 800, 4000, and 10,000 ppm in females for 2 years. The equivalent dose levels in both male and female rats were reported to be 39/49, 200/248, and 402/647 mg/kg bw per day. No neoplastic changes were observed in females, including the high-dose group given 60% more than the high-dose males. Histopathological findings in mid-dose and high-dose males were characterized as structural alterations in the kidney and urinary bladder, including urothelial hyperplasia and/or neoplasia (papilloma and transitional cell carcinoma). A statistically significant increase in incidence of these neoplasms was seen only in male rats given 402 mg OPP/kgbw daily for 2 years (666).

The U.S. National Toxicology Program conducted a skin-painting study with OPP in groups of 50 mice per sex. The OPP was applied as an acetone solution on 3 days per week for 2 years, both alone and as a promoter with 7, 12-dimethylbenz(*a*)anthracene (DMBA). No skin neoplasms were observed in either sex treated with OPP alone, and there were no tumor enhancing or inhibiting effects when OPP and DMBA were given in combination (673).

16.4.1.6 Genetic and Related Cellular Effects Studies OPP, SOPP, and the oxidative metabolites phenylhyroquinone (PHQ) and phenylbenzoquinone (PBQ) have been tested for genotoxic properties in a variety of test systems. Most *in vitro* and *in vivo* assays were negative, but the metabolites had a tendency to bind with DNA. OPP is probably not genotoxic, but SOPP and PBQ are possibly genotoxic at high doses (658, 659).

16.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization No evidence of delayed contact hypersensitivity was found in standard Buehler tests with OPP and SOPP in guinea pigs (658, 659). In an early study in humans, the potential for skin sensitization was tested in 200 unselected subjects, 100 males and 100 females, by placing patches impregnated with OPP or SOPP in direct contact with the skin on the back, covering with an impervious film and taping into place. The first application was kept in constant contact with the skin for 5 days before removal, and any reaction was recorded. A second application was made in the same way 3 weeks later and kept in direct contact for 48 h before removal. Each subject was examined immediately and again 3 days and 8 days later. OPP did not cause primary irritation when tested as a 5% solution in sesame oil, and did not cause sensitization. Applications of aqueous solutions of SOPP caused no irritation at 0.1% and very slight simple irritation at 0.5%, but were significantly irritating at 1 and 5%. However, no skin sensitization was produced by SOPP at these concentrations (674).

16.4.2 Human Experience 16.4.2.1 General Information Products containing OPP or SOPP have been used extensively as antimicrobials and sanitizers, and for fungicidal treatment of fruits and vegetables since the 1940s without adverse effects.

16.4.2.2 Clinical Cases 16.4.2.2.1 Acute Toxicity: NA

16.4.2.2.2 Chronic and Subchronic Toxicity: NA

16.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms OPP was rapidly eliminated following dermal exposure to a single dose of ~0.4 mg on the forearm of six human male volunteers. The radiolabeled test substance was applied to a 4 × 6-cm area of shaved volar surface as a 100-mL aliquot of a 0.4% w/v solution in isopropyl alcohol. A protective dome was placed over the treatment site and was left in place for 8h. The treated sites were then wiped with cotton swabs dipped in isopropanol, rinsed with alcohol, and stripped with tape at ~1, 23, and 46 h after removal of the protective dome to determine the amount of residual activity associated with surface layer of skin. The radioactivity in blood, urine, and feces was measured at intervals for 5 days. Under the conditions of this study, ~43% of the applied OPP was absorbed through the skin, and 99% of the absorbed dose was recovered in the urine collected within the first 48 h after exposure. The urinary metabolites consisted of 69% OPP sulfate, 4% OPP glucuronide, 15% as conjugated phenylhydroquinone (PHQ), and 13% as the sulfate of 2,4'-dihyroxybiphenyl. Little or no free OPP, and no free PHQ or PBQ metabolites were found in urine following this dermal exposure to a representative low level in humans (667).

Using data from this dermal exposure study, a pharmacokinetic model was developed to simulate the potential for bioaccumulation of OPP from repeated dermal exposures. A worst-case occupational scenario was selected, with continuous occluded dermal exposure to 6 mg OPP/kg body weight for 8 h per day on 5 consecutive days per week. The calculated half-lives for absorption and excretion were 10 and 0.8h, respectively, indicating that OPP is unlikely to bioaccumulate in exposed workers (675).

16.5 Standards, Regulations, or Guidelines of Exposure

National and international tolerances or maximum residue limits (MRLs) were established in many countries during the past 45 years for residues remaining on the surface of fresh fruits and vegetables treated post-harvest with either OPP or SOPP to retard spoilage during storage and transportation to market. These MRLs have ranged from 3 ppm in/on cherries and nectarines to 25 ppm in/on apples and pears (676), but many have been rescined in the absence of new data reflecting current good agricultural practice. At their joint meeting in Rome in September 1999, the United Nations food and Agriculture Organisation (FAO) and the World Health Organization (WHO) recommended withdrawl of remaining MRLs except for 10 ppm in/on citrus fruits, and added 0.05 ppm for orange juice and 60 ppm for dried citrus pulp. FAO/WHO also increased the Acceptable Daily Intake (ADI) to 0.4 mg/kg bw for humans and agreed that an acute RfD was not necessary (659).

16.6 Studies on Environmental Impact

Metabolism on OPP in soil and and by aquatic microorganisms is fairly rapid and is complete under conditions resembling those of activated sludge systems, under both aerobic and anaerobic conditions. Complete degradation OPP of was obtained within 2 days under simulated biological wastewater treatment conditions for loadings at 30 and 100 mg/L. However, the antimicrobial properties of OPP slowed its degradation at levels higher than 100 mg/L in wastewater. Studies with ^{14}C-OPP showed that it is readily degraded to CO_2 at the low concentrations likely to occur in the natural environment, such as in river water, and that the rate of degradation is enhanced in activated sludge, especially after acclimation (678).

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17.0 Di-**tert**-Butylmethylphenol

17.0.1 CAS Number:

[*29759-28-2*]

17.0.2 Synonyms:
DBMP, 4-methyl-2,6-di-*tert*-butylphenol, 2,6-di-*tert*-butyl-*p*-cresol, di-*tert*-butylhydroxytoluene
17.0.3 Trade Names:
Deenax, Paranox, DBPC Antioxidant, Ionil
17.0.4 Molecular Weight:
17.0.5 Molecular Formula:
17.0.6 Molecular Structure:
17.1 Chemical and Physical Properties
17.1.1 General

Physical state	Slightly yellow, crystalline solid
Melting Point	70°C
Boiling point	265°C

17.2 Production and Use
Di-*tert*-butylmethylphenol (DBMP) is an antioxidant that prevents the deterioration of fats, oils, waxes, resins, and plastic films. It is incorporated into many edible vegetable or animal fats and oils, into baked and fried foods, and into waxes or plastic films used for coating food wrappers or containers. It acts as an anti-skidding agent when added to paints and inks, and its antioxidant qualities allow it to be used in cosmetics and pharmaceuticals (11).
17.3 Exposure Assessment:
NA
17.4 Toxic Effects
17.4.1 Experimental Studies 17.4.1.1 Acute Toxicity When absorbed in toxic concentrations into the tissues of unanesthetized animals, DBMP induced signs of intoxication resembling those seen after absorption of a toxic dose of a parasympathetic drug (salivation, a mild degree of miosis, unsteadiness, restlessness, hyperexcitability, diarrhea, and tremors) (13). When given intravenously to a dog under pentobarbital anesthesia, DBMP (25 mg/kg) induced a prompt reduction of blood pressure. Atropine sulfate partially antagonized this depressor effect. Large doses of DBMP produced a gross disturbance of sodium, potassium, and water balance in the rabbit (13). It was concluded that the increase in sodium and aldosterone excretion was due to pyelonephritis, and that death was due to potassium depletion.

17.4.1.2 Chronic and Subchronic Toxicity From the results of chronic toxicity studies using dogs and rats (13), it was concluded that DBMP is a relatively innocuous compound for occupational handling.

17.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Metabolism studies in rats, dogs, and humans showed some differences in excretion patterns (13). In the rat there was slower excretion than in humans, and evidence of enterohepatic circulation was not apparent in humans. In humans more metabolites are excreted in the urine and overall excretion is more rapid than in rats (13).

17.4.1.4 Reproductive and Developmental: NA

17.4.1.5 Carcinogenesis The oral feeding of DBMP increased the detoxification and inhibited cancer induction by known carcinogens (2).

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18.0 Dodecylthiophenol
18.0.1 CAS Number:
[*36612-94-9*]
18.0.2 Synonyms:
NA
18.0.3 Trade Names:
NA
18.0.4 Molecular Weight:
NA
18.0.5 Molecular Formula:
NA
18.0.6 Molecular Structure:
NA
18.1 Chemical and Physical Properties:
NA
18.2 Production and Use:
NA
18.3 Exposure Assessment:
NA
18.4 Toxic Effects
18.4.1 Experimental Studies 18.4.1.1 Acute Toxicity The acute toxicity of this material is of a low order. An intramuscular dose of 20 g/kg is not fatal in the rat; lethal oral doses range from 20 to 30 g/kg. When applied to the skin of the rat, rabbit, and guinea pig, the material induces loss of hair in 6–12 days. When applied to the human skin, the material may induce local eczema but apparently does not cause loss of hair (13).

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Aliphatic Nitro, Nitrate, And Nitrite Compounds
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A. Aliphatic Nitro Compounds

Nitroalkanes, or nitroparaffins, are derivatives of alkanes with the general formula C_nH_{2n+1}, in which one or more hydrogen atoms are replaced by the electronegative nitro group ($–NO_2$). Nitroalkanes are classed as primary, RCH_2NO_2, secondary, R_2CHNO_2, and tertiary, R_3CNO_2, using the same convention as for alcohols. Some examples of commercial nitroalkanes, are nitromethane, nitroethane, 1-nitropropane, and tetranitromethane (1).

The nitroalkanes are produced in large commercial quantities by direct vapor-phase nitration of propane with nitric acid or nitrogen peroxide. The reaction product is a mixture of nitromethane, nitroethane, and 1- and 2-nitropropane. The individual compounds are obtained by fractional distillation.

The chemical and physical properties of a number of nitroalkanes are described in Table 54.1 and in the individual summaries following. Nitroparaffins are colorless, oily liquids with relatively high vapor pressures. Their solubility in water decreases with increasing hydrocarbon chain length and number of nitro groups. As expected, their boiling and flash points are higher than their corresponding hydrocarbons.

Table 54.1. Properties of the Mononitroalkanes and Tetranitromethane

Name	Mol. wt.	B.p. (°C)	Specific gravity	Solubility in H_2O at 20°C (% by vol.)	Vapor pressure (mmHg) (°C)	Vapor density (Air = 1)	(Closed/open) flash point (° F)	Conver unit 1 mg/L (ppm)	1 (r
Nitromethane	61.04	101.2	1.139 (20/20°C)	9.5	27.8 (20)	2.11	95/110	400.7	
Tetranitromethane	196.04	125.7	1.6629 (25°C)	Insoluble	8.4(20)	0.8	—	124.7	
Nitroethane	75.07	114.8	1.052 (20/20°C)	4.5	15.6 (20)	2.58	82/106	325.7	
1-Nitropropane	89.09	131.6	1.003 (20/20°C)	1.4	7.5 (20)	3.06	96/120	274.7	
2-Nitropropane	89.09	120.3	0.992 (20/20°C)	1.7	12.9 (20)	3.06	—/102	274.7	
1-Nitrobutane	103.12	153	0.9728 (15.6/15.6° C)	0.5	5(25)	3.6	—	237.1	
2-Nitrobutane	103.12	139	0.9728 (15.6/15.6° C)	0.9	8(25)	3.6	—	237.1	

The uses of nitroalkanes depend on their strong solvent power for a wide variety of substances including many coating materials, waxes, gums, resins, dyes, and numerous organic chemicals. Most organic compounds, including aromatic hydrocarbons, alcohols, esters, ketones, ethers, and

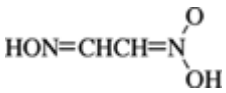
carboxylic acids, are miscible with nitroalkanes. Thus, they are used in products such as inks, paints, varnishes, and adhesives. Another important use is in the production of derivatives such as nitroalcohols, alkanolamines, and polynitro compounds. In some cases, they provide better methods of manufacturing well-known chemicals such as chloropicrin and hydroxylamine. They are also used as special fuel additives, rocket propellants, and explosives.

Nitroalkane vapor pressures are sufficient to produce high vapor levels in the workplace unless controlled. Thus, the chief industrial hazard is respiratory irritation when these compounds are inhaled. The odors of nitroalkanes are easily detectable, and concentrations below 200 ppm are disagreeable to most observers (2). However, the odor and sensory symptoms are not considered dependable warning properties.

The fire and explosion hazards of nitroalkanes are considered low for they have relatively high flash points. Despite these high flash points, shock explosion can result under certain conditions of temperature, chemical reaction, and confinement.

Nitroalkanes are acidic substances. Polynitro compounds are even stronger acids than the corresponding mononitroalkanes. They are rapidly neutralized with strong bases and readily titrated. Tautomerism, a general property of primary and secondary mononitroalkanes, gives rise to a more acidic “aci” form, or nitronic acid. In organic solvents, primary and secondary mononitroalkanes exist as neutral nitroalkanes. However, in aqueous solutions, they exist in a state of equilibrium between the protonated neutral nitroalkane, the nonprotonated nitronic acid and its anion, or nitronate. Tautomerism is important for understanding the biological effects of nitroalkanes and also forms the basis of a number of important chemical reactions through the formation of nitroalkane salts. Mercury fulminate, $Hg(ON{=}C)_2$, is one of the better-known compounds that is derived from the mercury salt of nitromethane $[(CH_2{=}NO_2)_2Hg]$.

Except for chloropicrin, the production of chloronitroparaffins, uses tautomerism. The important intermediate methazonic acid, which is a starting product for a number of



well-known compounds (e.g., nitroacetic acid and glycine) also uses tautomerism. Additionally, many nitro derivatives are a source of guanidine $[H_2NC({=}NH)NH_2]$ by reaction with ammonia. A number of other useful products such as primary amines, nitrohydroxy compounds, aromatic amines, and b-dioximes, which in turn can yield isoxazoles by hydrolysis, are also among the armamentarium of the nitroalkane reaction possibilities.

Early methods (1940–1959) of determining nitroalkanes used colorimetric procedures (see chemical summaries below for more details). Since 1970 these have been replaced by instrumental methods. References to the colorimetric procedures are included here because these procedures were used for monitoring animal exposures, which provide the toxicity data in Table 54.2. Instrumental methods of mass spectroscopy and gas chromatography are now used routinely, and infrared has been used in animal exposure studies (3).

Table 54.2. Results of Inhalation Experiments (13)[a]

Nitromethane		Nitroethane	
	No.		**No.**

Concn (%)	Time (hr)	Concn × time	No. rabbits killed	guinea pigs killed	Concn (%)	Time (hr)	Concn × time	No. rabbits killed	guinea pigs killed	Concn (%)	Ti (h
1.0	6	6	2	2							
3.0	2	6	2	2							
5.0	1	5	2	2							
					2.5	2	5	2	0		
					3.0	1.25	3.75	2	2		
3.0	1	3	0	2	3.0	1	3	1	1		
1.0	3	3	0	2	1.0	3	3	2	1	1.0	3
0.5	6	3	1	1							
0.25	12	3	2	1							
0.10	30	3	0	2							
2.25	1	2.25	0	1							
3.0	0.5	1.5	0	1	3.0	0.5	1.5	1	0		
0.5	3	1.5	0	1	0.5	3	1.5	2	0	0.5	3
					0.1	12	1.2	1	0		
					0.5	2	1	1	0		
1.0	1	1	0	0	1.0	1	1	1	0	1.0	1
3.0	0.25	0.75	0	0	0.25	3	0.75	0	0		
					0.1	6	0.6	0	0		
					0.05	30	1.5	0	[b]		
0.05	140	7.0	0	0[c]	0.05	140	7.0	0	0[c]		
0.1	48	4.8	1[c]	1[c]							

[a] Two rabbits and two guinea pigs in each experiment.
[b] No animals exposed.
[c] One monkey exposed.

The primary mononitroalkanes on which toxicity data were determined, were analyzed colorimetrically by measuring the color developed from an HCl-acidified alkaline solution containing $FeCl_3$ (4). Analytical data on the secondary nitroalkanes were determined by measuring ultraviolet radiation at a wavelength of 2775 Å through an alcoholic solution in a Beckman spectrophotometer (5). A more sensitive spectrophotometric determination of primary nitroalkanes uses the coupling reaction with *p*-diazobenzenesulfonic acid (3). Simple, secondary nitroalkanes do not interfere as do some complex secondary nitro alcohols.

Mass spectrography, gas chromatography, and infrared spectroscopy are the current methods of choice for determining nitroalkanes in air (6). Mass spectra have been determined for eight C_1 to C_4 mononitroalkanes (6, p. 418). The different conditions recommended for analyzing nitroalkane mixtures including chloronitroparaffins by gas chromatography, along with their chromatograms, are given in Ref. 6 on pp. 425–429 and 430–433, and for nitroalcohols, on pp. 441–443.

Because nitroparaffins can cause respiratory irritation, inhalation toxicity data have always been of interest. The inhalation toxicity data on the nitroalkanes gathered in the late 1930s and summarized

below lacked some of the refinements of late work with these compounds. Exposure “chambers” consisting of steel drums of 233-liter capacity lacked the space to expose what is now considered an adequately sized complement of animal species (7). The exposure concentrations at levels of 5000 to 50,000 ppm must be considered “nominal” because of measurement by interferometer, the chamber airflow characteristics, and fan circulation of air.

Incomplete information on polynitroalkanes indicates that an increased number of nitro groups results in increased irritant properties. Thus, the chlorinated nitroparaffins are more irritating than the unchlorinated compounds (8). This reaches a severe degree with trichloronitromethane (chloropicrin). Unsaturation of the hydrocarbon chain in the nitroolefins also increases the irritant effects (9, 10).

The primary nitroalkanes fail to show significant pharmacological effects on blood pressure or respiration (11). Oral doses result in symptoms similar to those produced by inhalation except for the additional evidence of gastrointestinal tract irritation. They are less potent methemoglobin formers than aromatic nitro compounds.

In general, applications of nitroalkanes to the skin give no evidence of sufficient absorption to result in systemic injury. After application of the nitroalkanes in five daily treatments to the clipped abdominal skin of rabbits, no systemic effects or evidence of weight loss was reported (2).

Nitroalkanes are readily absorbed through the lungs and through the gastrointestinal tract (12). Animals that die following brief inhalation of the nitroalkanes show general visceral and cerebral congestion. After exposure at high concentrations, there is pulmonary irritation and edema, but the latter is inadequate to be the sole cause of death.

Oxidative denitrification of nitroalkanes occurs by two mechanisms. The microsomal cytochrome P450 monooxygenase system of rat and mouse liver metabolizes nitroparaffins *in vitro* (13, 14). Specific activities are greatest for 2-nitropropane, followed by 1-nitropropane, nitromethane, and tetranitromethane. One study found up to 25% of residual denitrifying activity with mouse liver microsomes under anaerobic conditions (15), suggesting that an oxygen-independent mechanism may exist. Dayal et al. found that 2-nitro-2-methylpropane was not denitrified by the monooxygenase system (16). This indicates that a hydrogen atom is required in the position alpha to the nitro group for oxidative cleavage of the neutral tautomeric form. They also showed that the nitronate anion of 2-nitropropane was denitrified 5 to 10 times faster than the neutral form. Because the tautomeric equilibrium of primary nitroalkanes, such as 1-nitropropane, lies far to the neutral side of physiological pH, the authors suggest that this may explain the slower reaction rate with these compounds relative to 2-nitropropane.

A second mechanism of oxidative denitrification has been demonstrated for various flavoenzyme oxidases (17–20). The relative reactivity rates of the nitroalkanes are similar to those of the microsomal systems, except that tetranitromethane was inert (18). The interesting aspect of this pathway is that a superoxide radical is produced either as an intermediate (18) or as an initiator/propagator of the reaction (20). Superoxide radical and other active oxygen species produced from it (oxygen free radicals, hydrogen peroxide, hydroxyl radical) have been associated with toxicity and mutagenicity.

Official Occupational Safety and Health Administration (OSHA) standards and ACGIH threshold limit values (TLVs) have been adopted for the seven nitroalkanes listed in Table 54.3. No TLVs have been established for any nitroolefin or nitroalcohol. For the basis of TLVs, see Documentation of TLVs published by the ACGIH.

Table 54.3. Occupational Exposure Limits for Nitroalkanes

	OSHA Standard		TLV[a]	
Compound	**ppm**	**mg/m^3**	**ppm**	**mg/m^3**
Nitromethane	100	250	20	50
Nitroethane	100	310	100	307
1-Nitropropane	25	90	25[b]	91
2-Nitropropane	25	90	10[c]	36, A2
Tetranitromethane	1	8	1	8
Chloropicrin	0.1	0.7	0.1	0.67
1-Chloro-1-nitropropane	20	100	2	10

[a] From 1999 list.
[b] Not classified as human carcinogen.
[c] Confirmed animal carcinogen with unknown relevance to humans.

Table 54.4. Acute Toxicity of Nitromethane (13, 27)

Route	Animal	Dose	Mortality
Oral	Dog	0.125 g/kg	0/2
		0.25–1.5 g/kg	12/12
	Rabbit	0.75–1.0 g/kg	Lethal dose
	Mouse	1.2 g/kg	1/5
		1.5 g/kg	6/10
Subcutaneous	Dog	0.5–1.0 ml/kg	Minimum lethal dose
Intravenous	Rabbit	0.8 g/kg	2/6
		1.0 g/kg	2/6
		1.25–2.0 g/kg	9/9
Inhalation	Rabbit	30,000 ppm <2 h	0/6
		2 h	2/2
		10,000 ppm 6 h	3/2
		1–3 h	0/4
		5,000 ppm, 6 h	1/2
		3 h	0/2
		500 ppm, 140 h	0/2
	Guinea pig	30,000 ppm, 1–2 h	4/4
		30 min	1/2
		15 min	0/2
		10,000 ppm, 3–6 h	4/4
		1 h	0/2

	1,000 ppm, 30 h	2/3
	500 ppm, 140 h	0/3
Monkey	1,000 ppm, 48 h	1/1
	500 ppm, 140 h	0/1

Table 54.5. Acute Toxicity of TMN to Rats and Mice (40)

Test	Rats	Mice
Oral LD_{50} (95% c.l.)	130 (83–205) mg/kg	375 (262–511) mg/kg
Intravenous LD_{50} (95% c.l.)	12.6 (10.0–15.9) mg/kg	63.1 (45.0–88.7) mg/kg
4-Hr Inhalation (95% c.l.)	17.5 (16.4–18.7) ppm	54.5 (48.0–61.7) ppm

Table 54.6. Effect of Various Concentrations of Tetranitromethane (TNM)

Animal	Concentration (ppm)	Duration of exposure	Effect (Ref.)
1 cat	100	20 min	Death in 1 h (41)
1 cat	10	20 min	Death in 10 days (41)
5 cats	7–25	2½–5 h	Death in 1–5½ h (25)
2 cats	3–9	6 h × 3	Severe irritation (25)
2 cats	0.1–0.4	6 h × 2	Mild irritation (25)
20 rats	1230	1 h	All died in 25–50 min (8)
20 rats	300	1½ h	All died in 40–90 min (8)
20 rats	33	10 h	All died in 3–10 h (8)
19 rats	6.35	6 months	11 deaths (8)
2 dogs	6.35	6 months	Mild symptoms (8)

Table 54.7. Response to Inhalation of Nitroethane (13)[a]

		Mortality

Concentration (ppm)	Time (h)	Rabbit	Guinea Pig
30,000	1.25	2	2
	1	1	1
	0.5	1	None
10,000	3	2	1
	1	1	None
5,000	3	2	None
	2	1	None
2,500	3	None	None
1,000	2	1	None
	6	None	None
500	30	None	None
	140[b]	None	None

[a] Two rabbits and two guinea pigs in each experiment.
[b] One monkey exposed, not fatal.

Table 54.8. Response to Inhalation of 2-Nitropropane (6)

	Highest tolerable concentration (ppm)			Lowest lethal concentration (ppm)		
Animal	**1 h**	**2.25 h**	**4.5 h**	**1 h**	**2.25 h**	**4.5 h**
Rat	2353	1372	714[a]	3865	2633	1513
Guinea pig	9523	4313	2381		9607	4622[b]
Rabbit	3865	2633	1401	9523	4313	2381
Cat	787	734	328	2353	1148	714

[a] Time 7 h.
[b] Time 5.5 h.

Table 54.9. Response to Inhalation of 1-Nitropropane

	Mortality[a]

Concentration (ppm)	Time (h)	Rabbit	Guinea Pig
10,000	3	2	2
10,000	1	None	1
5,000	3	2	2

[a] Two rabbits and two guinea pigs in each experiment.

Table 54.10. Chemical and Physical Properties of Chlorinated Mononitroparaffins

Name	Mol. wt.	BP (° C)	Specific gravity	H_2O solubility at 20°C (% by vol.)	Vapor pressure (mmHg) (25°C)	Vapor density (Air = 1)	Flash point (°F)	Conversion units: 1 mg/L (ppm)	Conversion units: 1 ppm (mg/m^3)
Trichloronitromethane (chloropicrin)	164.38	111.84	1.656 (20/4° C)	Insoluble	16.9 (20°)C	5.7	—	148.8	6.72
1-Chloro-1-nitroethane	109.51	127.5	1.2860 (20/20° C)	0.4	11.9	3.6	133	237	4.21
1,1-Dichloro-1-nitroethane	143.9	124	1.4271 (20/20° C)	0.25	16	5.0	168	169.9	5.89
1-Chloro-1-nitropropane	123.5	139.5–143.3	1.209 (20/20° C)	0.5	5.8	4.3	144	198	5.05
2-Chloro-2-nitropropane	123.5	133.6	1.197 (20/20° C)	0.5	8.5	4.3	135	198	5.05

[a] Ref. 9.

Table 54.11. Response to Inhalation of 1,1-Dichloronitroethane (9)

Average concentration (ppm)	Duration of exposure	Mortality[a]: Rabbit	Mortality[a]: Guinea pig
4910	30 min	2	2

985	3½ h	2	1
594	2½ h	1	None
254	1 h	None	None
169	2 h	1	1
100	6 h	2	2
60	2 h	None	None
52	18 h, 40 min	2	None
34	4 h	None	None
25	204 h	None	None

[a] Two rabbits and two guinea pigs in each experiment.

Table 54.12. Response to Inhalation of 1-Chloro-1-nitropropane (10)

		Mortality[a]	
Average concentration (ppm)	**Duration of exposure**	**Rabbit**	**Guinea pig**
4950	60 min	2	1
2574	2 h	2	None
2178	1 h	None	1
1069	1 h	None	None
693	2 h	None	None
393	6 h	1	None

[a] Two rabbits and two guinea pigs in each experiment.

Table 54.13. Effects of Various Concentrations of Trichloronitromethane in Animals[a]

	Concentration			
Animal	**mg/L**	**ppm**	**Duration of exposure (min)**	**Effects**
Dog	1.05	155	12	Became ill
	0.08–0.95	117–140	30	Death of 43% of the animals
Mouse	0.85	125	15	Death in 3 h to 1 day
Cat	0.51	76	25	Death usually in 1 day

Mouse	0.34	50	15	Death after 10 days
Dog	0.32	48	15	Tolerated
Cat	0.32	48	20	Death after 8 to 12 days
	0.26	38	21	Survived 7 days
Mouse	0.17	25	15	Tolerated

[a] Refs. 41, 80, 81.

Table 54.14. Effects of Various Concentrations of Trichloronitromethane in Humans

Concentration			
mg/L	ppm	Duration of exposure (min)	Effect
2.0	297.6	10	Lethal concentration
0.8	119.0	30	Lethal concentration
0.1	15.0	1	Intolerable
0.050	7.5	10	Intolerable
0.009	1.3		Lowest irritant concentration
0.0073	1.1		Odor detectable
0.002–0.025	0.3–3.7	3–30 s	Closing of eyelids according to individual sensitivity

Table 54.15. Acute Effects of Nitroolefins (14)

	Vapor exposure (5 h)		Oral toxicity, rats, undiluted (approx. lethal dose)		Intraperitoneal toxicity, rats, undiluted (approx. lethal dose)		Dermal toxicity, rabbits, open, 5-h (approx. lethal dose)	
Name	Concn. (ppm)	Survival times, rats, 47% humidity	g/kg	mmol/kg	g/kg	mmol/kg	g/kg	mmol/kg
2-Nitro-	1400	100 min	0.28	2.8	0.08	0.8	0.62	6.1

2-butene								
2-Nitro-2-pentene	240 55	240 min Survived	0.28	2.4	0.08	0.7	0.94	5.4
3-Nitro-2-pentene	268	280 min	0.42	3.7	0.05	0.4	0.62	8.2
2-Nitro-2-hexene	515 152	50–85 min Survived	0.42	3.3	0.12	0.9	1.40	7.3
3-Nitro-3-hexene	557 50	30–70 min Survived	0.42	3.3	0.08	0.6	0.94	10.9
2-Nitro-2-heptene	308 135	3–18 h Survived	0.94	6.6	0.28	2.0	0.94	6.6
3-Nitro-3-heptene			0.62	4.3	0.28	2.0	1.40	9.8
2-Nitro-2-octene	54 47	24 h Survived	1.4	9.0	0.28	1.8	0.62	4.0
3-Nitro-3-octene	142 72	18–24 h Survived	0.62	4.0	0.18	1.2	0.94	6.0
3-Nitro-2-octene	141 44	18–72 h Survived	0.62	4.0	0.18	1.2	0.62	4.0
2-Nitro-2-nonene	64	Survived	2.1	12.3	0.28	1.6	0.62	3.6
3-Nitro-3-nonene	59 10	24 h Survived	2.1	12.3	0.42	2.5	0.42	2.5

Aliphatic Nitro, Nitrate, And Nitrite Compounds
Candace Lippoli Doepker, Ph.D.

B. Aliphatic Nitrates

Aliphatic nitrates are nitric acid esters of mono- and polyhydric aliphatic alcohols. The nitrate group has the structure –C–O–NO_2, where the N is linked to C through O, as contrasted to the nitroalkanes in which N is linked directly to C.

The nitric acid esters of the lower mono- di- and trihydric alcohols are liquids (methyl nitrate, ethylene glycol dinitrate, trinitroglycerin), whereas those of the tetrahydric alcohols (erythritol tetranitrate, pentaerythritol tetranitrate) and hexahydric alcohol (mannitol hexanitrate) are solids. They are generally insoluble, or only very slightly soluble in water, but are more soluble in alcohol or other organic solvents. Some chemical and physical properties of this group of compounds are shown in Table 54.16.

Table 54.16. Chemical and Physical Properties of Aliphatic Nitrates and Related Explosive Compounds

Name	Mol. wt.	Physical state	BP (°C)	Vapor density (air = 1)	H_2O solubility
Methyl nitrate	77.04	Volatile liquid	66 (explodes)	2.66	Slight
Ethyl nitrate	91.07	Colorless liquid	87.6	3.14	1.3% (55° C)
Isopropyl nitrate	105.09	Pale yellow liquid	110.5	3.62	Very slight
Amyl nitrate	133.15	Slightly yellow liquid	150 (unstable)	—	0.3%
Ethylene glycol dinitrate	152.07	Colorless liquid	114 (explodes)	5.24	0.52%
Glyceryl trinitrate (nitroglycerin)	227.10	Colorless oily liquid	260 (explodes)	7.80	Slight
Propylene glycol-1,2-dinitrate	166.09	Red-orange liquid	121 (decomp)	—	—
Pentaerythriol tetranitrate	316.15	Water-wet solid	180 (50 mm Hg)	—	Very slight
Cyclonite (RDX)	222.26	White crystalline solid	276–280 (mp)	—	Insoluble
HMX	296.16	Colorless crystalline solid	204 (mp)	—	Insoluble

Uses of aliphatic nitrates are chiefly as explosives and blasting powders. The lower aliphatic nitrates, methyl, ethyl, propyl, and isopropyl have also been used as rocket propellants and special jet fuels.

Trimethylenetrinitramine (cyclonite, RDX) and cyclotetramethylene tetranitramine (HMX) have been included in this section because they are also used as explosives.

Early methods used for determining aliphatic nitrate esters consisted of various colorimetric or spectrophotometric procedures. These have now been largely replaced by instrumental methods (since mid-1960). References to the colorimetric procedures are included here (29, 104–111) because they were used for monitoring animal or worker exposures in work, summarized later in the sections on specific compounds.

Colorimetric procedures used for determining "traces" of polynitrate esters were reported in the mid-1930s and early 1940s (106, 107). These procedures appear relatively crude by present-day standards, for they were based on the nitration of reagents by the aliphatic nitrate being determined. More precise methods were developed later (108) and used to monitor animal exposures. Colorimetric methods were still being used as late as 1966 for determining of aliphatic nitrates, nitroglycerin, and ethylene glycol dinitrate in workplace air (109).

Instrumental methods, such as infrared spectrography, are generally considered satisfactory for identifying of aliphatic nitrate esters (104, 105). Spectral correlations have been compiled by Pristera et al. using band assignments at 6.0, 7.8, and 12.0 mm. Gas chromatographic procedures have been used for determining certain aliphatic nitrates (isopropyl nitrate, ethylene glycol dinitrate, and nitroglycerin in blood and urine (112–114). A comparison of solid sorbents in air sampling using a chromatographic method has been published (115). These methods have the advantage of greater precision and ease of manipulation of samples and have thus largely replaced the colorimetric methods of the past. More advanced methods of liquid chromatography to measure RDX in biological fluids (116) and ion mobility spectrometry to measure ethylene glycol dinitrate in air (117) have been reported. More recently, the detection of C_1–C_5 alkyl nitrates in snow, frost, and surface water has been demonstrated with a new water co-distillation enrichment technique coupled with on-column head-space gas chromatography (118).

The chief physiological effects of the aliphatic nitrates are dilation of blood vessels and methemoglobin formation. Vascular dilation accounts for the characteristic lowering of blood pressure and headache. Animals given effective doses orally or parenterally exhibit such signs as marked depression in blood pressure, tremors, ataxia, lethargy, alteration in respiration (usually hyperpnea), cyanosis, prostration, and convulsions. When death occurs, it is either from respiratory or cardiac arrest. Animals that survive the acute exposure recover promptly.

Aliphatic nitrates (e.g., nitroglycerin, erythritol tetranitrate, pentaerythritol tetranitrate, and methyl nitrate) can produce varying degrees of hypotension in humans. Headache is the outstanding symptom produced in humans following exposure. This is usually described as very severe and throbbing and is often associated with flushing, palpitation, nausea, and less frequently, vomiting and abdominal discomfort. Temporary tolerance develops from continued or repeated daily exposures (119). Pentaerythritol tetranitrate is the least effective at inducing such headaches and nitroglycerin is considered the most potent for headache induction. Other pharmacological consequences of vasodilation are increased pulse rate, an increase in cardiac stroke volume, variable cardiac dilation and cardiac output, and a shift in blood distribution with increased stasis and pressure in pulmonary arteries (128).

For some members of the series, the ease of hydrolysis to the alcohol and nitrate and the degree of

blood pressure lowering are parallel. Early studies suggested little evidence that hydrolysis to nitrate is necessary for hypotensive action (120–122). It appears that this effect of the nitrate esters does not depend exclusively on the liberation of nitrite groups. Dilation can occur without measurable nitrite in the blood or when the amount measured is not sufficient to account for the effect observed. Direct effects of nitrates on smooth muscle cells include stimulation of guanylate cyclase producing increased cyclic guanosine monophosphate (cGMP) levels. cGMP in turn lowers intracellular calcium concentrations, thus relaxing contractile protein and causing vasodilation (119).

The *in vivo* formation of nitrite is commonly assumed to be the explanation for the methemoglobin-forming properties of the aliphatic nitrates (123). The mechanism of formation of nitrite is not clear (124). It is possible that reduction to nitrite occurs before hydrolysis as follows (125):

$$RONO_2 \xrightarrow{+2H} RONO \xrightarrow{+H_2O} ROH + NO_2^-$$

Some aliphatic nitrates cause methemoglobin formation in experimental animals. For example, ethyl nitrate is a weak methemoglobin former, nitroglycerin is a moderately active methemoglobin former, and ethylene glycol dinitrate is considerably more effective (approximately four times). Ethylene glycol mononitrate, on the other hand, is not very active in this respect (126).

Heinz body formation has been observed following treatment of animals with certain aliphatic nitrates (e.g., ethyl, propyl, and amyl nitrates, ethylene glycol dintrate, and nitroglycerin). The precise nature of these small, rounded inclusion bodies in the red blood cells, described by Heinz in 1890, is not clear. They have been observed in humans and animals after absorption of a variety of chemical compounds, the most prominent of which are the aromatic nitrogen compounds, inorganic nitrites, and the aliphatic nitrates. Their appearance is commonly associated with anemia and the production of methemoglobin. Some evidence indicates that they are proteins, possibly hemoglobin degradation products. Red blood cells containing the inclusion bodies have a shorter life span and are removed from the circulation by the spleen. Special stains are required to demonstrate their presence satisfactorily. In the case of the aliphatic nitrates, erythrocytes containing Heinz bodies disappear from the circulating blood more slowly than methemoglobin (108, 125, 127).

Alkyl nitrates are absorbed from the gastrointestinal tract (128). Certain alkyl nitrates are better absorbed (see following for detail) than others through the skin and through the lung. The nitric acid esters of the monovalent alcohols are rapidly absorbed from the lung. Pathological examinations of animals that died following acute intoxication have been negative or have revealed only slight nonspecific pathological changes consisting of congestion of internal organs.

No injuries to workers from exposure to any of the lower monohydric alcohol esters of nitric acid (methyl, ethyl, *n*-propyl, amyl isomers) have appeared in the published literature. However, for polynitrate esters such as nitroglycerin or ethylene glycol dinitrate, the occurrence of characteristic and severe headaches in workers was so frequent that such acquired names as “dynamite head” and “powder headache” were common. Similar effects were reported for exposure to ethylhexyl nitrate (129). Since the 1950s, hypotension and peripheral vascular collapse have been associated with these headaches (129). It is now clear that NG and especially EGDN increase the risk of cardiovascular disease through attacks due to nitrate withdrawal, 1 to 3 days after last exposure, and through a long-term risk which persists long after exposure ceases (130, 131). The short-term risk was noted first and termed “Monday morning angina.” This includes findings of angina, myocardial infarction, arrhythmia, and sudden death. Generally, symptoms are not induced by exercise or psychic arousal, and no vascular lesions have been found at autopsy. Occupational or other exposures to NG involving repeated dermal contact cause irritant contact dermatitis (72).

The mechanism for tolerance development, a common response to organic nitrates, has been elucidated generally (130). This work was performed because the treatment of angina is hindered by the development of tolerance to the vasodilator action of these esters. See nitoglycerin section later

for more detail.

Table 54.17. Acute Effects of *n*-Propyl Nitrate—Animals (117, 129)

Animal	Dose (g/kg)	Route	Effect
Rat	7.5	Oral	Approximate lethal dose (sample I)
Rat	5.0	Oral	Approximate lethal dose (sample II)
Rat	1.0	Oral	Weakness, incoordination, cyanosis
Rat	1.5 × 10	Oral	Weakness, cyanosis, weight loss (first week)
Rabbit	11, 17	Skin	Essentially none
Rabbit	0.2–0.25	IV	Approximate LD_{50}
Dog	0.005	IV	Slight fall in blood pressure
	0.050	IV	Hypotension, cyanosis
	0.2–0.25	IV	Death in respiratory arrest
Cat	0.1–0.25	IV	6/7 died in 1 min
	0.025–0.075	IV	Hypotension, methemoglobinemia, survived

Table 54.18. Response to Inhalation of Various Concentrations of Amyl Nitrates (116)

		Mortality[a]			
Concentration (ppm)	Duration (h)	Guinea pigs	Rabbits	Rats	Mice
3730	7	2/2	2/2	3/4	5/5
3593	3.5	0/2	2/2	1/4	4/5
3227	1	0/2	0/2	0/4	0/5
3072	3 × 1	2/2	2/2	4/4	5/5
2774	3.5	0/2	0/2	0/4	2/4
2549	0.33	0/2	0/2	0/4	0/5
2380	2 × 7	2/2	2/2	0/4	5/5
2305	1	0/2	0/2	0/4	5/5
1807	7	0/2	1/2	0/4	4/4
1703	3 × 7	2/2	1/2	2/4	5/5
1612	7	0/2	0/2	0/4	0/5
599	9 × 7 + 6.25	0/2	0/2	0/4	0/2
262	20 × 7	0/2	0/2	0/3	0/5

[a] No cats died following any of these exposures.

Aliphatic Nitro, Nitrate, And Nitrite Compounds
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C. Alkyl Nitrites

Alkyl nitrites are aliphatic esters of nitrous acid. The nitrite group has the structure–CONO. Except for methyl nitrite, which is a gas, the lower molecular weight members of the series are volatile liquids. In general they are insoluble or only very slightly soluble in water but are soluble or miscible with alcohol and ether in most proportions. They tend to decompose to oxides of nitrogen when exposed to light or heat. Violent decomposition can occur. As a group, they tend to be flammable and potentially explosive. They are oxidizing materials that present the possibility of violent reactions from contact with readily oxidized compounds. The chemical and physical properties of alkyl nitrites are given in Table 54.19.

Table 54.19. Chemical and Physical Properties of Alkyl Nitrites

Name	CAS #	Molecular formula	Molecular weight	Physical state	Boiling point (° C)	Specific gravity
Methyl nitrite	[*624-91-9*]	CH_3NO_2	61.04	Gas	–12	0.991 (15°C)
Ethyl nitrite	[*109-95-5*]	$C_2H_5NO_2$	75.07	Colorless liquid	17	0.900 (15.5°C)
n-Propyl nitrite	[*543-67-9*]	$C_3H_7NO_2$	89.09	Liquid	57	0.935
Isopropyl nitrite	[*541-42-4*]	$C_3H_7NO_2$	89.09	Pale yellow oil	45	0.844 (25.4°C)
n-Butyl nitrite	[*544-16-1*]	$C_4H_9NO_2$	103.12	Oily liquid	78.2	0.9114 (0/4°C)
Isobutyl nitrite	[*542-56-3*]	$C_4H_9NO_2$	103.12	Colorless liquid	67	0.8702 (20/20°C)
sec-Butyl nitrite	[*924-43-6*]	$C_4H_9NO_2$	103.12	Liquid	68	0.8981 (0/4°C)
tert-Butyl nitrite	[*540-80-7*]	$C_4H_9NO_2$	103.12	Yellow liquid	63	0.8941 (0/4°C)
n-Amyl nitrite	[*463-04-7*]	$C_5H_{11}NO_2$	117.15	Pale yellow liquid	104	0.8528 (20/4°C)
Isoamyl nitrite	[*110-46-3*]	$C_5H_{11}NO_2$	117.15	Transparent liquid	97–99	0.872
n-Hexyl nitrite		$C_6H_{13}NO_2$	131.17	Liquid	129–130	0.8851 (20/4°C)
n-Heptyl nitrite		$C_7H_{15}NO_2$	145.20	Yellow liquid	155	0.8939 (0/4°C)

n-Octyl nitrite	$C_8H_{17}NO_2$	159.23	Greenish liquid	174–175	0.862 (17°C)

Aliphatic nitrites have been of interest mainly because of their pharmacological properties and therapeutic use. They have been used to treat angina. More recently they have been sold as "room odorizers" without prescription and abused for their euphoric effects by adolescents (178) and for their sexual stimulatory effects by homosexual men (179). Amyl nitrite has important use as an antidote in the clinical management of poisoning (180, 181). Aliphate nitrites are used also to a limited extent as intermediates in chemical syntheses. *n*-Propyl nitrite, isopropyl nitrite, and *tert*-butyl nitrite have been used as jet propellants and to prepare fuels.

The pharmacological and toxicological effects of aliphatic nitrites are chiefly characterized by vasodilation resulting in a fall in blood pressure and tachycardia. Methemoglobin is produced by larger doses. Severe complications have been described following ingestion of large quantities of certain nitrites (e.g., amyl, butyl, or isobutyl), including a deficiency in hemoglobin reductase (182). With respect to toxicological effects, alkyl nitrites resemble closely inorganic nitrites (sodium nitrite) and aliphatic nitrates. Inhalation by animals and humans results in smooth muscle relaxation, vasodilation, increased pulse rate, and decreased blood pressure progressing to unconsciousness with shock and cyanosis. Headache is often a prominent symptom and may be due to meningeal congestion and vascular dilation. The development of tolerance has been observed with the therapeutic use of amyl nitrite for angina pectoris. This disappears after a week or so after discontinuation of use. Methods for determining nitrites in air and in biological fluids have been described (128).

Branched-chain compounds are more effective than straight-chain compounds in lowering blood pressure. Isopropyl nitrite is considerably more effective than *n*-propyl nitrite and isobutyl nitrite more than *n*-butyl. Secondary and tertiary butyl compounds also have a more pronounced hypotensive effect than *n*-butyl nitrite. Methyl nitrite is more effective than ethyl and propyl nitrites, and amyl nitrite is more effective than ethyl nitrite. As far as the duration of the hypotensive effect is concerned, methyl and ethyl nitrites are more persistent, *n*-propyl is the least persistent of the lower alkyl nitrites, and the iso derivatives of propyl and butyl nitrite are more persistent than the normal compounds (128). However, the hypotensive effects of these compounds are relatively transient. Amyl nitrite, for example, produces a rapid fall in blood pressure, which lasts only a few minutes after inhalation.

Krantz et al. conducted extensive studies on the pharmacology of alkyl nitrites (120–122). They found that when administering 0.3 mL through an aspirating bottle into the trachea of exposed dogs, the degree of hypotension produced decreased from n-hexyl (58% fall) to *n*-heptyl (47%), *n*-octyl (30%), and *n*-decyl (16%). Alkyl nitrites that have 11 to 18 carbon atoms in their chains showed slight or no effect on blood pressure under these conditions. If injected, however, they produced hypotension. With chains longer than 2-ethyl-*n*-hexyl-1-nitrite, the duration of action became shorter. Cyclohexyl nitrite produced a fall in blood pressure equivalent to ethyl nitrite or amyl nitrite, but the duration was longer. In humans, it produced severe headache. Krantz et al. believe that the major effects are related to the relaxing action of the nitrites on smooth muscle.

Methemoglobin formation has been repeatedly observed following administration to humans and animals. Aliphatic nitrites act as direct oxidants of hemoglobin. One molecule of nitrite and two molecules of hemoglobin can react to form two methemoglobin molecules under appropriate conditions. Side reactions to form nitrosohemoglobin and nitrosomethemoglobin may occur. The amount of methemoglobin formed in cats is directly proportional to the intravenous dose (123). The longer chain compounds induce more methemoglobin formation relative to their hypotensive effect

(120).

The therapeutic usefulness of methylene blue in acute intoxications accompanied by methemoglobinemia remains controversial, even though support for its effectiveness in severe methemoglobinemia continues to appear (183, 184). Although methemoglobinemia is a prominent effect of nitrite absorption, the action of alkyl nitrites on the vascular system is also a major determinant in their toxicity.

Reports of industrial intoxications are limited (185–188), but reports of poisoning resulting from "recreational use" have been numerous during the past 15 years and have included fatalities (189).

Because of the widespread use of alkyl nitrites by homosexual men, prior to the discovery of the HIV virus as the causative agent, it was postulated that alkyl nitrites might be involved in the development of AIDS (179). This led to extensive research (190), particularly in the areas of genetic toxicity and immunotoxicity.

Methyl (191), ethyl (192), propyl (193), butyl (193, 194), isobutyl, *sec*-butyl, amyl, and isoamyl (193) nitrite are mutagenic in the Ames test. Of the six nitrites tested (propyl to isoamyl in the previous list), only amyl nitrite was not mutagenic in the mouse lymphoma assay (193). Ethyl nitrite also induced sex-linked recessive lethal mutations in *Drosophila* but did not induce micronuclei in mouse bone marrow cells (192). Isobutyl nitrite did not cause mutations in the *Drosophila* test (195).

Studies of the effects on immune parameters have produced contradictory results. Amyl nitrite caused functional deficits and structural alterations (seen by electron microscopy) in human mononuclear lymphocytes exposed *in vitro*(130). However, in a study of mice exposed to 50 or 300 ppm isobutyl nitrite 6.5 h/day, 5 day/week, for up to 18 weeks, no adverse effect on B-cell or T-cell function was detected (196). Another study in mice was done at higher exposure concentrations based on the expectation that abusers use higher concentrations for shorter durations (197). Mice were exposed to increasing isobutyl nitrite concentrations, 100 ppm for 1 day, 600 ppm for 3 days, then 900 ppm for 10 days. Specific decrements in T-cell responsiveness to mitogenic stimulants were seen, but B-cell responsiveness was unchanged.

The acute inhalation LC_{50}values for various alkyl nitrites are shown in Table 54.20. In general, potency decreases as alkyl chain length and branching increase. Very steep dose–response curves were seen for all compounds, indicating that relatively small increases of exposure concentration would produce large increases of mortality. Klonne et al. stated that the concentration range corresponding to 0 and 100% mortality in four exposures of rats was less than 100 ppm for most of the nitrites (198). The LC_{50}/EC_{50} (for decreased motor performance) ratio for a 30-min exposure of mice ranged from 2.0 to 2.4 (199). Therefore, acute inhalation exposure hazard for the alkyl nitrites is greater than would be indicated by their LC_{50}s alone.

Table 54.20. Acute Inhalation Toxicity of Alkyl Nitrites

Nitrite compound	4-h rat LC_{50} (ppm) (180)	1-h mouse LC_{50} (ppm) (181)	½-h mouse LC_{50} (ppm) (182)
Methyl	176	—	—
Ethyl	160	—	—
Propyl	300	—	—
Butyl	420	567	949

Isobutyl	777	1033	1346
sec-Butyl	—	1753	—
tert-Butyl	—	10,852	—
Isoamyl	716	—	1430

McFadden et al. measured methemoglobin levels *in vivo* and *in vitro* for butyl nitrite isomers (200). *tert*-Butyl was significantly less toxic than the other isomers and was the least potent methemoglobin inducer. Pretreatment with methylene blue before nitrite exposure also greatly increased the mean time to death for butyl, isobutyl, and *sec*-butyl, but only doubled the value for *tert*-butyl. The authors concluded from this that methemoglobin formation is the cause of death from butyl nitrite isomers except for *tert*-butyl. However, Klonne et al. point out that deaths occurred rapidly and always during exposure (198). This was a consistent finding of the other acute inhalation studies (199, 200). Animals recovered rapidly from all signs of exposure except for those associated with methemoglobinemia (cyanosis, bluish coloration of ears and feet). Exposure concentration rather than cumulative inhaled concentration was also the primary determination for mortality (198). Severe hypotension and cardiovascular collapse are more consistent with these findings as a cause of death. Most likely, both vasodilation and methemoglobinemia play a role in alkyl nitrite-induced mortality.

The lower aliphatic nitrites are promptly absorbed from the lung. Amyl nitrite is ineffective orally because it is destroyed in the gut. It is less effective by injection than by inhalation. Octyl nitrite (2-ethyl-*n*-hexyl-1-nitrite) is not absorbed through the mucous membranes and is ineffective sublingually. It appears that the nitrites are hydrolyzed *in vivo* to nitrite and the corresponding alcohol, which is then partly oxidized and partly exhaled unchanged.

The pharmacological properties determined in animals are so uniform within this group that information on the nitrites following can be taken as illustrative of the effects and potential hazards of the other members of the series (see Table 54.20 and Table 54.21).

Table 54.21. Comparative Toxicity Data for Aliphatic Nitro, Nitrate and Nitrite Compounds

Chemical group	Skin absorption	Irritation	Vascular dilatation	Methemoglobin formation	Industrial experience
Aliphatic nitro compounds (R_3CNO_2)					
Nitroalkanes	None	Moderate	None	Positive	Irritation, systemic symptoms
Chlorinated nitroparaffins	None	Marked	None	Unknown	Lung injury
Nitroolefins	Positive	Marked	Unknown	Not observed	None
Aliphatic nitrates (R_3CONO_2)	Positive	None	Marked	Positive	Systemic symptoms, possible deaths
Aliphatic	Unknown	None	Marked	Positive	Systemic

nitrites (R_3CONO)					symptoms, fatalities
Nitramines (R_3CNHNO_2)	None	None	None	None	Convulsions

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D. Summary

Although aliphatic nitro compounds, aliphatic nitrates, and aliphatic nitrites have several features in common (nitrogen-oxygen grouping, explosiveness, methemoglobin formation), there are significant differences in their toxic effects. Some of their attributes are summarized in Table 54.21. The esters of nitric and nitrous acid, whose nitrogen is linked to carbon through oxygen, are very similar in their pharmacological effects. Both produce methemoglobinemia and vascular dilatation with hypotension and headache. These effects are transient. None of the series has appreciable irritant properties. Pathological changes occur in animals only after high levels of exposure and are generally nonspecific and reversible. The nitric acid esters of the monofunctional and lower polyfunctional alcohols are absorbed through the skin. Information is not available on the skin absorption of alkyl nitrites. Members of both groups are well absorbed from the mucous membranes and lungs. Heinz body formation has been observed with the nitrates but not with the nitrites.

Nitro compounds, like nitrates and nitrites, cause methemoglobinemia in animals. Heinz body formation parallels this activity within the series. Although some members are metabolized to nitrate and nitrite, there is no significant effect on blood pressure or respiration. As with the lower nitrates and nitrites, anesthetic symptoms are observed in animals during acute exposures, but these occur late. The prominent effect is irritation of the skin, mucous membranes, and respiratory tract. This is most marked with chlorinated nitroparaffins and nitroolefins. In addition to respiratory tract injury, cellular damage may be observed in the liver and kidneys. Skin absorption is negligible except for the nitroolefins.

The nitramines have entirely different activity. RDX is a convulsant for humans and animals. Skin absorption, irritation, vasodilatation, methemoglobin formation, and permanent pathological damage are either insignificant or absent after repeated doses.

Transient illness has been associated with the industrial use or manufacture of these materials, but fatalities and chronic intoxication have been uncommon. Some members of each group present extremely high fire and explosion hazards.

Aliphatic Nitro, Nitrate, And Nitrite Compounds
Candace Lippoli Doepker, Ph.D.

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Aliphatic Nitro, Nitrate, And Nitrite Compounds

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N-Nitroso Compounds

William Lijinsky

A. Toxicity of N-nitroso Compounds

As noted with other groups of carcinogens, the test species often showed considerable variation in toxic and carcinogenic responses to a particular *N*-nitroso compound. For example, nitrosodimethylamine (NDMA) is more toxic to rats than nitrosodiethylamine (NDEA), but NDEA is a more potent carcinogen to rats than NDMA (6); in the Syrian hamster, NDMA is a more potent carcinogen than NDEA (6), whereas NDEA is less toxic than NDMA in hamsters (6). Moreover, the acute toxicity of most nitrosamines was expressed in the liver or lung of rats, mice, and hamsters (and sometimes in the gastrointestinal tract), whereas carcinogenicity was expressed in a variety of organs including liver, lung, stomach, bladder, pancreas, esophagus, and kidney (32). The considerable number of nitrosamines that were toxic to the liver but did not induce liver tumors was curious and suggested that whatever mechanisms caused liver damage were not the same as those that caused liver cancer. Of course, it has long been known that nitrosamines do not act directly but have to be activated metabolically to cause toxicity or carcinogenicity (33). Nitrosamines, as distinct from the directly acting alkylnitrosamides, are not mutagenic to bacteria or cells in culture, nor cytotoxic without metabolic activation by enzyme mixtures (e.g., S9 fractions from liver or other organs). Strangely, single doses of nitrosamines, however large, rarely induce tumors, although single doses of alkylnitrosamides often do. Almost all of the carcinogenic studies referred to here involve frequent administration of small doses (too small to have noticeable toxic effects) for many weeks, after which the animals are maintained until death (from tumors). This mode of treatment is believed to mimic usual human exposure more closely than single or few larger doses.

In general—and counterintuitively—most alkylnitrosamides are less toxic than analogous nitrosamines that give rise by metabolic activation to the same reactive intermediate (an alkyldiazonium ion) that is formed spontaneously from the alkylnitrosamide. This suggests that the

alkyldiazonium ion which alkylates DNA and other macromolecules is not the common intermediate that is responsible for the toxicity, mutagenicity, and carcinogenicity of these compounds, but that alternative mechanisms might be involved (34) in one or more of these biological activities. What seem to be surprising and perhaps illogical is that toxic effects are seen by comparing methylnitrosourea with methylnitrosourethane, both given to rats by intravenous injection, in the case of MNU into the hepatic portal vein at 30 mg/kg body weight (and cause sufficient methylation of liver nucleic acids to be identified by mass spectrometry (35), but cause no liver tumors). The LD_{50} of MNU was 110 mg/kg body weight and that of methylnitrosourethane was 4 mg/kg, both by intravenous injection. Yet, no toxic effects were seen in the liver examined by electron microscopy.

The difference in acute toxicity in rats or in mice or hamsters between *N*-nitroso compounds that, according to conventional wisdom, exert their biological effects by forming of the same putative reactive intermediate (e.g., the methyldiazonium ion) poses a dilemma. For example, why is a directly acting *N*-nitroso compound (MNU, MNNG, or methylnitroso-urethane) less toxic than many methylnitrosoalkylamines which must be activated to form the toxic agent? Although numerous methylnitrosoalkylamines have similarly high toxicities, many are also considerably less toxic (Table 55.3) with no apparent explanation. However, the simple explanation of formation of the same toxic intermediate is probably wrong or at least incomplete.

Table 55.3. Toxicity and Carcinogenicity of Some *N*-Nitroso Compounds

	Toxicity			Carcinogenicity	
***N*-Nitroso-**	**Species**	**Route**	**LD_{50}[a]**	**Route**	**Organ**
dimethylamine	Mouse	i.p.	20	Oral	Liver, lung
	Rat	Oral, i.p.	30	Oral	Liver, kidney
	Hamster	s.c.	30	Oral	Liver, nasal
	G.pig	i.p.	16	Oral	Liver
diethylamine	Mouse	Oral	220	Oral	Liver, esoph.
	Rat	Oral	280	Oral	Liver, esoph.
	Hamster	s.c.	250	Oral	Liver, nasal
	G.pig	i.p.	190	Oral	Liver
methylethylamine	Rat	Oral	90	Oral	Liver, esoph.
di-*n*-butylamine	Rat	Oral	1,200	Oral	Liver, bladder
	Hamster	Oral	2,150	Oral	Liver, bladder
di-*n*-propylamine	Rat	Oral	480	Oral	Liver, esoph.
	Hamster	s.c.	600	Oral	Nasal, trachea
methylvinylamine	Rat	Oral	22	Oral	Lung, nasal
diethanolamine	Rat	Oral	>7,500	Oral	Liver, nasal
	Hamster	s.c.	11,300	Oral	Nasal
morpholine	Rat	Oral	280	Oral	Liver, esoph.
	Hamster	Oral	1050	Oral	Nasal, trachea
2,6-dimethyl-morpholine	Rat	s.c.	430	Oral	Esoph, nasal
	Hamster	Oral	370	Oral	Pancreas, liver
piperidine	Rat	Oral	200	Oral	Esoph, nasal

pyrrolidine	Rat	Oral	900	Oral	Liver
diphenylamine	Rat	Oral	3,000	Oral	Bladder
sarcosine	Rat	Oral	5,000	Oral	Esophagus
proline	Rat	Oral	5,000	Oral	Inactive -
dibenzylamine	Rat	Oral	900	Oral	Inactive -
nornicotine	Rat	s.c.	1,000	Oral	Esoph, nasal
methylurea	Rat	Oral	180	Oral i.v.	Brain, stomach, uterus, breast
	Hamster	s.c.	70	Oral	Spleen, stomach
ethylurea	Rat	Oral	300	Oral	Breast, stom. etc
methylnitro-guanidine	Rat	Oral	100	Oral	Gland. stomach

[a] mg/kg body weight as a single dose by gavage or injection.

Although it is understandable that some nitrosamines might be toxic but not carcinogenic (e.g., nitrosiminodiacetonitrile, methylnitroso-*tert*-butylamine, methylnitrosomethoxyamine, nitrosodiallylamine in rats) because their toxicity is through some unconventional mechanism, it is more difficult to understand why some reasonably potent carcinogens (e.g., nitrososarcosine, nitrosodiethanolamine, ethylnitrosoethanolamine) are not toxic (or not measurably so). The cyclic nitrosamines pose a particular dilemma because little is known about their activation, the products of their metabolism, or the reasons for the differences in their carcinogenicity. The simplest cyclic compound, nitrosoazetidine, is almost not toxic; toxicity increases up to nitrosopiperidine and nitrosohexamethyleneimine and declines as the ring grows larger. All are toxic to rat liver, although not all induce liver tumors in rats (5, 6). There are differences between species in response to the toxicity of a given *N*-nitroso compound, as there are to carcinogenicity; mice are often less responsive than rats, as mice are to carcinogenesis by many *N*-nitroso compounds. However, most *N*-nitroso compounds are both toxic and carcinogenic (6). As already mentioned, there is no parallel between toxicity and carcinogenicity among different species or within structurally related groups of *N*-nitroso compounds.

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B. Mutagenesis and Cell Transformation

One *N*-nitroso compound, *N*-methyl-*N*-nitroso-*N*'-nitroguanidine (MNNG), was one of the first known chemical mutagens (36) and since then a large number of *N*-nitroso compounds have been examined for mutagenic and cell-transforming properties, apparently propelled by the wish to develop quick ways of identifying carcinogens instead of the lengthy and expensive chronic toxicity test in animals (rodents). In looking for parallels between carcinogenic and mutagenic activities, there are striking differences, even among groups of *N*-nitroso compounds of similar structure. It is almost always necessary to test a nitrosamine for mutagenicity by incorporating a metabolic activation system, usually the S-9 fraction of liver homogenate, called the "microsomal fraction," which was introduced by Ames into his microbial (*Salmonella*) mutagenic assay (37). It is assumed that this mimics the activation of nitrosamines *in vivo*.

Most alkylnitrosamides are directly acting mutagens (i.e., they do not need metabolic activation), although not proportional in activity to their carcinogenic activity. On the other hand, almost all nitrosamines require metabolic activation to uncover their mutagenic activity. A large proportion of the nitrosamines that have been tested for carcinogenic activity have also undergone mutagenic

testing, exhaustive in the case of some compounds, (e.g., NDMA, NDEA). NDMA with rat liver microsomal activation is not measurably mutagenic to *Salmonella* strain TA1535 in the simple "plate test," although it is powerfully carcinogenic to rat liver. Both NDMA and NDEA are more readily activated to bacterial mutagens by hamster liver microsomes than by rat liver microsomes, although by no means are these two nitrosamines more potent carcinogens in hamsters than in rats (38). The greater activity of hamster liver microsomes in this regard is true for a large proportion of nitrosamines tested, although most are more potent carcinogens in rats than in hamsters (6, 39), and includes the large series of methylnitrosoalkylamines, which, it is assumed, act (as mutagens and carcinogens) by metabolic formation of the same methylating intermediate. These comparisons throw into doubt the current concept of the close relationship—perhaps identity—of the mechanisms of carcinogenesis and mutagenesis.

These discrepancies also apply to the large number of cyclic nitrosamines that have been studied, in which the superiority of hamster liver microsomes over rat liver microsomes in activating them to mutagens is even greater to the extent that several compounds are activated to mutagens only by hamster liver enzymes, not by rat liver enzymes. This is also true of many acyclic nitrosamines, and especially so of those nitrosamines that have oxygen functions (hydroxyl- or carbonyl-) in their side chains. A number of carcinogenic nitrosamines are not activated by either rat or hamster liver microsomes to mutagens (39); these include such liver carcinogens as nitrosodiethanolamine, methylnitrosoethylamine, nitroso-3-hydroxypyrrolidine, and methylnitrosoethanolamine, as well as methylnitrosoaniline, methylnitroso-3-carboxypropylamine, and nitrosodiphenylamine, which induce tumors in other organs, but not in the liver (40). Most of the noncarcinogenic nitrosamines (which include most nitrosamino acids) are not mutagenic, but some that are mutagenic are not carcinogens (nitrosoguvacoline, nitrosophenmetrazine, nitrosodi-*n*-octylamine). The usefulness of the mutagenic assays in predicting the probable carcinogenicity of *N*-nitroso compounds is obvious, although there is no quantitative parallel, but the many unexpected exceptions (e.g., MNEA) indicate that mutagenesis is not a guide to understanding the carcinogenic mechanisms of these compounds.

This conclusion is fortified by the mutagenic studies of alkylnitrosamides, which show a huge disparity between carcinogenic potency and mutagenic effectiveness. For example, a series of methylnitrosocarbamate esters (most of which are *N*-nitroso derivatives of pesticides, e.g., nitrosocarbaryl) vary 10- to 200-fold in mutagenicity (41, 42), but have very similar carcinogenic potencies (43); the ratio of their mutagenicities is similarly large versus methylnitrosourea, which is a much more potent carcinogen. Yet, all of these compounds, it is believed, act as mutagens or carcinogens by directly forming the same alkylating intermediate, the methyldiazonium ion. Part of the discrepancies might be explained by differences in uptake by the bacteria, as shown in *Hemophilus influenzae* (44).

Among the many alkylnitrosoureas tested as bacterial mutagens, which, it is believed, act by forming the corresponding alkyldiazonium ion, there is not a large difference among most of them in mutagenic potency, although this tends to increase with increasing molecular weight (45). Some unusual structures such as hydroxyethylnitrosourea, isopropanolnitrosourea, and 2-phenylethyl-nitrosourea are especially potent, whereas benzylnitrosourea and *n*-tridecylnitrosourea are almost inactive, but overall there is no parallel between mutagenicity and carcinogenicity among these directly acting *N*-nitroso compounds. The same is true of the limited number of alkylnitrosoguanidines tested, of which MNNG is almost the standard mutagen but is not a particularly potent carcinogen; the nitroso derivative of a widely used drug, nitrosocimetidine, is quite mutagenic but is not a carcinogen (46).

N-nitroso compounds act as mutagens or transforming agents in mammalian cells in culture or in bacteriophage induction. It is claimed that their activity depends largely on the formation, directly or following enzymic activation, of an alkyldiazonium ion that alkylates DNA. All have the same or similar drawbacks and discrepancies which have been discussed earlier in connection with bacterial mutagenic assays. The cell transformation assays (47) seem to have some characteristics that do not depend on alkylation of DNA because compounds such as nitrosodiphenylamine, which do not form

an alkylating product, produce positive results in these assays. However, the results do not uniformly parallel the carcinogenic activity of these compounds, indicating again that the mechanisms of the various biological activities differ (47).

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C. Metabolism and Activation

Although there are differences and discrepancies among the mutagenicity, carcinogenicity, and other biological activities of the directly acting alkylnitrosamides, it is credible that one of the underlying actions is the direct formation of a reactive intermediate, such as an alkyldiazonium ion, common to many of them (e.g., the methylating compounds). On the other hand, in the case of the nitrosamines, it is not readily apparent that formation of a simple alkylating intermediate (such as an alkyldiazonium ion) is the underlying process. Rather, there is evidence that extensive and varied metabolism is frequently required to bring about carcinogenesis, or even mutagenesis. As shown by the lower activity as mutagens or carcinogens of nitrosamines labeled with deuterium in the positions alpha to the nitroso group, alpha-oxidation is a rate-limiting step in the biological activation of most nitrosamines (48–50). This finding is fortified by the observation that substituting methyl or other alkyl groups in the alpha positions of nitrosamines, cyclic or acyclic, reduces or abolishes carcinogenic or mutagenic activity. In the case of acyclic nitrosamines, alpha-oxidation forms an unstable alpha-hydroxy derivative (51), which is reactive and decomposes to release an alkyldiazonium ion, that can alkylate macromolecules (and presumably the alpha-hydroxy derivative can also). In the case of cyclic nitrosamines, such as nitrosomorpholine or nitrosopiperidine, the fate of the alpha-hydroxy derivative is much less clear, particularly the identity of the products related to carcinogenesis or mutagenesis, and those that are simply products of detoxication.

There have been many studies of the metabolism and activation of nitrosamines, including those of the series of methylnitroso-*n*-alkylamines, that show striking differences in the target organ for carcinogenesis as the chain becomes longer. In fact, it is through beta-oxidative chain shortening (Knoop) that the longer chain compounds produce a metabolite (methylnitroso-2-oxopropylamine) that induces bladder tumors in rats (39), whereas the short-chain compounds induce tumors of the liver or esophagus.

Oxidation of nitrosamines in animals can be extensive, as shown by the formation and excretion of derivatives of nitroso dialkylamines such as nitrosodi-*n*-propylamine and nitrosodi-*n*-butylamine hydroxylated at most positions of the alkyl chain (52) and in the studies of metabolites of methylnitroso-*n*-amylamine by Mirvish (53).

The complex interrelationships between 2,6-dimethylnitrosomorpholine (DMNM—which unlike nitrosomorpholine induces no liver tumors in rats, although it does in hamsters, together with pancreas tumors), nitrosobis-2-oxopropylamine (NBOPA), nitrosobis-2-hydroxypropylamine (nitrosodi-isopropanolamine—NBHPA) and nitrosohydroxypropyl-oxopropylamine (NHPOPA) pose another unsolved problem in explaining their carcinogenic properties (54, 55).

The conventional wisdom is that *N*-nitroso compounds exert their carcinogenic (and probably toxic) effects by forming of an alkylating intermediate (alkyldiazonium compound) that alkylates DNA, causes mutations (and leads to cancer), but this is an oversimplified and unsatisfactory explanation of the experimental data. For example, the compounds in the preceding paragraph all methylate DNA of the liver and other organs *in vivo* in rats and hamsters to similar extents (somewhat lower with DMNM). They all induce liver tumors in hamsters (but to different extents) but in rats DMNM and NBHPA induce only tumors of the esophagus, NBOPA induces liver tumors, and NHPOPA induces both (39, 56). These results indicate that alkylation of DNA by these nitrosamines might

play a role in inducing of tumors (in the liver, for example), that alone is insufficient and other factors and properties of the nitrosamine are equally or more important, but these are largely unknown. And so it is with a large number of *N*-nitroso compounds that methylate DNA, for example, in rat liver. Only some of them give rise to liver tumors, but often to tumors in other organs in which they produce less methylation of DNA. Examples are methylnitrosourea, MNNG, NDMA in high doses (at which kidney tumors are induced) (57), although at low doses liver tumors are induced, and not kidney tumors (58); the same is true of azoxymethane (isomeric with NDMA), which induces tumors in the colon, as well as the liver (59).

Most *N*-nitroso compounds are both carcinogenic and mutagenic, but about 10% of those tested (more than 300) are not carcinogenic. Few of the noncarcinogens are mutagens, but several carcinogens are not mutagenic. Particularly interesting are those nitrosamines that are rat liver carcinogens, yet are not activated to mutagens by rat liver enzymes (e.g., nitrosodiethanolamine, nitrosodi-isopropanolamine, and methylnitrosoethylamine), although several of them are activated by hamster liver enzymes. In the context of this volume, this fact is important only because there is increasing reliance on "short-term" assays for predicting the carcinogenicity of newly discovered substances, and it would be easy to overlook a nonmutagenic nitrosamine as unlikely to be a carcinogen, forestalling a chronic toxicity test. Whether a nonmutagen (e.g., NDELA) alkylates DNA to a very small extent, usually remains to be determined (60).

Another important consideration is that there are considerable differences in susceptibility to toxicity and carcinogenicity among species, even those as closely related as rats, mice, and hamsters. In general, rats are more susceptible than either hamsters or mice (in that order). In the case of NDELA, massive doses are needed to induce liver tumors in mice, whereas modest doses are adequate in rats; NDELA did not induce liver tumors in hamsters, but did induce tumors of the nasal cavity (61, 62). This suggests that it might be unwise to consider that rats represent the species most sensitive to *N*-nitroso compounds and that humans are no more sensitive. In fact there is evidence from the great effectiveness of tobacco-specific nitrosamines in cigarette smokers and in smokeless tobacco users (in whom exposure is small, but the cancer incidence high) compared with the comparable responsiveness of rats or hamsters to much higher doses, that humans might be considerably more susceptible to the carcinogenic effects of *N*-nitroso compounds than the routinely used test animals.

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D. Chronic Effects—Carcinogenicity

From the extensive literature on the biological testing and evaluation of *N*-nitroso compounds, numerous results frustrate the proposal of a single mechanism by which these compounds induce tumors because of the complexity of the tumor responses in different species to a particular *N*-nitroso compound. For example, consider the series of methylnitroso-*n*-alkylamines from C_2 (methylnitrosoethylamine, MNEA) to C_{12} (methylnitroso-*n*-dodecylamine) all of which are metabolized to form a methylating agent that methylates DNA in rat liver (63) (although not necessarily to the same extent) and all of which are carcinogenic (64). In contrast, methylnitroso-*tert*-butylamine, which cannot be metabolized to form a methylating agent, is not carcinogenic; on the other hand, methylnitrosoaniline, which also cannot be metabolized to form a methylating agent is carcinogenic to rats and forms esophageal tumors. However, there the simplicity ends because the lowest members of the homologous series, NDMA and MNEA, induce tumors of the liver and lung in rats (as well as tumors of the esophagus in the case of MNEA). The C_3, C_4 and C_5 compounds give rise only to tumors of the esophagus in rats, whereas the C_6, C_7 and C_8 compounds induce tumors of the esophagus, liver, and lung in rats, the proportions depend on whether the nitrosamine

is administered in drinking water or by gavage. Methylnitroso-*n*-octylamine (C_8) also causes bladder tumors in many rats. The larger C_9 to C_{12} molecules are almost insoluble in water and had to be administered by gavage in oil, and compounds with an odd number of carbons in the chain induced liver and lung tumors in rats. Those with an even number of carbons in the chain induced tumors of the bladder and lung, but seldom liver tumors, although these nitrosamines are extensively metabolized in the rat liver. The metabolism (beta-oxidation) of those compounds with even-numbered carbon chains terminates at methylnitroso-3-carboxypropylamine, which is beta-oxidized and decarboxylates to form methylnitroso-2-oxopropylamine, which induces bladder tumors in rats when injected into the bladder (65). Beta-oxidation of nitrosamines that have odd-numbered carbon chains produces a different end product. In contrast with their varied carcinogenic properties in rats, the response to this series of methylnitroso-*n*-alkylamines is quite uniform in hamsters and consists of liver and lung tumors and occasionally tumors of the nasal cavity and bladder tumors with the even-numbered carbon chain compounds larger than C_6; there were no esophageal tumors in hamsters (no *N*-nitroso compound induces esophageal tumors in hamsters, although a large proportion of nitrosamines given to rats has induced tumors of the esophagus).

This leads to another perplexing finding, that no alkylnitrosamide—although they are directly acting alkylating agents—induces tumors of the esophagus or nasal cavity in rats, even when given in drinking water; many nitrosamines induce tumors of the esophagus in rats, whether given in drinking water or by gavage, even when administered by intraurethral injection or by subcutaneous injection. Such findings led to the conclusion that *N*-nitroso compounds usually act systemically, rather than locally. However, several alkylnitrosamides produce skin tumors when painted frequently on the skin of mice (66), as well as systemically in rats by oral administration (6). No nitrosamine has produced skin tumors by local action, although when painted on the skin, they can be absorbed and in some cases induce tumors of internal organs. Alkylnitrosoureas in rats induce tumors of the nervous system, of the glandular stomach (similar to human stomach), and of the mammary gland and mesotheliomas (in males), which have not been induced by any nitrosamine; in hamsters, alkylnitrosoureas have induced hemangiosarcomas of the spleen almost exclusively (together with tumors of the forestomach, probably induced locally); in splenectomized hamsters, few tumors were induced by 2-hydroxyethylnitrosourea, mainly some forestomach tumors (67). Alkylnitrosoureas did not induce tumors of the nervous system, glandular stomach, mammary gland or mesotheliomas in hamsters, although they are directly acting alkylating agents. There has been no adequate explanation of these profound differences, which do not depend primarily on the presence of particular activating enzymes in certain tissues or organs, and the results make it difficult to accept the conventional simple alkylation of DNA as the mechanism of such organ and species-specific carcinogenesis by *N*-nitroso compounds.

The difference in response of different species to *N*-nitroso compounds has been discussed using rats and hamsters as examples. Mice tend to follow rats in the pattern of tumors induced by particular *N*-nitroso compounds, although rats seem to be more sensitive than mice or hamsters (perhaps by a factor of 10). The limited evidence that can be used to compare humans with rats suggests that humans might be considerably more sensitive (68).

Perhaps the most important property of carcinogens in relation to human health is the ability to induce tumors transplacentally because a fetus is more susceptible (i.e., responsive to smaller doses) to the action of many carcinogens than adults (as is true also of infants and young children). In the case of *N*-nitroso compounds, there has been considerable interest in this aspect, particularly by Ivankovic who induced tumors of the nervous system in rats transplacentally by treating their mothers with alkylnitrosoureas during the last third of pregnancy (21). The same result was achieved using *N*-methylnitroso ethyl carbamate (methylnitrosourethane) (69). This use of an alkylnitrosamide is one of the few models for human childhood brain cancer. No nitrosamine administered to pregnant animals has induced brain cancer in offspring, although several nitrosamines have induced other types of tumor transplacentally, albeit not with as great efficacy as alkylnitrosoureas. Usually, one or two mice or rats per litter with tumors has resulted, even after a substantial dose to the mother.

Because humans are exposed to rather small quantities of *N*-nitroso compounds, the importance of transplacental exposure to other than alkylnitrosamides might be small.

The large difference in the incidence of many common cancers between the industrialized world and the "less-developed" world (70) is a conundrum, compounded by the studies of vast populations of migrants, who within one or two generations often develop the pattern of cancer of their new country, instead of that of their ancestors. This suggests that environmental exposure to carcinogens is a large factor in many common cancers, compared with a smaller genetic factor. (The difference in the incidence of some cancers, such as breast cancer, in black Americans compared with West African women can be as much as tenfold or more higher in the United States.)

A subject of great interest is the extent to which tumor models in animals can be used as surrogates for human cancers. In some cases, *N*-nitroso compounds represent the best or only models. For example, derivatives of *N*-nitroso-2-oxopropylamine given to hamsters give rise to tumors of the pancreatic ducts, a common and nasty human cancer, prevalent in idustrialized countries (Western Europe and North America). A number of nitrosamines that have this structure (or convertible metabolically into it) have induced pancreatic tumors more or less effectively; the most effective is nitrosobis-(2-oxopropyl)-amine; strangely, 2-oxopropylnitrosoureas, although quite carcinogenic, do not have this property (71). Many nitrosamines have induced tumors of the esophagus in rats (although not in hamsters) and provide a model for the human tumor, which is common in certain areas of the world and is often associated with smoking tobacco and drinking alcoholic beverages. The linking of alkylnitrosoureas (and probably alkylnitrosocarbamate esters) with transplacentally induced brain and nervous system tumors in rats provides another rare model of common human cancers. The same alkylnitrosoureas in rats give rise to tumors of the colon and other parts of the lower gastrointestinal tract, another rare model of common human tumors, whereas in hamsters they induce mainly hemangioendothelial sarcomas of the spleen (but not of other organs) and few other tumors. This and other species differences in response to *N*-nitroso compounds is one of the intriguing aspects of carcinogenic studies and has a probable bearing on understanding the induction and development of cancer in general. Perhaps less important in relevance to human cancer is the large number of nitrosamines that induce tumors of the nasal cavity in rats, mice and hamsters and that do not have to be inhaled to do so (these tumors appear when the nitrosamines are given by gavage or even when injected into the bladder), in contrast with formaldehyde, acetaldehyde, and numerous halogenated hydrocarbons.

The marked difference in response of different species to many *N*-nitroso compounds make it impossible to predict which organs or tissues in humans would be responsive to those same compounds. But it is unwise to assume that any *N*-nitroso compound that is carcinogenic in rodents would be inactive in humans. Indeed, it is not improbable that humans are more susceptible to carcinogenic *N*-nitroso compounds than rats, which are more susceptible than hamsters or mice. The great effectiveness of cigarette smoke in producing lung cancer (and other cancers) in human smokers is surprising because cigarette smoke has a low content of carcinogens, of which nitrosamines are the most important. The dose of nitrosamines to a heavy cigarette smoker is approximately 0.06 mg/kg body weight/day (72), compared with the minimal effective dose of the most potent carcinogenic nitrosamines in rats (NDMA and NDEA) of 20–40 mg/kg body weight/day (58). Like most carcinogens, with increasing doses, *N*-nitroso compounds show an increase in the proportion of animals with tumors or a decrease in the time before tumors appear, or both (4, 73). Dose–response studies, mainly in rats, with a number of nitrosamines (including nitrosodiethylamine, nitrosomorpholine, nitrosopiperidine, nitrosopyrrolidine, nitrosodiethanolamine, nitroso-1,2,3,6-tetrahydropyridine, dinitrosohomopiperazine, and nitrosoheptamethyleneimine) have shown the same effect, often down to very low doses of a few micrograms per day. At this level there was virtually no life-shortening effect because tumors arose toward the end of the life span. These compounds induced a variety of tumors including those of liver, esophagus, and lung at the higher dose rates.

E. Risk Assessment

Because NDMA is the *N*-nitroso compound that has the most widespread human exposure (but possibly not the largest), risk assessment has focused on this compound and the possibility that exposure to it increases the risk of cancer. Although it is highly toxic, the possibility nowadays that exposure to it could be in such high concentrations as to lead to immediate toxic effects is essentially nil (other than deliberate poisoning) (74). In few cases, governmental regulatory agencies have calculated the long-term cancer risks of exposure, based on the results of tests in animals. The U. S. Environmental Protection Agency has declared that a concentration of 7 parts per trillion (10^{12}) of NDMA in drinking water or water for recreation represents a cancer risk of 1 in 10^6, and the State of California claims that exposure to 0.004 mg of NDMA per day presents a cancer risk of 10^{-6}. In the case of nitrosodiethanolamine (NDELA), the EPA has determined that the cancer risk of occupational exposure to 10^{-5} mg per kg per day is 10^{-6}, and in Europe a similar risk is posed by exposure to 0.0002 mg of NDELA per kg per day in cosmetics. These numbers are quite approximate.

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F. Specific Chemicals

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Aliphatic and Alicyclic Amines
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1 General Considerations

Aliphatic and alicyclic amines are nonaromatic amines that have a straight chain, a branched chain, or a cyclic alkyl moiety attached to the nitrogen atom.

Aliphatic amines are highly alkaline and tend to be fat soluble. As such, they have the potential to produce severe irritation to skin, eyes, and mucous membranes. Corrosive burns as well as marked

allergic sensitization may also occur (1). Volatile amines, which are characterized by boiling points lower than 100°C, are highly irritating and include methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, *n*-propylamine, isopropylamine, diisopropylamine, allylamine, *n*-butylamine, isobutylamine, *sec*-butylamine, *tert*-butylamine, and dimethylbutylamine. Workplace practice must consider these properties in developing strategies to protect workers. Toxicity information in humans continues to be limited. Although great strides in understanding the process of carcinogenicity have been made in recent years, controversies regarding potential aliphatic amine carcinogenicity are far from being resolved. Of considerable interest is the possibility of nitrosamine formation, which is both compound specific and pH dependent.

1.1 Chemical and Physical Properties

Aliphatic amines are highly alkaline derivatives of ammonia where one, two, or three of the hydrogen atoms are replaced by alkyl or alkanol radicals of six carbons or fewer. In addition, primary and secondary amines can also act as very weak acids (K_a approximately 10–33) (2). Many of the lower aliphatic amines have low flash points and are flammable liquids or gases. Branching of the alkyl chain tends to enhance volatility, whereas hydroxy substitution as in the alkanolamines decreases volatility (2a–2c). Methylamine solutions are good solvents for many inorganic and organic compounds.

Most aliphatic amines have a distinctly unpleasant odor. The fishy or fishlike odor of methylamines increases from mono- to trimethylamine, and in high concentrations they all have the odor of ammonia (2). Olfactory fatigue occurs readily. No symptoms of irritation are produced from chronic exposures to less than 10 ppm (1). Deodorization of ammonia and amines can be achieved with the use of dihydroxyacetone, which is reportedly nontoxic to humans and domestic animals and reacts rapidly with ammonia or amines (1b).

Amoore and Furrester reported that about 7% of humans are unable to smell (Anosmic) trimethylamine (1c). Odor threshold measurements on 16 aliphatic amines were made with panels of specific anosmics and normal observers. The anosmia was most pronounced with low-molecular-weight tertiary amines, but was also observed to a lesser degree with primary and secondary amines. This specific anosmia apparently corresponds with the absence of a new olfactory primary sensation, the fishlike odor.

The aliphatic amines are conveniently classified as primary, secondary, and tertiary amines according to the number of substitutions on the nitrogen atom. If only one hydrogen is replaced with an alkyl group, the amine is a primary amine, even though the alkyl substituent may have a secondary or tertiary structure (1).

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

2 Methylamine

2.0.1 CAS Number:

[*74-89-5*]

2.0.2 Synonyms:

Monomethylamine, anhydrous monomethylamine, aminomethane, methanamine, and MMA

2.0.3 Trade Names:

NA

2.0.4 Molecular Weight:

31.06

2.0.5 Molecular Formula:

CH_5N

2.0.6 Molecular Structure:

2.1 Chemical and Physical Properties
2.1.1 General Methylamine is a colorless, flammable gas at room temperature and atmospheric pressure. It is readily liquefied and is shipped as a liquefied gas under its own vapor pressure.

2.1.2 Odor and Warning Properties It has a characteristic fishlike odor in lower concentrations, readily detectable at 10 ppm, becomes strong at 20–100 ppm, and becomes intolerably ammoniacal at 100–500 ppm (8b). The odor threshold reportedly ranges from 0.0009 to 4.68 ppm, and becomes irritating at 24 mg/m^3 (62, 63).
2.2 Production and Use
Methylamine can be manufactured by reacting ammonia and methyl alcohol in the presence of silica–alumina catylst at elevated temperature and pressure; by reductive amination of formaldehyde; or by heating methyl alcohol, ammonium chloride, and zinc chloride to about 300°C. It is used in tanning, fuel additives, photographic developers, and rocket propellants (64), in the manufacture of dyestuffs, in the treatment of cellulose acetate rayon, and in organic synthesis.
2.3 Exposure Assessment
2.3.1 Air NIOSH (65).

2.3.2 Background Levels Bouyoucos and Melcher (66).

2.3.3 Workplace Methods Fuselli et al. (67). OSHA method #40 is recommended for determining workplace exposure (OSHA Analytical Methods, 1990, 1993).

2.3.4 Community Methods Leenheer et al. (68).
2.4 Toxic Effects
2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity Methylamine has been reported to cause liver toxicity in laboratory animals (69). A drop of 5 percent solution in water applied to animal eyes was reported to cause hemorrhages in the conjunctiva, superficial corneal opacities, and edema (70, 71, p. 680).

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms When administered to humans, dogs, or rabbits as the hydrochloride, methylamine is rapidly absorbed and only traces of the unchanged compound was observed to be excreted in the urine by early investigators (Salkowski, 1877; Schiffer, 1880) (15). Salkowski claimed that very small amounts of methylurea were excreted by rabbits, but this was not observed in the case of dogs by Schmiedeberg (1878) (15). In 1893, Pohl claimed that small amounts of formate were excreted by dogs receiving methylamine hydrochloride (15), and urea formation was demonstrated in a perfused dog liver experiment by Loffler in 1918 (15). Kapellar-Adler and Krael (1931) were the first to postulate that the amino group was probably split off as ammonia (26).

In 1937 Richter put the two concepts together and proposed that the reaction may be split into two stages in which the amine is first dehydrogenated to the corresponding intermediate imine, which reacts spontaneously with water forming an aldehyde and ammonia. Richter believed that most amines were oxidized by amine oxidase, according to the following reaction in the case of primary amines (26):

$$RCH_2NH_2 + O_2 \rightleftharpoons RCH{=}NH + H_2O_2 RCH{=}NH + H_2 \rightleftharpoons RCHO + NH_3 \quad (1)$$

Methylamine and trimethylamine are also reportedly metabolized to a small extent to dimethylamine in the body (8), and Alles and Heegaard (1943) demonstrated that methylamine could be oxidized, although with difficulty, *in vitro* by MAO (9, 10).

2.4.1.4 Reproductive and Developmental Treatment of CD-1 mice by daily intraperitoneal injection of 0.25, 1, 2.5, or 5 mmol/kg from day 1 to day 17 of gestation demonstrated no adverse reproductive effects. In the same experiment, dimethylamine was also without effect; trimethylamine decreased fetal weight without affecting maternal body weight gain. None of the amines caused a significant increase in external or internal organ or skeletal abnormalities (8).

2.4.2 Human Experience Brief exposures to 20–100 ppm produce transient eye, nose, and throat irritation; no symptoms of iritation are produced from longer exposures at less than 10 ppm; olfactory fatigue occurs readily (8b).

In one plant a case of allergic or chemical bronchitis occurred in a worker exposed to 2–60 ppm, although masks or respirators were reportedly worn during "greatest exposures" (64).
2.5 Standards, Regulations, or Guidelines of Exposure
An ACGIH threshold limit value (TLV)-time-weighted average (TWA) value of 5 ppm (6.4 mg/m^3) and a short-term exposure limit (STEL) of 15 ppm (19 mg/m^3) have been adopted (72). The OSHA PEL and NIOSH REL is 10 ppm.
2.6 Studies on Environmental Impact
Aliphatic amines including methylamine were determined in oil-shale retort water (68).

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

3 Dimethylamine
3.0.1 CAS Number:
[*124-40-3*]
3.0.2 Synonyms:
DMA, *N*-methylmethanamine
3.0.3 Trade Names:
NA
3.0.4 Molecular Weight:
45.08
3.0.5 Molecular Formula:
C_2H_7N
3.0.6 Molecular Structure:

3.1 Chemical and Physical Properties
3.1.1 General The molecular formula for dimethylamine is $(CH_3)_2NH$. DMA is a flammable, alkaline, colorless gas at room temperature and atmospheric pressure (73, 74). It is readily liquefied and is shipped in steel cylinders as a liquefied gas under its own vapor pressure (75).

3.1.2 Odor and Warning Properties DMA has a characteristic rotten fishlike odor in lower concentrations (62, 63). The odor threshold ranges from 0.00076 to 1.6 ppm, and becomes irritating

at 175 mg/m^3 (62, 63). In higher concentrations (100–500 ppm) the fishlike odor is no longer detectable and the odor is more like that of ammonia.

3.2 Production and Use

Dimethylamine is manufactured by reaction of ammonia and methanol over dehydrating catalysts at 300–500°C or by catalytic hydrogenation of nitrosodimethylamine (51). DMA has been used as an accelerator in vulcanizing rubber, in the manufacture of detergent soaps, and for attracting boll weevils for extermination (73, 74). It has been used as a depilating agent in tanning, as an acid gas absorbent, in dyes, as a flotation agent, as a gasoline stabilizer, in pharmaceuticals, in soaps and cleaning compounds, in the treatment of cellulose acetate rayon, in organic syntheses, and as an agricultural fungicide (75).

3.3 Exposure Assessment

3.3.1 Air NIOSH (65).

3.3.2 Background Levels NIOSH (76).

3.3.3 Workplace Method NIOSH Method 201D (65).

3.3.4 Community Methods Cross et al. (77).

3.4 Toxic Effects

3.4.1 Experimental Studies Dimethylamine is irritating and corrosive to both the eyes and skin of test animals (78).

Several DMA inhalation studies have been reported. Exposure of rats, mice, guinea pigs, and rabbits to 97 or 185 ppm of DMA 7 h/d, 5 d/wk for 18–20 wk revealed corneal injury in eyes of guinea pigs and rabbits as well as central lobular fatty degeneration and necrosis of the liver in all species (79). However, histopathological examination of rats, guinea pigs, rabbits, monkeys and dogs exposed to 9 mg/m^3 of DMA continuously for 90 d produced only mild inflammatory changes in the lungs of all species; dilated bronchi in rabbits and monkeys were noted (80).

Steinhagen et al. reported an acute 6-h whole-body exposure of male F344 rats to DMA concentrations ranging from 600 to 6000 ppm for 6 h, which produced a spectrum of pathological changes in the nasal passages, including severe congestion, ulcerative rhinitis, and necrosis of the nasal turbinates (81). Lesions outside the respiratory tract were evident in livers of rats exposed to 2500–6000 ppm, and corneal edema was observed in the eyes of rats at 1000 ppm; corneal ulceration, keratitis, edema, and loss of Descement's membrane was present at 2500–6000 ppm; in addition, many rats exposed to 4000 or 6000 ppm had necrosis of the iris and severe degeneration of the lens, suggestive of acute cataract formation. From a 10-min head-only exposure of male F344 rats to DMA concentrations ranging from 49 to 1576 ppm, a concentration–response curve indicated that a 10-min exposure of 600 ppm would be expected to result in a 51% decrease in respiratory rate; the corresponding calculated response dose, RD50, was 573 ppm.

In an experiment to determine whether pathological changes occurred in the respiratory tract of mice after inhalation exposure to various sensory irritants at their respective RD50 concentrations, 16–24 male Swiss–Webster mice were exposed to 510 ppm DMA, 6 h/d for 5 d; lesions induced in the respiratory epithelium ranged from epithelial hypertrophy or hyperplasia to erosion, ulceration, inflammation, and squamous metaplasia (82).

In a 1-year inhalation study, male and female F344 rats and B6C3F$_1$ mice were exposed to 0, 10, 50, or 175 ppm DMA for 6 h/d, 5 d/wk for 12 months. The mean body weight gain of rats and mice exposed to 175 ppm was depressed to 90% of control after 3 weeks of exposure. The only other treatment-related effects were the dose-related lesions confined to the nasal passages, which were very similar in rats and mice; however, after 12 months of exposure, rats had more extensive olfactory lesions (83).

DMA was not shown to have reproductive effects in mice by intraperitoneal injection (8).

3.4.1.5 Carcinogenesis In a 2-year inhalation study in male F344 rats exposed to 175 ppm, no evidence of carcinogenicity was observed, and in addition, despite severe tissue destruction in the anterior nose following a single 6-h exposure, the nasal lesions exhibited very little evidence of progression, even at 2 years of exposure; it was concluded that this indicated possible regional susceptibility to DMA toxicity or a degree of adaptation by the rat to continued DMA exposure.

A detailed evaluation of mucociliary apparatus function and response to alterations of nasal structure was presented by the authors (84).

3.4.2 Human Experience DMA is considered to be a severe lung and skin irritant in humans (85). Occupational exposure to vapors of DMA at concentrations too low to cause discomfort or disability during several hours of exposure have been associated with misty vision and halos that appeared several hours after the exposure occurred. Therefore, DMA does not have good warning properties. Edema of the corneal epithelium, the effect principally responsible for disturbance of vision, usually clears without treatment within 24 h. However, after exceptionally intense exposures, the edema and blurring have taken several days to clear and have been accompanied by photophobia and discomfort from roughness of the corneal surface (86).
3.5 Standards, Regulations, or Guidelines of Exposure
An ACGIH TLV-TWA value of 5 ppm (9.2 mg/m^3) and a STEL of 15 ppm (27.6 mg/m^3) have been adopted (72). The NIOSH REL and OSHA PEL is 10 ppm.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

4 Trimethylamine
4.0.1 CAS Number:
[*75-50-3*]
4.0.2 Synonyms:
TMA, *N*,*N*-dimethylmethanamine, and *N*,*N*-dimethylmethamine
4.0.3 Trade Names:
NA
4.0.4 Molecular Weight:
59.11
4.0.5 Molecular Formula:
C_3H_9N
4.0.6 Molecular Structure:

4.1 Chemical and Physical Properties
4.1.1 General It is readily soluble in water and is also soluble in ether, benzene, toluene, xylene, ethylbenzene, and chloroform. TMA is a flammable, alkaline, colorless gas at ambient temperature and atmospheric pressure. Trimethylamine is shipped as a liquefied compressed gas in cylinders, tank cars, and cargo tank trucks.

4.1.2 Odor and Warning Properties The odor threshold reportedly ranges from 0.00011 to 0.87 ppm and the odor is a characteristic pungent, fishlike one in low concentrations, but in higher

concentrations (100–500 ppm) the fishy odoer is no longer detectable, and the odor is more like that of ammonia (63, 75).

4.2 Production and Use

Trimethylamine is manufactured by heating methanol and ammonia over a catalyst at high temperatures; or by heating paraformaldehyde and ammonium chloride; or by the action of formaldehyde and formic acid on ammonia (51). TMA is used primarily in the manufacture of quaternary ammonium compounds, in the manufacture of disinfectants, as a corrosion inhibitor, in the preparation of choline chloride, in various organic syntheses (75), and as a warning agent for natural gas (64).

4.3 Exposure Assessment

4.3.1 Air None available.

4.3.2 Background Levels Bouyoucos and Melcher (66).

4.3.3 Workplace Methods None available.

4.3.4 Community Methods Hoshika (77).

4.4 Toxic Effects

4.4.1 Experimental Studies A 1% solution applied to animal eyes resulted in severe irritation, 5% causes hemorrhagic conjunctivitis, and 16.5% causes a severe reaction with conjunctival hemorrhages, corneal edema, and opacities, followed by some clearing but much vascularization (71, p. 1060).

In contrast to MMA and DMA, TMA has been demonstrated to cause embryo toxicity in mice (decreased fetal weight of CD-1 pups) (8).

4.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms TMA can be detected in mammalian urine and may arise from choline. When administered to humans, dogs, or rabbits (Linzel, 1934; Hoppe-Seyler, 1934), it is partly degraded to ammonia and subsequently to urea, and oxidized to trimethylamine oxide (15); according to Muller (1940) about 50% of the dose of trimethylamine hydrochloride (administered orally to dogs) was eliminated unchanged together with traces of dimethylamine, suggesting that trimethylamine was N-dealkylated (26).

In 1941, Green reported that tertiary amines are also oxidized by amine oxidase to the corresponding formaldehyde and secondary amine and proposed the following reaction (26):

$$RCH_2NR'R'' \rightleftharpoons RCHO + R'R''NH$$

It was also proposed that the secondary amine can then form a primary amine and this eventually would yield ammonia. *In vivo*, therefore, the nitrogen of a tertiary amine could be expected to appear in part as urea.

The second reaction involved the oxidation of the amine to the amine oxide as follows (15):

$$RR'R''N \rightleftharpoons RR'R''NO$$

N-dealkylation can be expected to occur with most amines, with an available a-carbon hydrogen. The reaction is essentially the same as oxidative deamination, that is, cleavage of the carbon–nitrogen bond with transfer of two electrons with the formation of a carbonyl compound and a dealkylated amine. It is therefore unlikely that tertiary aliphatic amines will be easily N-dealkylated to secondary amines. However, it may depend on the size of the alkyl groups. For example, trimethylamine has been reported to be N-dealkylated to dimethylamine, and studies have also shown that a *t*-butyl group can be removed through initial hydroxylation of one of the *t*-methyl groups, resulting in C-dealkylation to the corresponding carbinol or alcohol product (87).

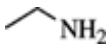
In cases, therefore, where tertiary amines have a small, easily removed group (methyl, ethyl, isopropyl), then oxidative N-dealkylation can probably proceed with preferential removal of the smaller substituents, dissociating into a secondary amine and aldehyde via microsomal P450 (88, 89).

Trimethylamine oxide occurs in large amounts in the tissues of fish, and its transformation into trimethylamine by bacteria containing trimethylamine oxide reductase is largely responsible for the spoiling of fish (15).

4.4.2 Human Experience In humans, N-oxidation to trimethylamine oxide is apparently the major route of metabolism; although N-demethylation to dimethylamine can also occur, it is a virtually negligible minor route (8, 90).
4.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA value of 5 ppm (12 mg/m^3) and a STEL of 15 ppm (36 mg/m^3) have been adopted (72). The NIOSH REL is 10 ppm.
4.6 Studies on Environmental Impact
In conjugated form, TMA is widely distributed in animal tissue and especially in fish (73, 74). It is also found in nature as a degradation product of nitrogenous plant and animal residues and is responsible for the odor of rotting cartilaginous marine fish (64).

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

5 Ethylamine
5.0.1 CAS Number:
[*75-04-7*]
5.0.2 Synonyms:
MEA, monoethylamine, aminoethane, ethanamine, and EA
5.0.3 Trade Names:
NA
5.0.4 Molecular Weight:
45.08
5.0.5 Molecular Formula:
C_2H_7N
5.0.6 Molecular Structure:



5.1 Chemical and Physical Properties
5.1.1 General It is a flammable, colorless gas.

5.1.2 Odor and Warning Properties The odor threshold reportedly ranges from 0.027 to 3.5 ppm, having a sharp fishy, ammoniacal odor, which becomes irritating at 180 mg/m^3 (62, 63). It is miscible with water, alcohol, and ether (71, p 76; 73, 74).
5.2 Production and Use
Ethylamine is manufactured by the hydrogenation of nitroethane; the reaction of ethyl chloride and alcohol ammonia under heat and pressure; or by the hydrogenation of aziridines in the presence of catalysts (51). It is used in resin chemistry, as a stabilizer for rubber latex, as an intermediate for dyestuffs, and in pharmaceuticals, and in oil refining and organic syntheses (73, 74).

5.3 Exposure Assessment
5.3.1 Air: NA

5.3.2 Background Levels: NA

5.3.3 Workplace Methods Analytical method S144 is recommended for determining workplace exposures to ethylamine (103).

5.3.4 Community Methods Hoshika (77).
5.4 Toxic Effects
5.4.1 Experimental Studies Ethylamine is a primary skin irritant (85), as well as an eye and mucous membrane irritant (77a), and when tested on rabbit eyes, was severely damaging (86). A 70% solution applied to the skin of guinea pigs resulted in prompt skin burns leading to necrosis; when it was held in contact with guinea pig skin for 2 h, there was severe skin irritation with extensive necrosis and deep scarring (8b).

In a comparative inhalation study, Brieger and Hodes exposed rabbits repeatedly to measured concentrations of ethylamine, diethylamine, and triethylamine (91, 92). The three amines produced lung, liver and kidney damage at 100 ppm. The triethylamine produced definite degenerative changes in the heart at 100 ppm, whereas this was an inconstant finding with ethylamine and diethylamine; 50 ppm of these amines was sufficient to produce lung irritation and corneal injury (delayed until 2 weeks with ethylamine).

Ethylamine has been reported to cause adrenal cortical gland necrosis, which, according to Ribelin (93), can also be expected following exposure to short three- or four-carbon chain alkyl compounds bearing terminal electronegative groups. Of the three adrenal gland areas, medulla, zona glomerulosa, and zona fasciculata/reticularis, the last is most sensitive to toxic injury, which is the case with ethylamine. Sensitivity of endocrine glands to toxic insult occurs in the following decreasing order: adrenal, testis, thyroid, ovary, pancreas, pituitary, and parathyroid (93).

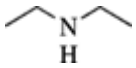
5.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Monoethylamine (MEA) is less readily metabolized than methylamine, and although a large proportion may be destroyed, its nitrogen being converted into urea (Schmiedeberg, 1878; Loffler, 1918), nearly one-third of the dose may be excreted unchanged by humans when administered as the hydrochloride. Schmiedeberg suggested that dogs might excrete traces of ethylurea after ethylamine (15).

5.4.2 Human Experience Ethylamine vapor has also reportedly produced vision disturbances and decreased olfaction sensitivity in humans (94); therefore, the warning properties associated with odor should not be relied upon.
5.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA value of 5 ppm (9 mg/m^3) has been adopted as well as a STEL of 15 ppm (72, 78). Both the NIOSH REL and OSHA PEL are 10 ppm.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

6 Diethylamine
6.0.1 CAS Number:
[*109-89-7*]
6.0.2 Synonyms:
DEA, *N*,*N*-diethylamine, diethamine, and *N*-ethylethanamine

6.0.3 Trade Names:
NA
6.0.4 Molecular Weight:
73.14
6.0.5 Molecular Formula:
$C_4H_{11}N$
6.0.6 Molecular Structure:



6.1 Chemical and Physical Properties
6.1.1 General The molecular formula for diethyalmine is $(C_2H_5)_2NH$. It is a colorless, flammable, strongly alkaline liquid, miscible with water and alcohol (73, 74).

6.1.2 Odor and Warning Properties The odor threshold ranges from 0.02 to 14 ppm, having a fishlike odor that becomes ammoniacal and irritating at 150 mg/m^3 (62, 63).
6.2 Production and Use
Diethylamine is manufactured by heating ethyl chloride and alcoholic ammonia under pressure or by hydrogenation of aziridines in the presence of catalysts (51). DEA is used as a solvent, as a rubber accelerator, in the organic synthesis of resins, dyes, pesticides, and pharmaceuticals, in electroplating, and as a polymerization inhibitor (73, 74). Other applications include uses as a corrosion inhibitor. It was reported noneffective as a skin depigmentator (95).
6.3 Exposure Assessment
6.3.1 Air: NA

6.3.2 Background Levels: NA

6.3.3 Workplace Methods NIOSH method 2010 is recommended for determining workplace exposures to diethylamine (65).

6.3.4 Community Methods Hoshika (77).
6.4 Toxic Effects
6.4.1 Experimental Studies DEA is an eye and mucous membrane irritant and primary skin irritant (85). Smyth et al. reported an acute 4-h LC_{50} value of 4000 ppm, the oral LD_{50} for rats was reported as 540 mg/kg, and the dermal LD_{50} in rabbits was reported to be 580 mg/kg; a 10% dilution caused severe eye burns (96). Drotman and Lawhorn reported histological evidence of liver damage and elevations of serum enzymes following intraperitoneal administration to rats (97). In addition to these acute studies, Brieger and Hodes exposed rabbits at 50 and 100 ppm DEA vapor for 7 h/d, 5 d/wk for 6 wk and all animals survived (91). Lungs exposed to 100 ppm exhibited cellular infiltration and bronchopneumonia, livers showed marked parenchymatous degeneration, and kidneys showed nephritis. Similar changes to a lesser degree were observed in animals exposed to 50 ppm. There was slight cardiac muscle degeneration at 50 ppm.

Lynch et al., in a followup study to investigate heart muscle degeneration reported by Brieger and Hodes were unable to find any evidence of cardiac muscle degeneration or any changes in electrocardiograms in F344 rats of both sexes exposed to DEA vapor concentrations of 25 or 250 ppm for 6.5 h/d, 5 d/wk for 30, 60, or 120 exposure days (91, 92). Rats exposed at 25 ppm showed no effect in any measured parameter. In contrast to DMA observations previously discussed the incidence of histopathological effects (bronchiolar lymphoid hyperplasia) was noted in both controls and the 25-ppm dosage groups; however, the incidence was not dose-related and did not increase with increasing DEA exposure (81). The authors therefore concluded that the lesions of the

respiratory epithelium (consisting of squamous metaplasia, suppurative rhinitis, and lymphoid hyperplasia) were not considerd to be of toxicologic significance but were considered a result of irritation. No evidence of cardiac muscle degeneration or of changes in electrocardiograms were seen for up to 24 weeks. It was noted that these negative findings may reflect a species difference in susceptibility to DEA cardiotoxicity previously reported by Brieger (91).

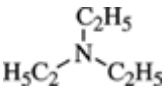
In a followup parallel inhalation study with DEA and triethylamine, no respiratory lesions were observed with triethylamine in F344 rats exposed to 25 or 250 ppm (98).

6.4.2 Human Experience Adverse ocular effects have been reported following human exposure (94).

6.4.2.2.3 Pharmacokinetis, Metabolism, and Mechanisms Diethylamine (DEA) is mainly excreted unchanged by humans when it is administered as the hydrochloride (15).
6.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA value of 5 ppm (15 mg/m^3) and a STEL of .5 ppm (37.5 mg/m^3) have been adopted (72). The NIOSH REL is 10 ppm and the OSHA PEL is 25 ppm.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

7 Triethylamine
7.0.1 CAS Number:
[*121-44-8*]
7.0.2 Synonyms:
N,*N*-diethylethanamine and TEA
7.0.3 Trade Names:
NA
7.0.4 Molecular Weight:
101.19
7.0.5 Molecular Formula:
$(C_2H_5)_3N$
7.0.6 Molecular Structure: Liquid,



7.1 Chemical and Physical Properties
7.1.1 General It is a colorless, flammable, volatile liquid. It is slightly soluble in water and miscible with alcohol and ether (73, 74).

7.1.2 Odor and Warning Properties The odor threshold reportedly ranges from 0.10 to 29 ppm, having a fishlike, pungent odor, which becomes ammoniacal and irritating at 200 mg/m^3 (62, 63).
7.2 Production and Use
Triethylamine is manufactured by heating ethyl chloride and alcoholic ammonia under pressure or by hydrogenation of aziridines in the presence of catalysts (51). TEA is used as a solvent and in the synthesis of quaternary ammonia wetting agents (73, 74); it is also reportedly used in penetrating and waterproofing agents, as a corrosion inhibitor, and in the synthesis of other organic compounds (73, 74).
7.3 Exposure Assessment
7.3.1 Air: NA

7.3.2 Background Levels: NA

7.3.3 Workplace Methods NIOSH method S152 is recommended for determining workplace exposure to triethylamine (103).

7.3.4 Community Methods Hoshika (77).
7.4 Toxic Effects
7.4.1 Experimental Studies TEA is a skin and eye irritant (85). The acute oral LD_{50} in rats has been reported to be 0.46 g/kg; the rabbit dermal LD_{50}, 0.57 mL/kg; and the acute 4 h LC_{50}, apparently 500 ppm (64). Chronic exposure of rabbits to TEA vapors at concentrations as low as 50 ppm causes multiple erosions of the cornea and conjuctiva, as well as injuries of the lungs in the course of 6 weeks (91).

Male and female F344 rats exposed to vapor concentrations of 0, 25, or 250 ppm up to 28 weeks showed no physiological or pathological evidence of cardioxicity; no treatment-related effects were observed (99). However, as in the case with diethylamine, this may be species dependent.

7.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Biotransformation metabolites eliminated in human urine following inhalation at 10, 20, 35, and 50 mg/m^3 for 4 or 8 h included unchanged TEA and triethylamine *N*-oxide (100).

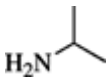
Pharmacokinetics in four male volunteers have been studied. The doses of TEA and TEAO were 25 and 15 mg orally and 15 mg/h × 1 h intravenously, respectively. TEA was efficiently absorbed from the gastrointestinal (GI) tract (90–97%), no significant first-pass metabolism. The apparent volumes of distribution during the elimination phase were 192 L for TEA and 103 L for TEAO. TEA was metabolized into triethylamine *N*-oxide (TEAO) by addition of oxygen to the nucleophilic nitrogen. TEAO was also absorbed from the GI tract. Both TEA and diethylamine (DEA) appeared in the urine after ingestion of TEAO, but not after an intravenous route of administration. This indicates that TEAO is reduced into TEA or dealkylated into DEA only within the GI tract. The TEA and TEAO had plasma half-lives of about 3 and 4 h, respectively. Exhalation of TEA was minimal; more than 90% of the dose was recovered in the urine as TEA and TEAO. The authors recommend that the sum of TEA and TEAO be used for biologic monitoring (101). Previously reported symptoms of visual disturbances in humans (foggy vision, blue haze) (102) were not observed following systemic administration (101).

7.4.2 Human Experience It has also been reported that TEA inhalation in humans has resulted in EEG changes (94).
7.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA value of 1 ppm (4.1 mg/m^3) and a STEL of 3 ppm (12.5 mg/m^3) have been adopted (72). The OSHA PEL is 25 ppm. NIOSH questions whether the OSHA PEL is adequate to protect workers.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

8 Isopropylamine
8.0.1 CAS Number:
[*75-31-0*]
8.0.2 Synonyms:
MIPA, 2-aminopropane, 2-propanamine, monisopropylamine, 2-propylamine, and *sec*-propylamine

8.0.3 Trade Names:
NA
8.0.4 Molecular Weight:
59.08
8.0.5 Molecular Formula:
$(CH_3)_2CHNH_2$
8.0.6 Molecular Structure:



8.1 Chemical and Physical Properties
8.1.1 General It is a colorless, flammable liquid. Isopropylamine is miscible with water, alcohol, and ether (73, 74).

8.1.2 Odor and Warning Properties The odor threshold reportedly ranges from 0.21 to 0.70 ppm; the pungent, ammoniacal odor becomes irritating at 24 mg/m^3 (63).
8.2 Production and Use
Isopropylamine is manufactured by reacting isopropanol and ammonia in the presence of dehydrating catalysts; by reacting isopropyl chloride and ammonia under pressure; or by the action of acetone and ammonia (51). It is used as a solvent, as a depilating agent (64), in the chemical synthesis of dyes and pharmaceuticals, and in other organic syntheses (64a).
8.3 Exposure Assessment
8.3.1 Air NIOSH Method S147 (103).

8.3.2 Background Levels Kuwata et al. (104).

8.3.3 Workplace Methods NIOSH Method S147 is recommended (103).

8.3.4 Community Methods Koga et al. (105).
8.4 Toxic Effects
8.4.1 Experimental Studies Isopropylamine in either liquid or vapor form is irritating to the skin and may cause burns; repeated lesser exposures may result in dermatitis (1, 85). The acute oral LD_{50} in rats is reportedly 820 mg/kg (96, in Ref. 73, 74).

Dudek (106) reported a no observable effect level (NOEL) in Sprague–Dawley rats to be 0.1 mg/L in air following a 30-d inhalation study.

8.4.2 Human Experience Humans exposed briefly to isopropylamine at 10–20 ppm experienced irritation of the nose and throat. Workers complained of transient visual disturbances (halos around lights) after exposure to the vapor for 8 h, probably owing to mild corneal edema, which usually cleared within 3–4 h. The liquid can cause severe eye burns and permanent visual impairment (107)
8.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA value of 5 ppm (12 mg/m^3) and a STEL of 10 ppm (24 mg/m^3) have been adopted (72). The OSHA PEL is 5 ppm. NIOSH questions whether 5 ppm is adequate.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

9 *n*-Propylamine
9.0.1 CAS Number:
[*107-10-8*]
9.0.2 Synonyms:
1-aminopropane, MNPA, 1-propanamine, propylamine, monopropylamine, propyl amines, propan-1-amine, and mono-*n*-propylamine
9.0.3 Trade Names:
NA
9.0.4 Molecular Weight:
59.11
9.0.5 Molecular Formula:
C_3H_9N
9.0.6 Molecular Structure:

9.1 Chemical and Physical Properties
9.1.1 General It is a colorless, flammable, alkaline liquid, and is miscible with water, alcohol, and ether (73, 74).

9.1.2 Odor and Warning Properties MNPA has a strong ammoniacal odor (73, 74).
9.2 Production and Use
n-Propylamine is manufactured by reacting propanol and ammonia in the presence of dehydrating catalysts; by reacting *n*-propyl chloride and ammonia under pressure; or by the action of acetone and ammonia (51). It is used as a solvent and in organic syntheses.
9.3 Exposure Assessment
9.3.1 Air NIOSH Method S147 (103).

9.3.2 Background Levels Kuwata et al. (104).

9.3.3 Workplace Methods None is recommended.

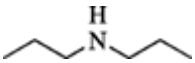
9.3.4 Community Methods Koga et al. (105).
9.4 Toxic Effects
9.4.1 Experimental Studies During lethal exposure in rats, *n*-propylamine caused clouding of the cornea at 800 ppm (108). Application to rabbit eyes caused severe injury after 24 h (109). The acute oral LD_{50} in rats is reportedly 0.57 g/kg (109, in Refs. 73, 74). It is a possible skin sensitizer (73, 74).

9.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms *n*-Propylamine appears to be more readily metabolized than ethylamine in humans, and in dogs Bernhard (1938) found none of the administered amine to be excreted unchanged (15).
9.5 Standards, Regulations, or Guidelines of Exposure
Standards have not been adopted.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

10 *n*-Dipropylamine

10.0.1 CAS Number:
[*142-84-7*]
10.0.2 Synonyms:
di-*n*-propylamine, DNPA, *N*-propyl-1-propanamine, and *N*,*N*-dipropylamine
10.0.3 Trade Names:
NA
10.0.4 Molecular Weight:
101.19
10.0.5 Molecular Formula:
$C_6H_{15}N$
10.0.6 Molecular Structure:



10.1 Chemical and Physical Properties
10.1.1 General It is a colorless, flammable liquid. *n*-Dipropylamine is freely soluble in water and alcohol (73, 74).

10.1.2 Odor and Warning Properties The odor threshold reportedly ranges from 0.08 to 227 mg/m^3; the odor is ammoniacal (62).
10.2 Production and Use
Di-*n*-propylamine is manufactured by reacting propanol and ammonia in the presence of dehydrating catalysts; *n*-propyl chloride and ammonia under pressure; or by the action of acetone and ammonia (51). Specific uses were not identified in the literature (51).
10.3 Exposure Assessment
10.3.1 Air None is recommended.

10.3.2 Background Levels None is recommended.

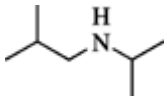
10.3.3 Workplace Methods None is recommended.

10.3.4 Community Methods Hoshika (77).
10.4 Toxic Effects
10.4.1 Experimental Studies Dipropylamine is a severe eye irritant (86), and the acute oral LD_{50} in rats is reportedly 0.93 g/kg (109, in Refs. 73, 74); it may also be a possible skin sensitizer (73, 74).
10.5 Standards, Regulations, or Guidelines of Exposure
Standards have not been adopted.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

11 Diisopropylamine
11.0.1 CAS Number:
[*108-18-9*]
11.0.2 Synonyms:
N,*N*-diisopropylamine and DIPA
11.0.3 Trade Names:
NA
11.0.4 Molecular Weight:

101.19
11.0.5 Molecular Formula:
$(CH_3)_2CHNHCH(CH_3)_2$
11.0.6 Molecular Structure:



11.1 Chemical and Physical Properties
11.1.1 General It is a flammable, strongly alkaline liquid. Diisopropylamine is soluble in water and alcohol (73, 74).

11.1.2 Odor and Warning Properties The odor threshold ranges from 0.017 to 4.2 ppm; the fishlike odor becomes irritating at 100 mg/m^3 (62, 63, 86).
11.2 Production and Use
Diisopropylamine is manufactured by reacting isopropanol and ammonia in the presence of dehydrating catalysts; by reacting isopropyl chloride an ammonia under pressure; or by the action of acetone and ammonia (51). It is used as a solvent and in the chemical synthesis of dyes, pharmaceuticals, and other organic syntheses (64a, 73, 74).
11.3 Exposure Assessment
11.3.1 Air NIOSH (65).

11.3.2 Background Levels Kuwata et al. (104).

11.3.3 Workplace Methods NIOSH Methods S141 (103).

11.3.4 Community Methods Koga et al. (105).
11.4 Toxic Effects
11.4.1 Experimental Studies The acute oral rat LD_{50} is reportedly 0.77 g/kg (110); the compound is irritating to the eyes, skin, and mucous membranes (73, 74, 85).

Experimental exposures of rabbits, guinea pigs, rats, and cats have established that the vapor is injurious to the corneal epithelium; this presumably is the cause of the visual disturbances observed in humans. Exposure of experimental animals to vapor concentrations from 260 to 2200 ppm for several hours causes clouding of the cornea from epithelial injury and stromal swelling. The highest concentrations were lethal in many instances, owing to severe pulmonary damage, but the corneas of surviving animals ultimately returned to normal (111).

Exposure of several species of animals to 2207 ppm for 3 h was fatal; effects were lacrimation, corneal clouding, and severe irritation of the respiratory tract. At autopsy, findings were pulmonary edema and hemorrhage (111a).

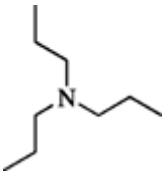
11.4.2 Human Experience Temporary impairment of vision has occurred in humans after exposure to vapor concentrations possibly as low as 25–50 ppm during distillation of diisopropylamine (111, 112).

Diisopropylamine is considered to be a severe pulmonary irritant in animals and humans (85). Workers exposed to concentrations between 25 and 50 ppm complained of disturbances of vision described as “haziness,” or “halos” around lights (85). Therefore, the warning properties of diisopropylamine are not protective. There have also been reports of nausea and headache (85a, 85b). Prolonged skin contact is likely to cause dermatitis (85c).

11.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA value of 5 ppm (21 mg/m^3) has been adopted (72). The NIOSH REL and OSHA PEL are the same.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

12 Tripropylamine
12.0.1 CAS Number:
[*102-69-2*]
12.0.2 Synonyms:
TNPA
12.0.3 Trade Names:
NA
12.0.4 Molecular Weight:
143.27
12.0.5 Molecular Formula:
$C_9H_{21}N$
12.0.6 Molecular Structure:



12.1 Chemical and Physical Properties
12.1.1 General It is a flammable liquid (73, 74).
12.2 Production and Use
Tripropylamine is manufactured by reacting propanol and ammonia in the presence of dehydrating catalysts; by reacting *n*-propyl chloride and ammonia under pressure; or by the action of acetone and ammonia. No specific uses were located in the literature.
12.3 Exposure Assessment
12.3.1 Air None available.

12.3.2 Background Levels None available.

12.3.3 Workplace Methods NIOSH Method S147 (103).

12.3.4 Community Methods Koga et al. (105).
12.4 Toxic Effects
No toxicology information was located.
12.5 Standards, Regulations, or Guidelines of Exposure
Standards have not been adopted (72).

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

13 **n**-Butylamine
13.0.1 CAS Number:
[*109-73-9*]
13.0.2 Synonyms:
MNBA, 1-butanamine, 1-aminobutane, aminobutane, butyl amine, 1-butanamine, norralamine, mono-*n*-butylamine, tutane, and monobutylamine
13.0.3 Trade Names:
NA
13.0.4 Molecular Weight:
73.14
13.0.5 Molecular Formula:
$C_4H_{11}N$
13.0.6 Molecular Structure:

13.1 Chemical and Physical Properties
13.1.1 General *n*-Butylamine is a flammable volatile liquid. It is miscible with water, alcohol, and ether (73, 74).

13.1.2 Odor and Warning Properties The odor threshold ranges from 0.24 to 13.9 ppm; the sour, fishlike, ammoniacal odor becomes irritating at 30 mg/m^3 (62, 63).
13.2 Production and Use
n-Butylamine is manufactured by the reaction of ammonia and *n*-butanol at elevated temperature and pressure in the presence of silica–alumina, by reductive amination of *n*-butyraldehyde; or by reduction of butyraldoxime. It is used as a solvent and as an intermediate for pharmaceuticals, dyestuffs, rubber chemicals, emulsifying agents, insecticides, and synthetic tanning agents (73, 74). It is also present in fertilizer manufacture, rendering plants, fish processing plants, and sewage plants (51) and has been reported to be effective (0.1*M*) in inhibiting the corrosion of iron in concentrated perchloric acid (6).
13.3 Exposure Assessment
13.3.1 Air: NA

13.3.2 Background Levels Kuwata et al. (104).

13.3.3 Workplace Methods NIOSH method 2012 is recommended for determining workplace exposure.

13.3.4 Community Methods Petronio and Russo (113).
13.4 Toxic Effects
13.4.1 Experimental Studies *n*-Butylamine vapor is only mildly irritating to the eyes, but the liquid tested on animals' eyes is as severely injurious as ammonium hydroxide; the injurious effect seems to be attributable to the alkalinity of butylamine because, as with other amines, its damaging effects on the cornea is prevented if it is neutralized with acid before testing (114–116). Other references indicate that *n*-butylamine is a potent skin, eye, and mucous membrane irritant, and direct skin contact causes severe primary irritation and blistering (73, 74). The acute oral LD_{50} for Sprague–Dawley rats (male + female) has been reevaluated and reported as 371 mg/kg (117).

n-Butylamine at measured concentrations of 3000–5000 ppm produces an immediate irritant response, labored breathing, and pulmonary edema, with death of all rats in minutes to hours. Ten and 50% vol/vol aqueous solutions and the undiluted base produce severe skin and eye burns in animals. The immediate skin and eye reactions are not appreciably altered by prolonged washing or

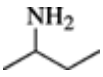
attempts at neutralization when these are commenced within 15 sec after application (8b).

13.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms *n*-Butylamine is as readily metabolized in humans as methylamine, and Pugh (1937) demonstrated in guinea pig liver slices that one of its metabolites is acetoacetic acid (15).

13.4.2 Human Experience Direct skin contact with the liquid causes severe primary irritation and deep second-degree burns (blistering) in humans. The odor of butylamine is slight at less than 1 ppm, noticeable at 2 ppm, moderately strong at 2–5 ppm, strong at 5–10 ppm, and strong and irritating at concentrations exceeding 10 ppm. Workers with daily exposures of from 5 to 10 ppm complain of nose, throat, and eye irritation, and headaches. Concentrations of 10–25 ppm are unpleasant to intolerable for more than a few minutes. Daily exposures to less than 5 ppm (most often between 1 and 2 ppm) produce no complaints or symptoms.
13.5 Standards, Regulations, or Guidelines of Exposure
NIOSH, OSHA, and the ACGIH have all adopted a ceiling value of 5 ppm (72).

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

14 2-Butylamine
14.0.1 CAS Number:
[*13952-84-6*]
14.0.2 Synonyms:
2-aminobutane, *sec*-butylamine, 2-butanamine, 1-methylpropylamine, and Butafume. Butafume is available as (R) B.P. 63°C, (+/–) B.P. 63°C, and (S) B.P. 62.5°C; the corresponding CASRNs are [*13250-12-9*], [*33966-50-6*], and [*513-49-5*] (73, 74)
14.0.3 Trade Name:
NA
14.0.4 Molecular Weight:
73.14
14.0.5 Molecular Formula:
$CH_3CH_2CH(NH_3)CH_3$
14.0.6 Molecular Structure:



14.1 Chemical and Physical Properties
14.1.1 General It is a flammable liquid.
14.2 Production and Use
2-Butylamine is manufactured by the condensation of methyl ethyl ketone with ammonia–hydrogen in the presence of Ni catalyst (51). It has been used as a fungistat (73, 74).
14.3 Exposure Assessment
14.3.1 Air None available, however, NIOSH methods may be applicable.

14.3.2 Background Levels Kuwata et al. (104).

14.3.3 Workplace Methods NIOSH method 2012 may be used.

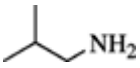
14.3.4 Community Methods Hoshika (77).

14.4 Toxic Effects
14.4.1 Experimental Studies The acute oral LD_{50} for Sprague–Dawley rats (males + females) has been reported to be 152 mg/kg (117). An earlier acute study reported an LD_{50} value of 380 mg/kg (female, Harlan Wistar rats) (118).

2-Butylamine is irritating to the skin and mucous membranes (73, 74). Seven male rats exposed to saturated vapor (280 mg/L) for 5 h exhibited intense eye and nose irritation, respiratory difficulty, and convulsions; all died. Cornea lesions were opaque and white, and all other organs appeared normal. All amines examined showed irritant and central nervous system stimulant effects; these increased with the degree of substitution, but the higher members had too low a volatility to present a significant vapor hazard. Other amino compounds studied included di-*sec*-butylamine, tributylamine, nonylamine, dinonylamine, trinonylamine, hexamethylenediamine, diethylenetriamine, 2-aminobutan-1-ol, and 1-diethylaminoentan-2-one (119).
14.5 Standards, Regulations, or Guidelines of Exposure
Standards have not been adopted.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

15 Isobutylamine
15.0.1 CAS Number:
[*78-81-9*]
15.0.2 Synonyms:
IBA, 1-amino-2-methylpropane, 2-methylpropylamine (73, 74), monoisobutylamine, valamine, 2-methyl-1-propanamine, and 2-methylpropanamine
15.0.3 Trade Names:
NA
15.0.4 Molecular Weight:
73.14
15.0.5 Molecular Formula:
$C_4H_{11}N$
15.0.6 Molecular Structure:



15.1 Chemical and Physical Properties
15.1.1 General It is a flammable liquid, miscible with water, alcohol, and ether (73, 74).
15.2 Production and Use
Isobutylamine is manufactured from isobutanol and ammonia or by the thermal decomposition of valine to isoleucine (51).
15.3 Exposure Assessment
15.3.1 Air Nishikawa and Kuwata (120).

15.3.2 Background Levels Kuwata et al. (104).

15.3.3 Workplace Methods: NA

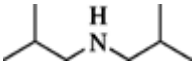
15.3.4 Community Methods Hoshika (77).

15.4 Toxic Effects
15.4.1 Experimental Studies The acute oral LD_{50} for Sprague–Dawley rats (males + females) has been reported to be 228 mg/kg (117).

15.4.2 Human Experience Skin contact can result in erythema and blistering; inhalation causes headache and dryness of the nose and throat (73, 74).
15.5 Standards, Regulations, or Guidelines of Exposure
Standards have not been adopted.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

16 Diisobutylamine
16.0.1 CAS Number:
[*110-96-3*]
16.0.2 Synonyms:
1-butamine, *N*-butyl, di-*N*-butylamine, DIBA, 2-methyl-*N*-(2-methylpropyl)-1-propanamine, and bis (2-methylpropyl) amine
16.0.3 Trade Names:
NA
16.0.4 Molecular Weight:
129.24
16.0.5 Molecular Formula:
$C_8H_{19}N$
16.0.6 Molecular Structure:



16.1 Chemical and Physical Properties
16.1.1 General It is a colorless, flammable liquid, very slightly soluble in water and soluble in alcohol or ether (73, 74).

16.1.2 Odor and Warning Properties
16.2 Production and Use
Diisobutylamine is manufactured from isobutanol and ammonia (51). Specific uses were not located in the literature (51).
16.3 Exposure Assessment
16.3.1 Air: NA

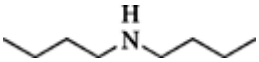
16.3.2 Background Levels Kuwata et al. (104).

16.3.3 Workplace Methods: NA

16.3.4 Community Methods Hoshika (121).
16.4 Toxic Effects
Specific toxicity data were not located in the literature.
16.5 Standards, Regulations, or Guidelines of Exposure
Standards have not been adopted.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

17 Di-**n**-butylamine
17.0.1 CAS Number:
[*111-92-2*]
17.0.2 Synonyms:
Dibutylamine, *n*-dibutylamine, DNBA, *N*-butyl-1-butanamine, di-*n*-butylamine, and *N*,*N*-dibutylamine
17.0.3 Trade Names:
NA
17.0.4 Molecular Weight:
129.24
17.0.5 Molecular Formula:
$C_8H_{19}N$
17.0.6 Molecular Structure:



17.1 Chemical and Physical Properties
17.1.1 General The molecular formula for di-*n*-butylamine is $(C_4H_9)_2NH$. It is colorless liquid, soluble in water, alcohol, and ether (73, 74).

17.1.2 Odor and Warning Properties The odor threshold reportedly ranges from 0.42 to 2.5 mg/m^3; the fishlike odor becomes ammoniacal at higher concentrations (62).
17.2 Production and Use
Dibutylamine is manufactured by the reaction of ammonia and *n*-butanol at elevated temperature and pressure in the presence of silica–alumina; from butyl bromide and ammonia; or by reaction of butyl chloride and ammonia (51). Dibutylamine is used as a solvent and in organic syntheses.
17.3 Exposure Assessment
17.3.1 Air: NA

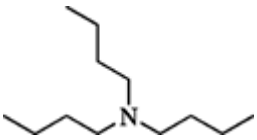
17.3.2 Background Levels Kuwata et al. (104).

17.3.3 Workplace Methods: NA

17.3.4 Community Methods Hoshika (121).
17.4 Toxic Effects
Animal studies have demonstrated that dibutylamine is severely irritating to the eyes (86). An acute oral rat LD_{50} value of 550 mg/kg has been reported (110)
17.5 Standards, Regulations, or Guidelines of Exposure
Standards have not been adopted.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

18 Tri-*n*-butylamine
18.0.1 CAS Number:
[*102-82-9*]
18.0.2 Synonyms:
Tributylamine, TNBA, *N*,*N*-dibutyl-1-butanamine; and *n*-tributylamine
18.0.3 Trade Names:
NA
18.0.4 Molecular Weight:
185.34
18.0.5 Molecular Formula:
$C_{12}H_{27}N$
18.0.6 Molecular Structure:



18.1 Chemical and Physical Properties
18.1.1 General It is a hygroscopic liquid, sparingly soluble in water and very soluble in alcohol and ether (73, 74).
18.2 Production and Use
Tributylamine is manufactured by the reaction of ammonia and *n*-butanol at elevated temperature and pressure in the presence of silica–alumina; from butyl bromide and ammonia; or by reaction of butyl chloride and ammonia. It is used as a solvent, an inhibitor in hydraulic fluids, a dental cement, and in isoprene polymerization (51).
18.3 Exposure Assessment
18.3.1 Air: NA

18.3.2 Background Levels Kuwata et al. (104).

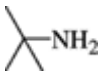
18.3.3 Workplace Methods: NA

18.3.4 Community Methods Hoshika (77).
18.4 Toxic Effects
Exposure of four male and four female rats to 120 ppm for 19 6-h exposures caused nose irritation, restlessness, incoordination, and tremors; organs appeared normal at autopsy (119). An LD_{50} (rat oral) of 540 mg/kg has been reported (122). Tributylamine has reportedly caused central nervous system (CNS) stimulation and skin irritation and sensitization (73, 74).
18.5 Standards, Regulations or Guidelines of Exposure
Standards have not been adopted.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

19 *tert*-Butylamine
19.0.1 CAS Number:
[*75-64-9*]
19.0.2 Synonyms:
Trimethylcarbinylamine, *t*-butylamine, 2-aminoisobutane, 1,1-dimethylethylamine, and

trimethylaminoethane
19.0.3 Trade Names:
NA
19.0.4 Molecular Weight:
73.14
19.0.5 Molecular Formula:
$(CH_3)_3CNH_2$
19.0.6 Molecular Structure:



19.1 Chemical and Physical Properties
19.1.1 General It is a colorless, flammable liquid, miscible with alcohol (73, 74).
19.2 Production and Use
tert-Butylamine is manufactured by reacting isobutylamine with sulfuric acid followed by cyanide to *tert*-butylformamide. Hydrolysis yields *t*-butylamine. It is used as a solvent and in organic syntheses.
19.3 Exposure Assessment
19.3.1 Air Nishikawa and Kuwata (120).

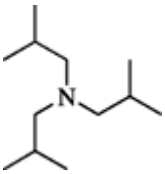
19.3.2 Background Levels Kuwata et al. (104).

19.3.3 Workplace Methods Crommen (123).

19.3.4 Community Methods Hoshika (77).
19.4 Toxic Effects
The acute oral LD_{50} for Sprague–Dawley rats (males + females) has been reported to be 80 mg/kg (117). Liver toxicity NOEL was reported to be 0.20 mg/L for female Sprague–Dawley rats (122).
19.5 Standards, Regulations, or Guidelines of Exposure
Standards have not been adopted.

Aliphatic and Alicyclic Amines
Finis L. Cavender, Ph.D., DABT, CIH

20 Triisobutylamine
20.0.1 CAS Number:
[*1116-40-1*]
20.0.2 Synonyms:
TIBA (73, 74), 2-methyl-*N*,*N*-*bis* (2-methylpropyl)-1-propanamine, and tris(2-methylpropyl)amine
20.0.3 Trade Names:
NA
20.0.4 Molecular Weight:
185.36
20.0.5 Molecular Formula:
$C_{12}H_{27}N$
20.0.6 Molecular Structure:



20.1 Chemical and Physical Properties
20.1.1 General
20.2 Production and Use
Triisobutylamine is manufactured from isobutanol and ammonia under heat and pressure (51).
20.3 Exposure Assessment
20.3.1 Air: NA

20.3.2 Background Levels Kuwata et al. (104).

20.3.3 Workplace Methods: NA

20.3.4 Community Methods Hoshika (77).
20.4 Toxic Effects
No toxicology information was located in the literature (51).
20.5 Standards, Regulations, or Guidelines of Exposure
Standards have not been adopted.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

General
Logically, aromatic nitro and amino compounds should be discussed together because their toxic responses are often similar due to a common metabolic intermediate. Synthetically, amines are generally derived from nitro compounds, but in some cases nitro compounds can be prepared through amines when other methods fail to afford specific compounds. There are good and bad attributes to these types of compounds. Some act as sensitizers and contingent on physical properties, may be absorbed through the skin or mucous membranes. They may also cause methemoglobinemia, depending on such factors as the structure and the particular organism. Some members of this class are known as animal and human carcinogens; for humans the urinary bladder is the most prominent target organ. Nevertheless, these compounds and their derivatives have enlivened our world through their use as dyestuff intermediates or as photographic chemicals, they alleviate pain as components of widely used analgesics, and they cushion or insulate us through their use in flexible and rigid foams. Other important uses include production of pesticides, including herbicides and fungicides, as ingredients in adhesives, paints and coatings, antioxidants, explosives, optical brighteners, rubber ingredients, and as intermediates in many other products.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

Aromatic Nitro Compounds
Aromatic nitro compounds are generally made by nitrating an aromatic hydrocarbon such as benzene

or toluene. Production has moved to continuous processes; in some facilities, jet impingement reactors allow more rapid production and lower formation of unwanted by-products; in vapor phase reactors, nitric acid and benzene flow through a solid catalyst in a continuous phase. These processes are beneficial in reducing waste. Production figures vary from year to year, depending on economic conditions, but in 1994 U.S. production of nitrobenzene was of the order of 740,000 tons (1). The nitro aromatics are starting materials for further syntheses. Most are reduced to the corresponding amines that provide convenient substituents or "handles" for many other syntheses.

The toxic properties of aromatic nitro compounds were discussed in the previous edition of this series (2). These attributes of the compounds are well-known and various regulatory agencies worldwide have set exposure limits for them.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

Aromatic Amino Compounds
Reduction of aromatic nitro compounds afford the amines that are starting materials for further syntheses. The amines share many of the toxic properties of the nitro compounds, as discussed previously (2), including skin sensitization, anemia, methemoglobinemia, irritation, hematuria, and for certain ones, bladder carcinogenesis. This aspect of aromatic amines has led to banning the manufacture of some and strict exposure limits on others. Nonetheless, research on some aromatic amines, especially 2-acetylaminofluorene (2-AAF), has led to a better understanding of the steps involved in carcinogenesis (3).
1.1 Chemical and Physical Properties
This topic was discussed fairly extensively in the previous edition, and no significant new information was found.
1.4 Toxic Effects
1.4.1 Experimental Studies One of the initial toxic responses to aromatic amines or nitro compounds is the formation of methemoglobin within the red blood cells and subsequent deleterious effects. There are decided species differences in response to methemoglobin formers (2). The complete tertiary structures of hemoglobin and its subunits have been mapped and described. Normal adult hemoglobin is an oligomeric protein (MW about 67,000) that has four separate globin peptide chains: two alpha chains and two beta chains (4). Each of these peptide chains has a noncovalently bound porphyrinic heme group that is enclosed in a hydrophobic pocket by the globin chain. If oxidation of the ferrous iron to ferric occurs in the center of the protoporphyrin IX ring, the resulting greenish-brown to black pigment cannot combine reversibly with oxygen, leading to symptoms of oxygen deficiency such as cyanosis and a consequent bluish tinge to the skin. There are three types of substances that produce methemoglobin (5):

1. Those active either *in vitro* or *in vivo* include sodium nitrite, aminophenols, phenyl- and other hydroxylamines, and amyl nitrite. Phenylhydroxylamine can act cyclically; after reducing oxyhemoglobin, it generates nitrosobenzene that is reduced again to phenylhydroxylamine by the red cell enzymes, thus generating more methemoglobin.
2. Those active only *in vivo*, indicating the need for some process before the primary compound interacts with hemoglobin; this group encompasses aromatic nitro and amino compounds. An example is that the *N*-hydroxy metabolite of *p*-aminopropiophenone (PAP) is recognized as the moiety actually responsible for the methemoglobin-inducing action of PAP.
3. A third group includes compounds that are more active in lysates or in solutions of hemoglobin than in intact cells; specific examples are potassium ferricyanide, molecular oxygen, and methylene blue.

Although methemoglobinemia from exogenous substances can induce a dramatic change in skin color and can be serious condition, a relatively benign hereditary type can also occur due to a genetic deficiency in cytochrome b_5 (6). Treatment of methemoglobinemia involves cessation of exposure to the toxin and limited intravenous administration of methylene blue due to possible hemolysis if more than two doses are given. Methemoglobin reductase enzyme or cytochrome b_5 is the electron carrier between NADH and methemoglobin, facilitated by formation of a complex between the two molecules. The cytochrome binds to four lysine moieties in the heme pocket in both chains, and a hydrogen bond between one of the lysines of the cytochrome is a bridge between two heme propionic acid side chains of both heme proteins and affords a micropath for electron transport.

In this chapter, occupational exposure to aromatic amines and nitro compounds is the primary concern. However, medicinal agents that contain aromatic amino or acetylamino groupings may also cause methemoglobinemia, especially from continued exposure (7–9). Thus, methemoglobinemia, besides being an occupational concern, can be an environmental one, if one considers the total environment.

1.4.2 Human Experience Research on aromatic amines has usually emphasized the adducts of the active metabolic intermediates with deoxyribonucleic acid (DNA) as indicators of possible genetic damage. It has been recognized that the metabolites also form hemoglobin adducts that are present in much larger amounts than DNA adducts. These adducts are not repaired as are DNA adducts, and they have a finite half-life (10–12). Using gas chromatography/mass spectrometry, hemoglobin-aromatic amine adducts can be measured fairly readily. These types of studies have demonstrated that aromatic amines, including aniline derivatives and the carcinogens 4-aminobiphenyl, 2-naphthylamine, and 2-aminofluorene, are present in tobacco smoke and form hemoglobin adducts (12, 13). Although there appeared to be a baseline level, adduct levels were increased 3- to 10-fold in the blood of smokers (9, 11) and were found in fetuses exposed to tobacco smoke in utero (12). Persons who acetylated aromatic amines more slowly had higher levels of the adducts than those who were rapid acetylators (10), implying that the free amine was necessary to initiate hemoglobin binding. This was supported by an extensive study of more than 20 nitroarenes and the corresponding amines that aimed at developing structure-activity relationships for hemoglobin binding in rats. The amine bound to a greater extent than the nitroarene. The highly substituted nitroarenes 2,4-dimethyl-, 3,4-dimethyl-, 2,6-dimethyl- and 2,4,6-trimethylnitrobenzene and 2,3,4,5,6-pentachloronitrobenzene did not bind to hemoglobin. All of the corresponding amines, except for pentachloroaniline, bound to hemoglobin. The implications were that due to structural interference, nitro reductase enzymes were prevented from acting on these nitroarenes, and thus hemoglobin binding was blocked (14).

1.4.3 Pharmacokinetics, Metabolism, and Mechanisms During metabolism, aromatic nitro and amino compounds may go by either of two pathways, detoxication or activation to toxic intermediates. Hydroxylation on the aromatic ring to yield a phenol is the first phase of detoxication. Further oxidative reactions may lead to demethylation of dimethylanilines or formation of quinoid derivatives of aminophenols. Conjugation of the phenol thus formed with glucuronic and/or sulfuric acid affords more soluble compounds that are readily excreted. Acetylation of an aromatic amine or formation of *N*-glucuronides are also detoxication pathways. Removal of a nitro group from some dinitroarenes and conjugation with glutathione ending as a mercapturic acid occurred (2, 15–17).

Activation to a toxic intermediate often leads to a common substance from nitro- or aminoarenes. Amines/amides undergo oxidation of the nitrogen to form *N*-hydroxylamines or amides; nitro compounds are reduced through nitroso and hydroxylamine stages. The hydroxylamines are largely responsible for the methemoglobinemia from these materials. Overall, many metabolites may be formed from one compound, depending on the structure and the animal species.

Carcinogenic aromatic amines follow the same metabolic paths as other amines, namely ring hydroxylation, conjugation, and excretion. Hydroxylation of the nitrogen, followed by formation of a

reactive sulfate or acetate ester that yields a reactive electrophilic arylnitrenium ion (Ar-N^+-H) is involved. The nitrenium ion can arylate DNA, which is considered a crucial event in carcinogenesis (17), at least for genotoxic carcinogens. Further discussion follows in Section 1.4.5.

Although the P450 system is a major factor in oxidative detoxication and activation of nitro- and aminoarenes (15, 18–20), flavine-dependent enzymes and peroxidases such as prostaglandin H synthase also oxidize amines, including benzidine and 2-aminofluorene (21).

The P450 system was so named for the wavelength of the carbon monoxide derivative of the reduced form of the hemoprotein, namely, 450 nm (20). Originally though to be only one protein, further research aided by better separation methods has indicated there may be several hundred, if not more, isoforms of this enzyme, depending on the species. Thus P450 consists of a superfamily of hemoproteins that are important in metabolizing both xenobiotics and endogenous substances.

Nomenclature of the P450 enzymes was originally based on the method used to induce them; this changed to a system based on the protein and now based on the chromosomal location (19, 20). Accordingly, P450IIA1 is being replaced by CYP2A1; corresponding changes for other isoforms hold.

There are seven steps involved in the oxidation of a chemical by a P450 isoform: (1) binding of the substrate to the ferric form of the enzyme, (2) reduction to the ferrous form by NADPH-cytochrome P450 reductase, (3) binding of molecular oxygen, (4) introduction of a second electron from P450 reductase and/or cytochrome b_5, (5) dioxygen cleavage that releases water and forms the active oxidizing species, (6) substrate oxygenation, and (7) product release (18).

The P450 enzymes can be induced by numerous substances, including phenobarbital, ethanol, aromatic hydrocarbons such as 3-methylcholanthrene, dioxin, and the pesticides DDT and chlordane. Likewise, they can be inhibited by certain benzoflavones, thiocarbamates, disulfiram, and some heterocyclic nitrogen compounds. Selective induction and inhibition of the P450 isoforms has been demonstrated in laboratory experiments. Experimentally, the carcinogenicity of aromatic amines could be decreased or inhibited by simultaneous administration of certain enzyme inducers. Similarly, deleterious effects in humans have sometimes occurred from drug/drug or drug/environmental substance interactions due to induction/inhibition of P450 enzymes. Environmental substances include those from occupations, hobbies, food, alcohol, and tobacco smoke.

P450 isozymes important in metabolizing nitro- and aminoarenes include CYP1A2 for phenacetin, 4-aminobiphenyl, 2-naphthylamine, and 2-AAF; CYP2A6 for 6-aminochrysene and 4,4'-methylene bis(2-chloroaniline) MOCA®; CYP2B for the same two compounds; CYP2E1 for aniline, acetaminophen, and *p*-nitrophenol. CYP3A is involved in oxidative metabolism of MOCA®, 6-amino- and 6-nitrochrysene, and 1-nitropyrene, among others (20).

The expression of the P450 enzymes is also mediated by the genetic background that leads to differences in the rate of oxidation. One study showed that most Australians were rapid metabolizers, but some were in the slow and intermediate categories. Chinese and Japanese were mostly intermediate, whereas residents of Arkansas and Georgia in the southern United States were largely intermediate, although persons in the slow and rapid classes were also in this population (22).

The relationships among aromatic amine acetylation, genetic background, and susceptibility to the carcinogenic effect of amines were recognized some decades ago. Interest in this area has been fairly intensive and led to many publications on *N*-acetyl-transferases. The acetyl transferase enzyme has at least two forms: NATI that is monomorphic and acetylates aromatic amines; NAT2 that is polymorphic and *N*-acetylates aromatic amines but also *O*-acetylates hydroxylamines. These enzymes have molecular weights of approximately 29 and 31 kDa (23, 24). Slow human acetylators

are associated with increased risk of bladder cancer, and rapid acetylators are associated with higher rates of colorectal cancer. The implication is that localized metabolic activation of arylamine type carcinogens is facilitated by NAT2 in colon tissue. Apart from occupational exposure to aromatic amines, other sources of exposure to such compounds are from smoking tobacco or eating large amounts of meat. Various heterocyclic amines are formed by the ordinary methods for cooking meat (grilling, frying) which are animal carcinogens and act like aromatic amines in their metabolic pathways. Only NAT2 acetylated these compounds (25).

Besides leading to partial identification of the acetyl transferase enzymes, molecular techniques, led to construction of transgenic animals which delineated the characteristics of the isozymes to a greater extent (26, 27). Experiments with such animals supported the human epidemiological results; animals that were rapid acetylators showed a higher response to colon carcinogens (28, 29).

1.4.4 Carcinogenesis The United States, as do many other developed countries, has an aging population and increased age leads to a higher risk of cancer. It is estimated that 565,000 people will die of cancer in 1998. During many decades of life, the cells in individual organs undergo trillions or more of cell divisions, and opportunities for error occur in each one of those divisions. Biologically, cell proliferation or division is considered a risk factor for cancer. In addition, many factors in the environment may be responsible for human cancer. A monumental epidemiological study concluded that 2-4% of cancers in the United States were ascribable to occupation, 8–28% to the use of tobacco, 40–57% to diet, 8% to exposure to sunlight, and unknown or undefined factors were responsible for 16–20% (30). Less well defined influences include genetic background, viruses, certain medicinal agents, radiation, alcohol use, certain types of behavior, socioeconomic status, and even methods for cooking or preserving foods (31, 32).

Although the estimate of the percentage of cancers ascribed to occupation is relatively low, it still is necessary to follow the guidelines promulgated by various regulatory and advisory agencies to minimize the risk of developing cancer. For nitro- and aminoarenes, avoidance of direct contact is important because they are fairly readily absorbed through the skin at levels sufficient to cause toxicity. Thus, the numerous “skin” notations in the advisory listings of the American Conference of Governmental and Industrial Hygienists (ACGIH) are necessary.

The carcinogenicity of aromatic amines for the human bladder was noted about 30 years after widespread use of these compounds occurred in dyestuff factories. After another 40 years, animal studies supported this premise (2, 3). Even with improved workplace conditions and much lower exposures than the original dyestuff workers had, more current surveys still indicate an increased risk of bladder cancer (33). Aromatic amines generally did not induce tumors at the point of application, but at distant sites, including liver, intestine, and bladder. The actual organs affected varied with the species and strain; 2-naphthylamine targets the bladder in humans, monkeys, dogs, and hamsters but has little effect in rabbits. 2-AAF affected the liver and mammary gland in most strains of rats and mice, but X/Gf mice and guinea pigs were resistant. Metabolic and mechanistic studies provided clues for the differences in some cases (i.e., guinea pigs do not *N*-hydroxylate 2-AAF) but not in others (34).

The carcinogenicity of any particular molecular structure can often be altered dramatically by adding substituents (35). A premise that adding a methyl group ortho to the amino moiety in 2-naphthylamine would reduce carcinogenicity was shown erroneous when 3-methyl-2-naphthylamine turned out to be more active than the parent amine (36). On the other hand, adding polar moieties has nullified carcinogenic action. Sulfonic acid derivatives of 2-naphthylamine (37) and 4,4'-diaminostilbene were inactive (38). However, even if an aromatic amine is not carcinogenic, other possible toxic effects such as methemoglobinemia should be kept in mind.

Carcinogens are divided into groupings, depending on their mode of action. Because of their structures, direct acting ones react as such with cellular macromolecules, especially DNA. Usually such compounds are not stable and are not a hazard to the general population. In contrast, nitro- and

aminoarenes, are indirect acting because they require metabolic activation before they interact with cellular targets. Metabolic activation is influenced by many factors: species, strain, sex, age, diet, enzyme inducers/inhibitors, and immune status, plus others. Once activated, the intermediates react with the cell's genetic material and thus are considered genotoxic carcinogens. Some carcinogens such as chloroform, trichloroacetic acid, and unleaded gasoline caused animal tumors but did not attach to cellular DNA. These compounds are called nongenotoxic or epigenetic carcinogens (39). Mechanisms for the action of epigenetic carcinogens are varied and usually show little or no relevance to human risk.

Classification of carcinogens has been addressed before (2), but changes have occurred to some extent in how governmental and other groups have developed systems for classifying the degree of risk associated with chemical carcinogens. In 1969, the International Agency for Research on Cancer (IARC) initiated a program to evaluate the risk in humans according to the following system: Group 1—The agent (mixture) is carcinogenic to humans; Group 2A—The agent is probably carcinogenic to humans; Group 2B—The agent is possibly carcinogenic to humans; Group 3—The agent is not classifiable as to its carcinogenicity to humans; Group 4—The agent is probably not carcinogenic to humans (40).

The National Toxicology Program (NTP) of the U.S. Department of Health and Human Services has only two categories in its various reports on carcinogens: (1) substances or groups of substances, occupational exposures associated with a technological process, and medical treatments that are known to be carcinogenic; and (2) substances or groups of substances and medical treatments that may reasonably be anticipated to be carcinogens. Known carcinogens are defined as those for which the evidence from human studies indicates that there is a causal relationship between exposure to the substance and human cancer. Reasonably anticipated to be carcinogens encompasses those for which there is limited evidence of carcinogenicity in humans or sufficient evidence from tests in experimental animals (41).

The U.S. Environmental Protection Agency (EPA) formerly had an A to E system as follows: A—known human carcinogen; B—probably carcinogenic to humans; C—possibly carcinogenic to humans; D—not adequately tested; E—tested and negative. The EPA is moving toward a narrative system that takes into account differences between humans and experimental animals in metabolism and mechanism of action. The system is as follows:

Known/likely—the available tumor effects and other key data are adequate to convincingly demonstrate carcinogenic potential for humans.

Cannot be determined—available tumor effects or other essential data are suggestive or conflicting or limited in quality and thus are not adequate to demonstrate a carcinogenic potential convincingly in humans.

Not likely—Experimental evidence is satisfactory to decide that there is no basis for concern as to human hazard.

The EPA system is not final, and new EPA classifications for industrial/environmental chemicals have not been published.

The U.S. Occupational Safety and Health Administration (OSHA) included the following aromatic amines or derivatives in its 1974 standards to minimize or control exposure: 2-AAF, 4-aminobiphenyl, benzidine, 3,3'-dichlorobenzidine, 4-dimethylaminoazobenzene, 1-naphthylamine, 2-naphthylamine, and 4-nitrobiphenyl (2).

The ACGIH, which is active in setting exposure limits for workplace chemicals, adopted the following system approximately 10 years ago:

1. Confirmed human carcinogen. The agent is carcinogenic to humans based on the weight of the evidence from epidemiologic studies.

2. Suspected human carcinogen. The agent is carcinogenic in experimental animals at dose levels, by route(s) of administration, at site(s) of histologic type(s), or by mechanism(s) that are considered relevant to worker exposure. Available epidemiological studies are conflicting or insufficient to confirm an increased risk of cancer in exposed humans.
3. Animal carcinogen. The agent is carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), of histological type(s) or by mechanisms(s) that are not considered relevant to worker exposure. Available epidemiological studies do not confirm an increased risk of cancer in exposed humans. Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure.
4. Not classifiable as a human carcinogen. There are inadequate data on which to classify the agent in terms of carcinogenicity in humans and/or animals. Substances for which animal tests are negative without further evidence of relevant mechanisms fall into this category.
5. Not suspected as a human carcinogen. The agent is not suspected to be a human carcinogen on the basis of properly conducted epidemiological studies in humans. These studies have sufficiently long follow-up, reliable exposure histories, sufficiently high dose, and adequate statistical power to conclude that exposure to the agent does not convey a significant risk of cancer to humans. Evidence that suggests a lack of carcinogenicity in animals will be considered if it is supported by other relevant data (42).

Increased emphasis on cooperation between countries and the formation of the European Union make it expedient to be informed of the systems employed by the Union and the German MAK (Maximum allowable concentration) Commission (43). The European Union proposes the following:

1. Substances known to be carcinogenic to humans
2. Substances that should be regarded as if they are carcinogenic to humans
3. Substances that cause concern for humans owing to possible carcinogenic effects

    1. Substances that are well investigated
    2. Substances that are insufficiently investigated

The German MAK system is as follows:

1. Substances that cause cancer in humans.
2. Substances that are considered carcinogenic to humans.
3. Substances that cause concern that they could be carcinogenic to humans but which cannot be assessed conclusively because of lack of data.
4. Substances with carcinogenic potential for which genotoxicity plays no or at most a minor role. No significant contribution to human cancer risk is expected, provided that the MAK value is observed.
5. Substances with carcinogenic and genotoxic potential, the potency of which is considered to be so low, provided that the MAK value is observed, that no significant contribution to human cancer risk is to be expected.

In the MAK system, more emphasis is placed on the genotoxicity of substances, as detected by mutagenicity or other short-term tests, than on animal tests for carcinogenicity. For reasons of cost and time, determining the mutagenic potential of a substance in specific strains of bacteria has become a surrogate for long-term studies. The most widely used of these tests involves measuring the ability of a substance to induce mutations and thus bacterial colony growth in strains of *Salmonella typhimurium*. Of the *S. typhimurium* strains, TA1538, which has a frameshift mutation, is more likely to respond to aromatic amines. New strains are developed frequently, but baseline data for many compounds have been obtained for strains TA100, TA98, TA1535, TA1537, and TA1538.

Addition of a liver fraction (S9) to the test culture allows measuring the effect of metabolic activation on mutagenicity (44).

However, the correlation between mutagenicity in bacteria and carcinogenicity in animals is not absolute and holds in approximately 60% of cases. It was found that using additional types of short-term tests involving animal cells or systems did not appreciably increase the accuracy of the test. Accordingly, the *Salmonella* system represents the easiest and least expensive of the short-term systems and has an accuracy comparable to other more expensive and more complicated tests.

On the downside, the *Salmonella* system is not totally accurate in detecting carcinogens, and the opposite can occur. Sodium azide was an active mutagen, but it was inactive in animal tests for carcinogenicity. Conversely, benzene and hexamethylphosphoramide are not mutagens in the usual test systems, but they are carcinogens in humans and animals, respectively. The fairly potent animal carcinogens *o*-anisidine and *p*-cresidine were not genotoxic in three animal-based short-term tests, namely, unscheduled DNA synthesis, DNA single-strand breaks, and effects in micronuclei. The tests were performed with four strains of rats and two strains of mice (45). Thus, total reliance on short-term tests can be misleading. Many potentially useful compounds have been discarded along the path to development because of positive mutagenicity tests. But the results from short-term tests, if used judiously, can afford clues as to which compounds are more likely to be active in long-term animal studies. Such efforts are costly and require several years and involvement from people trained in many disciplines to complete a study well (46). In the United States, the NTP is the one agency that is primarily responsible for testing compounds in chronic studies.

1.4.5 Genetic and Related Cellular Effects Studies The advances in knowledge about the association between specific enzymes and the possible increased risk of developing cancer from occupational exposure have led to a new social concern. Employers may wish to use genetic screening to differentiate workers at greater risk from those less likely to be affected, but there are many uncertainties in the screening tests that make total reliance on them problematic (47–49). Furthermore, because of the genetic polymorphisms that involve enzymes which metabolize xenobiotics such as aromatic amines, matters of individual variation and individual rights must be considered. As mentioned previously, there are slow, intermediate, and rapid metabolizers of xenobiotics due to levels of expression of CYP1A2 in most populations. Likewise, although persons of certain backgrounds are more likely to acetylate aromatic amines rapidly, this is not absolute. Based on the identification of up to 9 different alleles for the slow acetylator phenotype, 45 different slow acetylator genotypes, 9 heterozygous rapid genotypes, and 1 homozygous wild-type rapid genotype, all combined with the slow, intermediate and rapid CYP1A2 types, it becomes evident that many combinations are possible. Thus an observed “polymorphism” may reflect a great number of genotypes. Instead of a well-defined genetic polymorphism, there can be much biochemical individuality in a population (22, 50).

Any test to differentiate individuals into the different categories must be accurate, but false negatives and false positives complicate the picture. In addition, enzyme induction by dietary or other exposures, including alcohol, tobacco, and medications is a further complication. Available genetic screening tests are not sufficiently validated for routine use.

For the individual, matters of decisional autonomy, confidentiality of medical information, beneficence, nonmaleficence, and equity are issues of concern. Possible discrimination, protection of equal employment opportunity, and potential stigmatization must also be considered. These concerns have been raised worldwide (51–55). Experts in this area concluded that in view of the uncertainties, removing the chemical carcinogen from the workplace by substituting a noncarcinogenic compound or achieving a zero level of exposure is more effective in preventing occupational cancer than genetic screening (50). These issues will probably remain a matter of discussion for years to come.

1.4.6 Reproductive and Developmental The previous edition of this chapter pointed out the toxicity of nitrobenzene for the male reproductive system when given at doses up to 30 times the limit set for

occupational exposure (2). The related substance, 1,3-dinitrobenzene, also produces testicular toxicity, affecting the Sertoli cells of the testis. Further studies have implicated the metabolite 3-nitrosonitrobenzene as the prime candidate for the toxic effect because the other metabolites 3-nitrophenylhydroxylamine and 3-nitroaniline were not active (56). Similarly, other nitroarenes such as 2,4- and 2,6-dinitrotoluene were toxic to the testis, indicating that workplace exposures to such compounds should be kept to a minimum.

Additional investigation revealed that nitrobenzene at 300 mg/kg and 1,3-dinitrobenzene at 30 mg/kg suppressed the formation of proteins usually secreted during spermatogenesis. With labeled methionine incorporation as a marker, nitrobenzene decreased formation of proteins usually secreted during stages VI-VIII and IX-XII, but had no effect in the earlier stages II–IV. Results were comparable for 1,3-dinitrobenzene except that incorporating methionine at stages II-V was increased. Six marker proteins for which secretion was reduced greatly after the nitobenzenes were studied; two of these proteins corresponded to two androgen-regulated proteins thought to be products of the Sertoli cell (57).

A survey of aromatic nitro and amino compounds tested for reproductive/teratogenic effects indicated that in general, relatively high doses of most aromatic amines to the maternal organism were required to produce a result. In some cases, doses of 5 g/kg or more were needed (2, 58). Thus, by observing hygienic guidelines, the risk of reproductive toxicity would be relatively small. However, aromatic amines may lead to “oxidative stress,” methemoglobinemia, anemia, and other types of toxicity. They may also target the hypothalamus and pituitary (59). Collectively, these actions are likely to influence fertility or successful completion of a pregnancy.

1.5 Studies on Environmental Impact

Although nitroarenes and amines are toxic to many species, biodegradation of such compounds is facilitated by the nitro reductase and oxidative enzymes present in sewage bacteria (60). Most of the aromatic amines are oxidatively degraded by bacteria in wastewater unless adsorbed to soil, where they are more resistant to action. However, in the presence of denitrifying and methanogenic microbial activity, aniline was released from the soil and degraded readily (61). Additional substituents in the molecule often led to slower breakdown (62). Acclimating activated sludge with both aniline and toluenediamine, which has been considered a resistant-type compound, led to a reasonable rate of biodegradation of the toluenediamine (63). Biodegradation of multiring aromatic amines was highly dependent on microbial activity, as shown by increases in decomposition at higher temperatures (30°C). Consistent relationships between breakdown of the amines and soil properties were not noted (64).

2,4,6-Trinitrotoluene (TNT) and associated compounds that occur in wastewaters are both toxic and phototoxic to many organisms usually found in streams; one metabolite 2-amino-4,6-dinitrotoluene was more phototoxic than TNT and 4-amino-2,6-dinitrotoluene. The toxicities of TNT and the two derivatives to stream organisms were decreased by glutathione conjugation (65).

Although 4-chloroaniline delayed somewhat the various lifestages of small fish (66), 3,4-dichloroaniline, a degradation product of the herbicide propanil, is of special concern. It affects various benthic invertebrates, leading to complete extinction of some and reduction in the number of surviving individuals in others (67, 68). A mixture of 3,4-dichloroaniline and lindane had an additive effect and influenced growth somewhat in early life stages of small fish (69). If the fish were exposed for the whole life span, they stopped reproducing (70). There was no single clear-cut mechanism to explain the toxicity of 4-nitro- and 2,4-dinitroaniline to various environmental eukaryotes and prokaryotes (71).

Currently, there are many efforts to develop special strains of bacteria to degrade industrial wastes. Similarly, production of bacterial strains with enhanced P450 protein expression has been suggested as a useful tool to biodegrade industrial and other contaminants (72). Such methods of cleaning industrial sites and waste dumps are less disruptive than other methods currently used or proposed.

Although most of the nitroarenes mentioned in this chapter generally are industrial materials, some have been detected in ambient airborn particulates, including those from diesel engine exhausts (Table 57.1). Nitrogen oxides react with polycyclic aromatic hydrocarbons (PAHs) in the heated engine exhaust to form nitroarenes at nano- to picogram/m^3 levels; at least 25 have been detected in such exhausts (73–76). Almost 100 PAHs have been found in engine exhausts (75), and the number of nitroarenes formed is correspondingly large because each PAH is amenable to nitration at several positions. However, only about 25 have been positively identified (74, 75). Nitroarenes generally are mutagens in *Salmonella* (77–79). Tests for carcinogenicity have shown varying potencies. 1-Nitronaphthalene was inactive in a feeding study with rats and mice (80), but most of the other environmental nitroarenes have shown surprising potency (81–84). Many organ systems were affected, including lung, colon, and breast. There have been any number of investigations on the metabolism and DNA binding of nitroarenes and only a few are cited here (85, 86). In general, these compounds are hydroxylated to phenols that are excreted as sulfate and glucuronide conjugates. Reduction to the amine with *N*-hydroxylation and DNA binding also occurs (87). The metabolic pattern and degree of DNA binding did not always correlate with the carcinogenic potency of a particular nitroarene (86).

Table 57.1. Physical Properties of Some Nitroarene Air Pollutants[a]

Compound	CAS Number	Molecular Weight	Melting Point (°C)	Physical Form
3,7-Dinitrofluoranthene	[*105735-71-5*]	292.3	203–204	Yellow needles
3,9-Dinitrofluoranthene	[*22506-53-2*]	292.3	275–276	Yellow-orange crystals
2,7-Dinitrofluorene	[*5405-53-8*]	256.2	334	Light yellow solid
2,7-Dinitrofluorenone	[*31551-45-8*]	270.2	292–295	Deep yellow solid
1,3-Dinitropyrene	[*75321-20-9*]	292.3	297–298	Orange crystals
1,6-Dinitropyrene	[*42397-64-8*]	292.3	310	Yellow crystals
1,8-Dinitropyrene	[*42397-65-9*]	292.3	300	Fluffy yellow crystals
9-Nitroanthracene	[*602-60-8*]	223.2	145–146	Yellow needles
7-Nitrobenzo[a] anthracene	[*20268-51-3*]	273.3	160–163	Yellow crystals
1-Nitrobenzo[a] pyrene	[*70021-99-7*]	297.3	250–250.5	Orange solid
3-Nitrobenzo[a] pyrene	[*70021-98-6*]	297.3	211–212	Orange solid
6-Nitrobenzo[a] pyrene	[*63041-90-7*]	297.3	255–256	Orange solid
6-Nitrochrysene	[*7496-02-8*]	273.3	209	Orange-yellow needles
3-Nitrofluoranthene	[*892-21-7*]	247.3	156–160	Yellow crystals
2-Nitrofluorene	[*607-57-8*]	211.2	156	Light yellow

				needles
4-Nitronaphthalene	[*86-57-7*]	173.2	61.5	Yellow needles
2-Nitronaphthalene	[*581-89-5*]	173.2	79	Yellow needles
3-Nitroperylene	[*20589-63-3*]	297.3	210–212	Brick-red crystals
1-Nitropyrene	[*5522-43-0*]	247.3	155	Yellow needles or prisms
2-Nitropyrene	[*789-07-1*]	247.3	197–199	Yellow crystals
4-Nitropyrene	[*57835-92-4*]	247.3	190–192	Orange needles

[a] Data bases: AIDSLINE, DART, EINECS, GENE-TOX, CANCERLIT, CCRIS, EMIC, EMICBACK, IARC, MEDLINE, MESH, RTECS, TSCAINV, TOXLINE, SUPERLIST.

The relevance to human cancer has been addressed both theoretically (88) and practically (89). Assays of excised lung tumors from nonsmoking Japanese demonstrated the presence of 1-nitropyrene, 1,3-dinitropyrene, and 1-nitro-3-hydroxypyrene in the tissues (89). In similar specimens from rural Chinese who had been exposed to open cooking fires, some 1-nitropyrene was detected, but the levels of PAHs were many times higher than in the Japanese specimens.

Nitroarenes could thus be a possible factor in lung and other types of cancers. Reduction in both PAHs and nitrogen oxides in engine exhausts is needed to decrease this possible cancer risk.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

Specific Compounds
In this section, compounds with one aromatic ring will be discussed first, then those with two rings, et cetera. Any new developments regarding toxicity or mechanisms of action are emphasized. Because this is an age of computerized databases or inventories, for each compound, the bases/inventories which list that specific compound will be mentioned. The codes for these lists or inventories are given in Table 57.2.

Table 57.2. Database/List Acronyms for Chemicals

Acronym	Name	Producer
ATSDR	Agency for Toxic Substances and Disease Registry	ATSDR, Atlanta, GA
CA65	California List of Chemicals Known to Cause Cancer or Reproductive Effects	CA EPA
CAA1	Hazardous Air Pollutants	US EPA, Washington, DC
CAA2	Ozone Depletion Chemicals List	US EPA, Washington, DC
CANCERLIT	Cancer Literature Bibliographic File	National Cancer Institute (NCI)

CATLINE	Catalog on Line	National Library of Medicine (NLM)
CCRIS	Chemical Carcinogenesis Research Information System	National Cancer Institute (NCI)
CGB	DOT Coast Guard Bulk Hazardous Materials	Coast Guard, DOT Washington, DC
CGN	DOT Coast Guard Noxious Liquid Substances	Coast Guard, DOT Washington, DC
ChemID	Chemical Identification File	National Library of Medicine (NLM)
DART	Developmental and Reproductive Toxicology	National Library of Medicine (NLM)
DEA	Drug Enforcement Administration Controlled Substances	Drug Enforcement Administration, Washington, DC
DIRLINE	Directory of Information Resources Online	National Library of Medicine (NLM)
DOT	DOT Hazardous Materials Table	US Dept. of Transportation, Washington, DC
DSL	Domestic Substances List of Canada	Dept. of The Environment Canada, Quebec, Canada
EINECS	European Inventory of Existing Commercial Chemical Substances	European Commission, Luxembourg
ELIN	European Inventory of Existing Commercial Chemical Substances Supplement	European Commission, Luxembourg
EMIC & EMICBACK	Environmental Mutagen Information Center and its Backfile	National Library of Medicine, EPA, NIEHS
ETICBACK	Environmental Teratology Information Center Backfile	NLM, EPA, NIEHS
FIFR	EPA Pesticide List	US EPA, Washington, DC
GENE-TOX	Genetic Toxicology Test Results Data Bank	US EPA, Washington, DC
GRAS	Direct Food Substances Generally Recognized as Safe	U.S. Food and Drug Administration, Washington DC
HSDB	Hazardous Substances Data Bank	National Library of Medicine (NLM)
IARC	International Agency for Research on Cancer List	IARC, WHO, Lyon, France
IL	The Toxic Substances List of Illinois Department of Labor	Illinois Dept. Of labor, Springfield, IL
INER	List of Pesticide Product Inert Ingredients	US EPA, Washington, DC
IRIS	Integrated Risk Information System	US EPA, Washington, DC
MA	Massachusetts Substances List	MA Dept. of Health,

		Boston, MA
MEDLINE	Medlars on Line	National Library of Medicine (NLM)
MPOL	Marine Pollutants List	International Maritime Organization
MI	Critical Materials Register of the State of Michigan	Michigan Dept. of Natural Resources
MTL	EPA Master Testing List	US EPA, Washington, DC
NJ	New Jersey Hazardous Substances List	NJ Department of Environmental Protection, Trenton, NJ
NJEH	New Jersey Extraordinarily Hazardous Substances List	Bureau of Release Prevention, Trenton, NJ
NTPA	NTP Carcinogens List	NTP, NIEHS, Research Triangle Park, NC
NTPT	NTP Technical Reports List	NTP, NIEHS, Research Triangle Park, NC
PA	Pennsylvania Right to Know List	PA Dept of Labor and Industry, Harrisburg, PA
PAFA	List of Substances Added to Food in the United States	US Food and Drug Administration, Washington DC
PEL	OSHA Toxic and Hazardous Substances	OSHA, U.S. Dept. of Labor, Washington, DC
REL	NIOSH Recommended Exposure Limits	National Institute for Occupational Safety and Health, Cincinnati, OH
RQ	CERCLA Hazardous Substances Table 302.4	US EPA, Washington, DC
S110	ATSDR/ EPA Priority List	ATSDR, Atlanta, GA
S302	Extremely Hazardous Substances	US EPA, Washington, DC
TOXLINE	Toxicology Information Online	National Library of Medicine (NLM)
TOXNET	Toxicology Data Network	National Library of Medicine (NLM)
TLV	ACGIH Threshold Limit Value List	ACGIH, Cincinnati, OH
TRI	Toxic Chemical Release Inventory	US EPA, Washington, DC
TSCAINV	Toxic Substances Control Act Chemical Substances Inventory	US EPA, Washington, DC
WHMI	Workplace Hazardous Materials Information System: Ingredient Disclosure List of Canada	Canadian Consumer and Corp. Affairs, Victoria, Quebec

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

Single-Ring-Compounds
1.0 Nitrobenzene
1.0.1 CAS Number: [*98-95-3*]

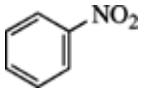
1.0.2 Synonyms: Nitrobenzol, and an old name of uncertain origin is oil of mirbane.

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 123.11

1.0.5 Molecular Formula: $C_6H_5NO_2$

1.0.6 Molecular Structure:



Databases or inventories where listed: CAA1, CA 65, CANCERLIT, CCRIS, CGN, DART, DOT, DSL, EINECS, HSDB, IARC, MA, MI, MPOL, NJ, PA, PEL, REL, RQ, RTECS, S302, TLV, TSCAINV
1.1 Chemical and Physical Properties (2)

Physical state	Colorless to pale yellow liquid
Density	1.2037 (20/4°C)
Melting point	5.7°C
Boiling point	210.9°C
Vapor density	4.1
Refractive index	1.55291
Solubility	Slightly soluble in water: very soluble in ethanol, ether; soluble in benzene, oils
Flash point	88°C (closed cup)
Odor	Bitter almond

1.2 Production and Use
Nitrobenzene is generally made by a continuous reaction process involving nitric acid and benzene in vapor-phase or jet-impingement reactors (1).

Nitrobenzene is an intermediate in the preparation of aniline, in making cellulose esters and acetate, in shoe and metal polishes, in soap perfumes, paint solvents, leather dressings, and in refining lubricating oils to the extent of close to 2 billion pounds/year.
1.3 Exposure Assessment
Analytical methods: NMAM 4th ed. method # 5053.
1.4 Toxic Effects
The previous edition of this chapter mentioned the toxic effects of nitrobenzene which include skin and eye irritation, cyanosis, methemoglobinemia, hemolytic anemia, spleen and liver damage, jaundice, neural toxicity with renal and testicular damage also present. Although nitrobenzene depressed the immune response of female $B6C3F_1$ mice, their resistance to microbial/viral infection

was not markedly altered (90).

Noteworthy new information on nitrobenzene is that it also is carcinogenic in mice and rats (91). The study included male and female $B6C3F_1$ mice, male and female F344 rats, and male CD rats. The mice were exposed by inhalation to 0,5, 25, or 50 ppm for 6 h/day, 5 days/week for 2 years, and rats were exposed to 0,1,5, or 25 ppm under the same time span as the mice. Survival of test animals was not significantly affected by nitrobenzene exposure, and body weights did not exceed a 10% deviation from controls.

The exposure affected hematic parameters in both mice and rats, and there were significant differences in the incidences of nonneoplastic and neoplastic lesions. The incidence of alveolar/bronchiolar adenomas increased to a significant degree in 25- and 50-ppm exposed male mice, and the number of mice that had either adenomas or carcinomas was higher in all exposed groups. Alveolar/bronchiolar hyperplasia was increased in the 25- and 50-ppm males. Follicular cell adenomas of the thyroid were significantly higher in the 50-ppm males, and hyperplasia occurred in the 25- and 50-ppm males.

In the female mice, mammary gland adenocarcinomas were increased at the 50-ppm level, plus a positive trend for hepatocellular adenoma related to nitrobenzene concentration.

Hepatocytomegaly, multinucleated hepatocytes, inflammatory lesions of the nose, epididymal hypospermia, and other nonneoplastic effects were noted in the mice.

In male F344 rats, nitrobenzene at 25 ppm led to increases in hepatocellular adenoma or carcinoma, renal tubular adenomas, or either renal adenoma or carcinoma with a positive trend for follicular cell adenoma or adenocarcinoma of the thyroid. Female F344 rats had a significant increase in endometrial stromal polyps of the uterus at 25 ppm. In both male and female rats, nitrobenzene exposures led to a striking decrease in mononuclear cell leukemia. Male F344 rats showed increases in extramedullary hematopoiesis (1 and 5 ppm) and pigmented macrophages (25 ppm). Increased focal inflammation of the olfactory region with pigment deposition was noted in both sexes.

The male CD rats responded to nitrobenzene with significant increases in hepatocellular adenomas and spongiosis hepatis in the 25-ppm group. Centrilobular hepatocytomegaly and Kupffer cell pigmentation, atrophy of the testes, and nasal pigment deposition also occurred.

The locations where tumors were induced differed based on species, sex, and for rats, on strain also. Some of the differences could possibly be related to differences in the metabolism of nitrobenzene, but the actual mechanism for the carcinogenicity of nitrobenzene has not been delineated. Because carcinogenic effects were noted at 25 ppm, industrial hygienists should monitor carefully so that workplace exposure does not exceed the permissible limit.

1.5 Standards, Regulations, or Guidelines of Exposure

The current ACGIH TLV-TWA is 1 ppm with a skin and A3 notation; Australia 1 ppm, skin; Germany (BAT value), 100 mg/l; Sweden, 1 ppm; United Kingdom, 1 ppm; OSHA PEL and NIOSH REL is 1 ppm.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

A. Monochloronitrobenzenes

2.0 1-Chloro-2-nitrobenzene

2.0.1 CAS Number: [*88-73-3*]

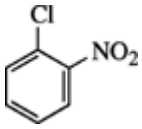
2.0.2 Synonyms: *o*-Chloronitrobenzene, 2-chloro-1-nitrobenzene, 2-chloronitrobenzene, 2-nitrochlorobenzene, 1-nitro-2-chlorobenzene, o-CNB, 2-CNB

2.0.3 Trade Names: NA

2.0.4 Molecular Weight: 157.56

2.0.5 Molecular Formula: $C_6H_4NO_2Cl$

2.0.6 Molecular Structure:



Databases or inventories where listed: CGB, CGN, DOT, IARC, MA, NTPT, PA, WHMI, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, ETICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

2.1 Chemical and Physical Properties (2)

Physical state	Yellow crystals
Melting point	34–35°C
Boiling point	245–246°C
Solubility	Soluble in ethanol, benzene, ether, acetone

2.2 Production and Uses

1-Chloro-2-nitrobenzene is an important intermediate in preparing dyes and lumber preservatives and in making photographic chemicals, corrosion inhibitors, and agricultural chemicals (92).

2.4 Toxic Effects

A 13-week inhalation study in male and female F344/N rats and male and female B6C3F$_1$ mice at levels of 0, 1.1, 2.3, 4.5, 9, and 18 ppm for 6 h/day 5 days a week, demonstrated that hepatocellular necrosis and inflammation occurred in mice along with lesions of the spleen and hemosiderin deposition. In rats, these exposures led to hyperplasia of the epithelium lining the nasal cavity. Methemoglobinemia was noted in the rats (93).

In the male mice and rats, there were decreases in sperm motility or spermatid count (92). A continuous breeding study in Swiss mice given 40, 80, or, 160 mg/kg by gavage showed no reproductive toxicity, but methemoglobinemia was observed in the parental animals (94).

1-Chloro-2-nitrobenzene was absorbed through the skin of male F344 rats to the extent of 33–40% in 72 h (92).

Metabolism studies with ^{14}C-labeled compound showed rapid excretion in the urine with up to 23 metabolites. Only about 5% remained in the animals by 72 h, mostly in the liver. Older rats absorbed and metabolized and then excreted the labeled compound at approximately the same rate as young rats. Hepatocytes from male F344 rats converted the nitro compound to 2-chloroaniline to a major extent, but 2-chloroaniline *N*-glucuronide, and S-(2-nitrophenyl)glutathione were also formed to an appreciable extent (92).

Oral administration to male and female CD-1 mice at 3000 or 6000 ppm for 8 months followed by 1500 or 3000 ppm for 10 months led to increases in hepatocellular carcinomas in both males and females. In male CD rats, 1000 or 2000 ppm for 6 months, followed by 500 or 1000 ppm for 12

months, led to increased numbers of rats with multiple tumors (92).

2.5 Standards, Regulations, or Guidelines of Exposure

Standards not assigned.

3.0 1-Chloro-3-nitrobenzene

3.0.1 CAS Number: [*121-73-3*]

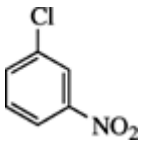
3.0.2 Synonyms: 1-Chloro-3-nitrobenzene, *m*-chloronitrobenzene, 3-chloro-1-nitrobenzene, 3-nitrochlorobenzene; 1-nitrochlorobenzene, MNCB, 3-CNB, *m*-CNB, nitrochlorobenzene

3.0.3 Trade Names: NA

3.0.4 Molecular Weight: 157.56

3.0.5 Molecular Formula: $C_6H_4NO_2Cl$

3.0.6 Molecular Structure:



Databases or inventories where listed: DOT, IARC, MA, PA, WHMI, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST

3.1 Chemical and Physical Properties (2)

Physical state	Yellow prisms from ethanol
Melting point	46°C
Boiling point	235–236°C
Solubility	Soluble in hot ethanol, chloroform, ether, carbon disulfide, benzene; insoluble in water
Flash point	103°C

3.2 Production and Use

1-Chloro-3-nitrobenzene is an intermediate in the production of dyes and fungicides (92).

3.4 Toxic Effects

In hepatocytes isolated from male rats, 1-chloro-3-nitrobenzene was converted mainly to 3-chloroaniline with much lower amounts of 3-chloroaniline *N*-glucuronide. No glutathione conjugate was found (92).

3.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

4.0 1-Chloro-4-nitrobenzene

4.0.1 CAS Number: [*100-00-5*]

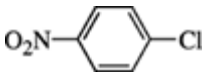
4.0.2 Synonyms: PNCB; nitrochlorobenzene; 1,4-chloronitrobenzene; 4-nitrochlorobenzene; 4-chloro-1-nitrobenzene; *para*-nitrochlorobenzene

4.0.3 Trade Names: NA

4.0.4 Molecular Weight: 157.56

4.0.5 Molecular Formula: $C_6H_4NO_2Cl$

4.0.6 Molecular Structure:



Databases and inventories where listed: DOT, IARC, IL, MA, MTL, NTPT, PA, PEL, PELS, REL, TLV, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, HSDB, MEDL, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

4.1 Chemical and Physical Properties (2)

Physical state	Yellow crystals
Specific gravity	1.52
Melting point	82–84°C
Boiling point	242°C
Vapor pressure	0.009 torr at 25°C
Flash point	127°C (closed cup)
Solubility	Sparingly soluble in water; soluble in ether, carbon disulfide, ethanol, acetone

4.2 Production and Use

1-Chloro-4-nitrobenzene is employed in producing dyes, drugs, herbicides, antioxidants, and as an intermediate in synthesizing various compounds (92).

4.4 Toxic Effects

A 13-week inhalation study in male and female F344/N rats and $B6C3F_1$ mice at levels of 0, 1.5, 3, 6, 12, and 24 ppm, 6 h/day for 5 days/week led to increases in liver and spleen weights in rats, along with changes in kidney tubules and hematopoiesis. Methemoglobinemia was more severe than with the 2-isomer. Mice also showed changes in liver and spleen, and in females hyperplasia of the forestomach epithelium was noted (93).

In male rats, spermatid counts were lower, but females were not affected. Mice showed no significant change (92). In a continuous breeding study with Swiss mice, exposure to 62.5, 125, or 250 mg/kg by gavage reduced the birth weight and viability of the pups (95).

A dermal absorption study with F344 rats demonstrated that 51–62% of labeled 1-chloro-4-nitrobenzene was absorbed within 72 h, and 43–45% was excreted in the urine. As with the 2-isomer, the metabolism of the 4-isomer was not greatly influenced by age (92).

In longshoremen accidentally exposed to 1-chloro-4-nitrobenzene, the same urinary metabolites were identified as in rats, namely, *N*-acetyl-S-(4-nitrophenyl)-L-cysteine, 4-chloroaniline, 4-chloroacetanilide, 4-chloro-oxanilic acid, 2-amino-5-chlorophenol, 4-chloro-2-hydroxyacetanilide, 2,4-dichloroaniline and 2-chloro-5-nitrophenol (96).

In a longer term study of 1-chloro-4-nitrobenzene, CD male and female mice fed 3000 or 6000 ppm in the diet for 18 months showed increases in hepatocellular carcinomas and vascular tumors in the males and vascular tumors in the females. Male CD rats given levels from 250 to 4000 ppm showed no increase in tumors (92).

4.5 Standards, Regulations, or Guidelines of Exposure

The current ACGIH TLV-TWA is 0.1 ppm (0.64 mg/m^3) with a skin notation; Australia, 0.1 ppm (skin); United Kingdom, 1 ppm (skin)

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

B. Chlorodinitrobenzenes
5.0 2-Chloro-1,3-dinitrobenzene
5.0.1 CAS Number: [*606-21-3*]

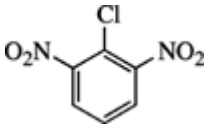
5.0.2 Synonyms: 1-Chloro-2,6-dinitrobenzene

5.0.3 Trade Names: NA

5.0.4 Molecular Weight: 202.55

5.0.5 Molecular Formula: $C_6H_3N_2O_4Cl$

5.0.6 Molecular Structure:



Databases or inventories where listed: EINECS, EMICBACK, GENETOX, HSDB, RTECS, TOXLINE, TSCAINV
5.1 Chemical and Physical Properties (2)

Physical state	Yellow crystals
Melting point	86–87°C
Boiling point	315°C
Solubility	Soluble in ethanol, ether, toluene

5.2 Production and Use
No specific uses were found, but the commercial mixture of chlorodinitrobenzenes is used to synthesize other compounds (2).
5.4 Toxic Effects
No toxicological information was found.
5.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
6.0 2-Chloro-1,4-dinitrobenzene
6.0.1 CAS Number: [*619-16-9*]

6.0.2 Synonyms: 1-Chloro-2,5-dinitrobenzene

6.0.3 Trade Names: NA

6.0.4 Molecular Weight: 202.55

6.0.5 Molecular Formula: $C_6H_3N_2O_4Cl$

6.0.6 Molecular Structure: NA

Databases or inventories where listed: TOXLINE.
6.1 Chemical and Physical Properties (2)

Physical state	Light yellow crystals
Melting point	64°C
Solubility	Soluble in ethanol, ether; insoluble in water

6.2 Production and Use
Uses are the same as other isomers such as 4-chloro-1,2-dinitrobenzene (2).
6.4 Toxic Effects
No specific information found.
6.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
7.0 3-Chloro-1,2-dinitrobenzene
7.0.1 CAS Number: [*602-02-8*]

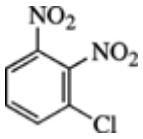
7.0.2 Synonyms: 1-Chloro-2,3-dinitrobenzene

7.0.3 Trade Names: NA

7.0.4 Molecular Weight: 202.55

7.0.5 Molecular Formula: $C_6H_3N_2O_4Cl$

7.0.6 Molecular Structure:



Databases or inventories where listed: None listed.
7.1 Chemical and Physical Properties (2)

Physical state	Crystals
Melting point	78°C
Boiling point	315°C
Refractive index	1.6867 (16.5°C)
Solubility	Soluble in ethanol, ether; insoluble in water

7.2 Production and Use
Uses are same as other isomers.
7.4 Toxic Effects
No specific information located.
7.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
8.0 4-Chloro-1,2-dinitrobenzene
8.0.1 CAS Number: [*610-40-2*]

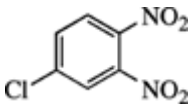
8.0.2 Synonyms: 1,2-Dinitro–4-chloro benzene; 3,4-dinitrochlorobenzene; 1-chloro-3,4-dinitrobenzene

8.0.3 Trade Names: NA

8.0.4 Molecular Weight: 202.55

8.0.5 Molecular Formula: $C_6H_3N_2O_4Cl$

8.0.6 Molecular Structure:



Databases or inventories where listed: EINECS, ETICBACK, TOXLINE, TSCAINV
8.1 Chemical and Physical Properties (2)

Physical state	Monoclinic prisms, needles
Melting point	a, 36°C; b, 37°C; g 40–41°C
Boiling point	16°C; 4 mmHg
Solubility	Soluble in ether, benzene, carbon disulfide, hot ethanol; insoluble in water

8.2 Production and Use
No specific uses found.
8.4 Toxic Effects
This compound is a sensitizer (2).
8.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
9.0 1-Chloro-2,4-dinitrobenzene
9.0.1 CAS Number: [*97-00-7*]

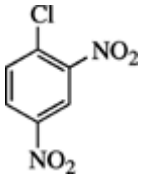
9.0.2 Synonyms: 2,4-Dinitro-1-chlorobenzene, 2,4-dinitrochlorobenzene, 1,3-dinitro-4-chlorobenzene, dinitrochlorobenzene, chlorodinitrobenzene, DNCB, 4-chloro-1,3-dinitrobenzene

9.0.3 Trade Names: NA

9.0.4 Molecular Weight: 202.55

9.0.5 Molecular Formula: $C_6H_3N_2O_4Cl$

9.0.6 Molecular Structure:



Databases or inventories where listed: AIDSDRUGS, AIDSLINE, AIDSTRIALS, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, HSDB, MA, MEDLINE, MESH, PA, RTECS, TOXLINE, TSCAINV, SUPERLIST.
9.1 Chemicals and Physical Properties (2)

Physical State	Yellow crystals
Melting point	a, 53°C; b, 43°C
Boiling point	315°C (762 mmHg)

Solubility Soluble in ether, benzene, hot ethanol; insoluble in water

9.2 Production and Use

DNCB is used in the manufacture of dyes and explosives, as a reagent, and as an algicide (2).

9.4 Toxic Effects

This compound is a potent sensitizer (2), and it has been used as such in many experiments. Examples include dose-response studies (97, 98), the effect of vehicle on absorption (99), and the effect of rat strain on sensitivity to DNCB (100). This compound depletes liver glutathione levels (2), and more recent data show that it irreversibly inhibits another enzyme involved with sulfur. Human thioredoxin, a dimeric enzyme that catalyzes reduction of the disulfide in oxidized thioredoxin, was inhibited and the effect persisted after removal of DNCB (101).

9.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

10.0 5-Chloro-1,3-dinitrobenzene

10.0.1 CAS Number: [*618-86-0*]

10.0.2 Synonyms: 1-Chloro-3,5-dinitrobenzene

10.0.3 Trade Names: NA

10.0.4 Molecular Weight: 202.55

10.0.5 Molecular Formula: $C_6H_3N_2O_4Cl$

10.0.6 Molecular Structure: NA

Databases or inventories where listed: None found.

10.1 Chemical and Physical Properties (2)

Physical state Colorless needles

Melting point 59°C

Solubility Soluble in ethanol, ether; insoluble in water

10.2 Production and Use

No specific uses were noted, but it reportedly could be used for the same purposes as 4-chloro-1,2-dinitrobenzene (2).

10.4 Toxic Effects

No new information was located.

10.5 Standards, Regulations, or Guidelines of Exposure

No standards assigned.

11.0 Pentachloronitrobenzene

11.0.1 CAS Number: [*82-68-8*]

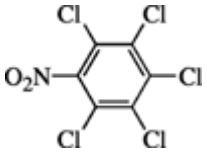
11.0.2 Synonyms: Avical; Eorthcicle; Fortox; Kobu; Marison Forte; Pkhnb; Terrafun; Tri PCNB; PCNB; Quintozine; quintobenzene; Terrachlor; Terraclor; Avicol; Botrilex; Earthcide; Kobutol; Pentagen; Tilcarex; SA Terraclor 2E; SA Terraclor; nitropentachlorobenzene; brassicol; quintocene; batrilex; fartox; fomac 2; fungiclor; gc 3944-3-4; KP 2; olpisan; quintozen; saniclor 30; tritisan

11.0.3 Trade Names: NA

11.0.4 Molecular Weight: 295.34

11.0.5 Molecular Formula: $C_6Cl_5NO_2$

11.0.6 Molecular Structure:



Databases or inventories where listed: CAA1, FIFR, IARC, MA, MI, NJ, NTPT, PA, RQ, TLV, TRI, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

11.1 Chemical and Physical Properties (2)

Physical state	Colorless solid
Specific gravity	1.718 at 25°C
Melting point	142–145°C technical grade
Boiling point	328°C at 760 mmHg
Solubility	Soluble in benzene, carbon disulfide, chloroform

11.2 Production and Uses

PCNB has been used as a fungicide for seeds, soil, and turf (2).

11.4 Toxic Effects

The previous edition provided a thorough account of the toxicity and metabolism of PCNB (2). It was not carcinogenic and did not act as a reproductive toxicant or a teratogen. It does lead to methemoglobinemia in cats. However, in a rat study, PCNB did not form an adduct with hemoglobin (14). probably due to steric hindrance from the chlorine substituents.

11.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA is 0.5 mg/m^3 with A4 notation.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

C. Dinitrobenzenes

12.0 1,2-Dinitrobenzene

12.0.1 CAS Number: [*528-29-0*]

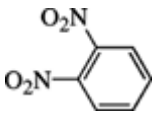
12.0.2 Synonyms: *o*-Dinitrobenzene; 1,2-dinitrobenzol

12.0.3 Trade Names: NA

12.0.4 Molecular Weight: 168.11

12.0.5 Molecular Formula: $C_6H_4N_2O_4$

12.0.6 Molecular Structure:



Databases or inventories where listed: CA65, DOT, MA, MTL, NJ, PA, PEL, RQ, TLV, TRI, WHMI, CANCERLIT, CCRIS, EINECS, EMIC, EMICBACK, HSDB, IRIS, MEDLINE, MESH,

RTECS, TOXLINE, SUPERLIST.
12.1 Chemical and Physical Properties (2)

Physical state	White to yellow, monoclinic plates
Density	1.565 (17/4°C)
Melting point	117–118.5°C
Boiling point	319°C (773 mm Hg)
Vapor density	5.79 (air = 1)
Flash point	302°F (closed cup)
Solubility	Soluble in ethanol, chloroform, benzene, methanol; slightly soluble in water

12.2 Production and Use
Dinitrobenzene is usually made as a mixture of three isomers that are used in producing dyestuffs, explosives, and other intermediates.
12.3 Exposure Assessment
NMAM IInd ed., vol 4, 1978 #S214.
12.4 Toxic Effects
1,2-DNB is the least toxic of the three isomers, but it is absorbed through the skin and can cause methemoglobinemia. It did not lead to testicular damage in rats at doses where 1,3-DNB had such an effect.
12.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA, NIOSH REL and OSHA PEL is 0.15 ppm (1 mg/m^3) with a skin notation.
13.0 1,3-Dinitrobenzene
13.0.1 CAS Number: [*99-65-0*]

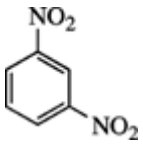
13.0.2 Synonyms: Dinitrobenzol; *m*-dinitrobenzene; 2,4-dinitrobenzene; binitrobenzene; 1,3-dinitrobenzol

13.0.3 Trade Names: NA

13.0.4 Molecular Weight: 168.11

13.0.5 Molecular Formula: $C_6H_4N_2O_4$

13.0.6 Molecular Structure:



Databases or inventories where listed: CA65, DOT, MA, MTL, NJ, PA, PEL, REL, RQ, S110, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE TSCAINV, SUPERLIST.
13.1 Chemical and Physical Properties (2)

Physical state	Colorless to yellow rhombic needles or plates
Density	1.571 (0/4°C)
Melting point	89–90°C
Boiling point	302.8°C (770 mmHg)

Flash point	302°F (closed cup)
Solubility	Soluble in ethanol, ether, benzene, toluene, chloroform, ethyl acetate; slightly soluble in water

13.2 Production and Uses

1,3-DNB is used in producing nitroaniline, 1,3-phenylenediamine, dye intermediates, and some explosives.

13.3 Exposure Assessment

NMAM IInd ed., vol. 4, 1978 method #S214.

13.4 Toxic Effects

The toxicity and metabolic reactions of 1,3-DNB were discussed in the previous edition (2). A major concern is testicular toxicity (56, 57) and reproductive effects. Additional studies showed that the toxicity of 1,3-DNB was greater in older rats, probably due to their slower rate of excretion (102). Route of administration, whether oral vs. i.p. had little effect on the degree of testicular damage in rats, although more was excreted in the feces after an oral dose (103). Examination of the metabolic capacity of different tissues from rats revealed that besides intestinal mucosa (104), rat brain also metabolized 1,3-DNB, presumably to toxic intermediates (105). The net result was that 1,3-DNB caused brain stem lesions in rats (106), which may explain the neurotoxicity noted in some previous studies (2).

13.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA, NIOSH REL and OSHA PEL is 0.15 ppm (1 mg/m^3), with a skin notation.

14.0 1,4-Dinitrobenzene

14.0.1 CAS Number: [*100-25-4*]

14.0.2 Synonyms: *p*-Dinitrobenzene

14.0.3 Trade Names: NA

14.0.4 Molecular Weight: 168.11

14.0.5 Molecular Formula: $C_6H_4N_2O_4$

14.0.6 Molecular Structure:

Databases or inventories where listed: CA65, DOT, MA, MTL, NJ, PA, PEL, RQ, TLV, TRI, WHMI, CCRIS, DSL, EINECS, EMIC, EMICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

14.1 Chemical and Physical Properties (2)

Physical state	Colorless to yellow monoclinic needles
Density	1.625 (20/4°C)
Melting point	173–174°C
Boiling point	298–299°C (777 mmHg) sublimes
Solubility	Soluble in chloroform, benzene, ethanol; somewhat soluble in water

14.2 Production and Use

Uses are identical with those of 1,2-dinitrobenzene (2).

14.3 Exposure Assessment

NMAM IInd ed., vol. 4, 1978 method #S214.

14.4 Toxic Effects

Although 1,4-DNB did not cause testicular toxicity in rats, it led to cyanosis, splenic enlargement,

and methemoglobinemia from prolonged exposure (2).

14.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA, NIOSH REL and OSHA PEL is 0.15 ppm (1 mg/m^3) with a skin notation.

15.0 Trinitrobenzene

15.0.1 CAS Number: [*99-35-4*]

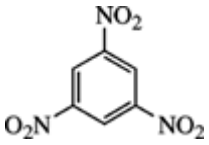
15.0.2 Synonyms: Benzite; 1,3,5-trinitrobenzene; *sym*-trinitrobenzene; trinitrobenzene, TNB

15.0.3 Trade Names: NA

15.0.4 Molecular Weight: 213.11

15.0.5 Molecular Formula: $C_6H_3N_3O_6$

15.0.6 Molecular Structure:



Databases or inventories where listed: DOT, MA, NJ, PA, RQ, S110, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

15.1 Chemical and Physical Properties (2)

Physical state	Orthorhombic bipyramidal plates
Melting point	121–122.5°C
Boiling point	315°C
Solubility	Soluble in acetone, benzene

15.2 Production and Use

Trinitrobenzene occurs as a by-product of trinitrotoluene (TNT) production and as a contaminant in water systems where it is formed by photolysis of TNT. It is not biodegraded readily and thus occurs in water, in TNT production waste disposal sites, and in soils at many military installations (107). It is not manufactured except for research purposes.

15.4 Toxic Effects

Since the previous edition, there has been appreciable interest in the toxicity of TNB. TNB was given to male and female rats at 0, 50, 200, 400, 800, or 1200 mg/kg diet for 14 days. Levels of 400 mg/kg and higher led to reduced food intake and lower body weights. Testicular weights were lower in males, and an increase in spleen weights was noted in both sexes. Susceptible organs were kidney (hyaline droplets), spleen (extramedullary hematopoiesis), brain (hemorrhage, malacia, and gliosis), and testes (seminiferous tubular degeneration). Red blood cell counts and hematocrit decreased while Heinz bodies and methemoglobin increased (107). Additional studies were done on the organ systems thus affected. TNB-treated male F344 rats had a dose-related accumulation of hyaline droplets with alpha-2-m-globulin in the proximal tubules of the kidney, but this did not occur in female F344 or male NBR rats (108). There was a steep dose-response curve for the effect on the brain (109). In a similar manner, the testicular effects were explored; 71 mg/kg for 10 days led to cessation of spermatogenesis, and half that dose for 10 days led to testicular lesions. The effects were partially reversible after a recovery period of 10 to 30 days (110, 111). However, although a reproductive toxicity screen with Sprague–Dawley rats given 30, 150, or 300 TNB mg/kg of diet for 14 days showed spleen depletion and degeneration of seminiferous tubules in males and methemoglobinemia and splenic hemosiderosis at higher doses in both sexes, no adverse effects were noted in mating or fertility indices, length of gestation, sex ratio, gestation index, or mean

number of pups per litter (112).

Absorption studies with human, rat, and hairless guinea pig skin showed that absorption through rat skin was very similar with either acetone or aqueous solutions of TNB. In human skin, absorption from water was much greater than from acetone, whereas the reverse held for guinea pig skin. The fluid in the receptor cell from human or rat skin contained 3,5-dinitroaniline and 1,3,5-triacetylaminobenzene. Guinea pig skin also metabolized TNB to 1-nitro-3,5-diacetamidobenzene and 3,5-diaminonitrobenzene to a minor extent (113). Thus, TNB was absorbed and metabolized to a similar extent by human and rodent skin. Liver microsomes from male F344 rats produced 3,5-diaminobenzene as a major metabolite of TNB (114).

15.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

D. Nitrophenols

16.0 2-Nitrophenol

16.0.1 CAS Number: [*88-75-5*]

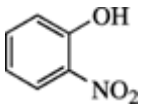
16.0.2 Synonyms: 2-Hydroxynitrobenzene; ONP

16.0.3 Trade Names: NA

16.0.4 Molecular Weight: 139.11

16.0.5 Molecular Formula: $C_6H_5NO_3$

16.0.6 Molecular Structure:



Databases and inventories where listed: CCRIS, EINECS, RTECS, TSCAINV, HSDB, CGB, MA, WHMI, NJ, TRI, RG, CGN, UN 1663, DOT, PA, EMIC, EMICBACK, GENETOX, MEDLINE, TOXLINE, SUPERLIST.

16.1 Chemical and Physical Properties (2)

Physical state	Light yellow crystals
Density	1.657 (20°C)
Melting point	44–46°C
Boiling point	214–216°C
Solubility	Soluble in ethanol, ether, acetone, benzene, alkali; somewhat soluble in water

16.2 Production and Use

2-Nitrophenol is an intermediate in dyestuff production and a chemical indicator.

16.4 Toxic Effects

No new information was found. *o*-Nitrophenol causes central and peripheral vagus stimulation, central nervous system (CNS) depression, methemoglobinemia, and dyspnea in animal experiments.

The oral LD_{50} in mice is 1.297 g/kg; in rats, 2.828 g/kg (2).

o-Nitrophenol was negative in the Ames mutagenicity test (115), and it was metabolically reduced less readily to the corresponding amino derivative than the *meta* or *para* isomers (116).

16.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

17.0 3-Nitrophenol

17.0.1 CAS Number: [*554-84-7*]

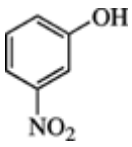
17.0.2 Synonyms: 3-Hydroxy-nitrobenzene; 3-hydroxy-1-nitrobenzene

17.0.3 Trade Names: NA

17.0.4 Molecular Weight: 139.11

17.0.5 Molecular Formula: $C_6H_5NO_3$

17.0.6 Molecular Structure:



Databases and inventories where listed: CCRIS, DART, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

17.1 Chemical and Physical Properties (2)

Physical state	Colorless to yellowish crystals
Density	1.485 (20°C)
Melting point	97°C
Boiling point	194°C (70 mmHg)
Solubility	Soluble in ether, benzene, alkali, ethanol, acetone; appreciably soluble in water

17.2 Production and Use

3-Nitrophenol is also used in synthesizing some dyestuffs and drugs and as an indicator, (117).

17.4 Toxic Effects

No new information found. In contrast to the ortho isomer, *m*-nitrophenol is more readily biotransformed to its corresponding amino derivative; however, it is reportedly nonmutagenic in the Ames bacterial mutagenicity test (2, 116).

17.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

18.0 4-Nitrophenol

18.0.1 CAS Number: [*100-02-7*]

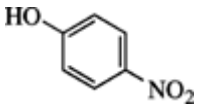
18.0.2 Synonyms: 4-Hydroxynitrobenzene; Niphen; PNP; mononitrophenol

18.0.3 Trade Names: NA

18.0.4 Molecular Weight: 139.11

18.0.5 Molecular Formula: $C_6H_5NO_3$

18.0.6 Molecular Structure:



Databases and inventories where listed: CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

18.1 Chemical and Physical Properties (2)

Physical state	Colorless to yellowish monoclinic prisms
Density	1.479 (20°C)
Melting point	113–116°C
Boiling point	279°C (sublimable)
Solubility	Soluble in ethanol, ether, benzene, acetone, alkali; somewhat soluble in water

18.2 Production and Use

4-Nitrophenol is used in dyestuff and pesticide synthesis, as a fungicide, bactericide, and wood preservative, as a chemical indicator, and as a substrate for experiments on cytochrome P450 2E1 (118).

18.4 Toxic Effects

p-Nitrophenol undergoes glutathione and glucuronide conjugation (119, 120). Isolation of a rat liver glucuronosyltransferase isozyme has also been reported; this enzyme is responsible for the glucuronide formation (121). In addition, *p*-nitrophenol can readily undergo reduction to its amino derivative. However, *in vivo* nitro reduction conditions require bacterial enzymes in the natural anaerobic environment of the gut (possibly in localized cellular ischemic conditions); *in vitro*, mammalian enzymes are required under artificial anaerobic conditions (116).

p-Nitrophenol is nonmutagenic in the Ames assay (2). The oral LD_{50} in mice is 467 mg/kg, and in rats, 616 mg/kg.

Since the last edition, there have been additional studies with 4-nitrophenol. Differences in sulfate conjugation by different species and organs were noted, using guinea pig, rat, and rabbit liver and platelets from rats, guinea pigs, rabbits, and dogs. Biphasic effects were observed in platelets and liver from rats and guinea pigs, similar to the result in humans (122). Abnormal physiological states such as bile duct ligation of rats increased 4-nitrophenol glucuronide formation at high doses; at low doses, ligation decreased conjugation (123). Hyperglycemia led to increased sulfate conjugation (124), but formation of a sulfate was practically nil in isolated rat intestinal loops (125). Cytochrome P450 2E1-mediated 4-nitrophenol hydroxylation was inhibited by benzene, toluene, and 2-bromophenol (126), whereas ethanol treatment of rats increased hydroxylation (127). When applied to porcine skin flaps, 4-nitrophenol did not evaporate significantly; there was greater penetration with acetone than with ethanol solutions (128). Data from a single chemical did not predict of absorption of binary mixtures of 4-nitrophenol and phenol (129). 4-Nitrophenol was tested by the NTP in a dermal study with mice; the results were negative for carcinogenicity (130).

18.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

E. Dinitrophenols

19.0 2,3-Dinitrophenol

19.0.1 CAS Number: [*66-56-8*]

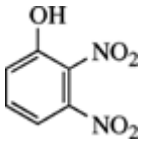
19.0.2 Synonyms: NA

19.0.3 Trade Names: NA

19.0.4 Molecular Weight: 184.11

19.0.5 Molecular Formula: $C_6H_4N_2O_5$

19.0.6 Molecular Structure:



Databases or inventories where mentioned: CANCERLIT, CCRIS, EINECS, MESH, RTECS, TOXLINE.

19.1 Chemical and Physical Properties (2)

Physical state	Yellow monoclinic prisms, flammable
Melting point	144–145°C
Solubility	Soluble in ether, benzene, ethanol; slightly soluble in water

19.2 Production and Use

Specific uses were not located.

19.4 Toxic Effects

No new information was found. Dermal exposure to 2,3-dinitrophenol causes yellow staining of skin and it may also cause dermatitis or allergic sensitivity. Systematically, it disrupts oxidative phosphorylation causing increased metabolism, oxygen consumption, and heat production. Chronic exposure may result in kidney and liver damage and cataract formation (2, 131).

19.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

20.0 2,4-Dinitrophenol

20.0.1 CAS Number: [*51-28-5*]

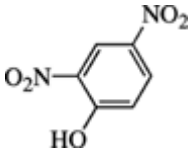
20.0.2 Synonyms: alpha-Dinitrophenol; aldifen; Fenoxyl Carbon N; 1-hydroxy-2,4-dinitrobenzene; 2,4-DNP; solfo black b; solfo black bb; tertrosulfur black pb; dinofan; maroxol-50; solfo black 2b supra; solfo black g; solfo black sb; tertrosulfur pbr; nitro kleenup; fenoxyl; dinitrophenols

20.0.3 Trade Names: NA

20.0.4 Molecular Weight: 184.11

20.0.5 Molecular Formula: $C_6H_4N_2O_5$

20.0.6 Molecular Structure:



Databases or inventories where mentioned: CAA, FIFR, MA, NJ, PA, RQ, S110, TRI, WHMI, AIDSLINE, CANCERLIT, CCRIS, DART, DSL, EINECS, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TRI, TSCAINV, SUPERLIST.

20.1 Chemical and Physical Properties (2)

Physical state	Pale yellow rhombic crystals or needles, flammable
Melting point	115–116°C
Solubility	Soluble in ethanol, ether, chloroform, benzene; somewhat soluble in water

20.2 Production and Use

Dinitrophenol is a dyestuff intermediate and is used as an insecticide, fungicide, bactericide, and wood preservative.

20.4 Toxic Effects

The action of 2,4-dinitrophenol in increasing metabolic rate was presented in the previous edition (2). Further work indicated that it could damage the myofilaments of the rat heart (132) and that various metabolic systems were activated in response (133, 134). High levels of environmental contamination could lead to adverse consequences in some wildlife.

20.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

21.0 2,5-Dinitrophenol

21.0.1 CAS Number: [*329-71-5*]

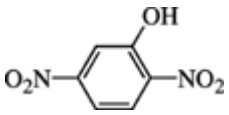
21.0.2 Synonyms: gamma-Dinitrophenol

21.0.3 Trade Names: NA

21.0.4 Molecular Weight: 184.11

21.0.5 Molecular Formula: $C_6H_4N_2O_5$

21.0.6 Molecular Structure:



Databases or inventories where mentioned: MA, NJ, PA, RQ, CCRIS, EINECS, EMICBACK, HSDB, MESH, RTECS, TOXLINE, SUPERLIST.

21.1 Chemical and Physical Properties (2)

Physical state	yellow needles, flammable
Melting point	108°C
Solubility	Soluble in ether, benzene, hot water and ethanol

21.2 Production and Use

Specific applications not located.

21.4 Toxic Effects

No specific studies located. Toxicity is assumed to be identical to that of 2,3-dinitrophenol (2, 131).

21.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
22.0 2,6-Dinitrophenol
22.0.1 CAS Number: [*573-56-8*]

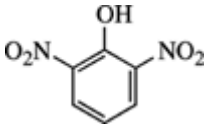
22.0.2 Synonyms: beta-Dinitrophenol

22.0.3 Trade Names: NA

22.0.4 Molecular Weight: 184.11

22.0.5 Molecular Formula: $C_6H_4N_2O_5$

22.0.6 Molecular Structure:



Databases or inventories where mentioned: MA, NJ, PA, RQ, CCRIS, EINECS, HSDB, MESH, RTECS, TOXLINE, SUPERLIST.
22.1 Chemical and Physical Properties (2)

Physical state	Pale yellow rhombic crystals, flammable
Melting point	63–64°C
Solubility	Soluble in benzene, acetone, hot water, ethanol, ether

22.2 Production and Use
No specific applications found.
22.4 Toxic Effects
No specific studies were located. Toxicity is assumed to be identical to that of 2,3-dinitrophenol (2, 131).
22.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
23.0 3,4-Dinitrophenol
23.0.1 CAS Number: [*577-71-9*]

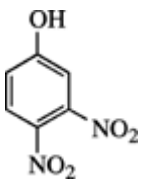
23.0.2 Synonyms: NA

23.0.3 Trade Names: NA

23.0.4 Molecular Weight: 184.11

23.0.5 Molecular Formula: $C_6H_4N_2O_5$

23.0.6 Molecular Structure:



Databases or inventories where mentioned: CCRIS, EINECS, RTECS, TOXLINE.
23.1 Chemical and Physical Properties (2)

Physical state	Colorless needles, flammable
Melting point	134°C
Solubility	Very soluble in ethanol, ether

23.2 Production and Use
Specific applications not located.
23.4 Toxic Effects
No new information located. No specific studies were located. Toxicity is assumed to be identical to that of 2,3-dinitrophenol (2, 131).
23.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
24.0 3,5-Dinitrophenol
24.0.1 CAS Number: [*586-11-8*]

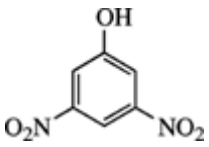
24.0.2 Synonyms: NA

24.0.3 Trade Names: NA

24.0.4 Molecular Weight: 184.11

24.0.5 Molecular Formula: $C_6H_4N_2O_5$

24.0.6 Molecular Structure:



Databases or inventories where mentioned: RTECS, TOXLINE.
24.1 Chemical and Physical Properties (2)

Physical state	Colorless monoclinic prisms, flammable
Melting point	134°C
Solubility	Soluble in ethanol, ether, chloroform, benzene

24.2 Production and Use
No specific uses located.
24.4 Toxic Effects
No new information located. No specific studies were located. Toxicity is assumed to be identical to that of 2,3-dinitrophenol (2, 131).
24.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
25.0 Picric Acid
25.0.1 CAS Number: [*88-89-1*]

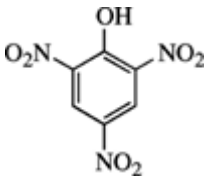
25.0.2 Synonyms: Picronitric acid; Melinite; pertite; carbazotic acid; 2,4,6-trinitrophenol; trinitrophenol; lyddite; shimose; phenol trinitrate; 2-hydroxy-1,3,5-trinitrobenzene; C. I. 10305; TNP

25.0.3 Trade Names: NA

25.0.4 Molecular Weight: 229.11

25.0.5 Molecular Formula: $C_6H_3N_3O_7$

25.0.6 Molecular Structure:



Databases or inventories where mentioned: DOT, IL, INER, MA, NJ, PA, PEL, REL, TLV, TRI, WHMI, AIDSLINE, CANCERLIT, CCRIS, DART, DSL, EINECS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

25.1 Chemical and Physical Properties (2)

Physical state	White to yellowish needles, flammable
Melting point	122–123°C
Boiling point	>300°C (sublimes, explodes)
Solubility	Soluble in ethanol, ether, benzene, acetone; slightly soluble in water

Cautionary note: Picric acid is very explosive when dry; for safety it is usually mixed with 10–20% water; it explodes when heated rapidly or subjected to percussion.

25.2 Production and Use

Picric acid is used in making explosives; as a burster in projectiles; in rocket fuels, fireworks, colored glass, batteries, and disinfectants; in the pharmaceutical and leather industries; as a fast dye for wool and silk; in metal etching and photographic chemicals; and as a laboratory reagent.

25.3 Exposure Assessment

NMAM IInd edition, vol 4, 1978 method #S228.

25.4 Toxic Effects

Picric acid causes sensitization dermatitis (135). Allergic hepatitis has been induced in guinea pigs by picric acid (136). Dust or fumes cause eye irritation, that can be aggravated by sensitization (137). It dyes animal fibers yellow (including skin) upon contact (2, 131).

Systemic absorption can cause weakness, myalgia, anuria, polyuria, headache, fever, hyperthermia, vertigo, nausea, vomiting, diarrhea, and coma. High doses may cause destruction of erythrocytes, hemorrhagic nephritis and hepatitis, yellow coloration of the skin ("pseudojaundice"), including conjunctiva and aqueous humor, and yellow vision (138, 139).

The strange visual effects where objects appear yellow may be related to the fact that systemic toxicity results in coloring all tissues yellow, including the conjunctiva and aqueous humor, so that yellow vision appearing under these circumstances is explained by optical effects (137). It is reportedly nonmutagenic in the Ames assay (115). Picric acid is metabolized largely to picramic acid.

A more definitive study of the metabolism of picric acid has appeared (140). In male F344 rats, the oral LD_{50} was 290 mg/kg; in females 200 mg/kg. After a single oral dose of ^{14}-C labeled compound, 56–60% appeared in the urine of the rats by 24 h, and 6–10% in feces. Gut contents accounted for

23% of the dose, and 3–6% remained in blood, muscle, and gut tissue. Up to 60% of the picric acid was excreted unchanged in the urine, and *N*-acetylisopicramic acid accounted for 15% of urinary activity, picramic acid 18.5%, and *N*-acetylpicramic acid for almost 5%, respectively. Thus, metabolic reactions consisted of reduction of the nitro to amino groups and conjugation with acetate.
25.5 Standards, Regulations, or Guidelines of Exposure
ACGIH TLV-TWA, 0.1 mg/m^3; OSHA PEL and NIOSH REL, 0.1 mg/m^3 (skin); Australia, 0.1 mg/m^3 (skin); Germany, 0.1 mg/m^3 (skin); United Kingdom, 0.1 mg/m^3.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

F. Dinitrocresols
26.0 4,6-Dinitro-**o**-cresol
26.0.1 CAS Number: [*534-52-1*]

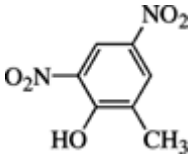
26.0.2 Synonyms: DNOC; DNC; 3,5-dinitro-2-hydroxytoluene; Nitrador; 2-methyl-4,6-dinitrophenol; dinitrocresol; antinonnin; Detal; Dinitrol; Elgetol; K III; K IV; Ditrosol; Prokarbol; Effusan; Lipan; Selinon; Dekrysil; 2,4-dinitro-*o*-cresol; 2,4-dinitro-6-methylphenol; antinonin; dinitrosol; Elgetox; 3,5-dinitro-6-hydroxy-toluene; 4,6-DNOC; Elgetol 30; methyl-4,6-dinitrophenol; Sinox; dinitro-*o*-cresol

26.0.3 Trade Names: NA

26.0.4 Molecular Weight: 198.13

26.0.5 Molecular Formula: $C_7H_6N_2O_5$

26.0.6 Molecular Structure:



Databases or inventories where listed: CAA1, DOT, FIFR, IL, MA, MI, MPOL, PA, PEL, REL, RQ, S110, S302, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.
26.1 Chemical and Physical Properties (2)

Physical state	Yellow prisms
Melting point	86.5°C
Solubility	Soluble in ether, acetone; slightly soluble in water

26.2 Production and Use
This compound and its isomers are used as herbicides, fungicides, and wood preservatives. Release into aquatic environments can be harmful to various organisms.
26.3 Exposure Assessment
NMAM, IInd edition, vol 5, 1979 Method #S166.
26.4 Toxic Effects

No new information was located.
26.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA, NIOSH REL and OSHA PEL is 0.2 mg/m^3 with a skin notation. A similar value holds for Australia, Germany, and the United Kingdom.
27.0 2,6-Dinitro-**p**-cresol
27.0.1 CAS Number: [*609-93-8*]

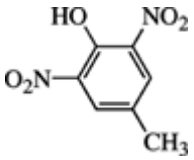
27.0.2 Synonyms: 2,6-DNPC; 4-methyl-2,6-dinitrophenol; 2,6-dinitro-*p*-cresol, moist solid containing up to 10% water

27.0.3 Trade Names: NA

27.0.4 Molecular Weight: 198.13

27.0.5 Molecular Formula: $C_7H_6N_2O_5$

27.0.6 Molecular Structure:



Databases or inventories where listed: DSL, EINECS, EMICBACK, HSDB, RTECS, TOXLINE, TSCAINV.
27.1 Chemical and Physical Properties (2)

Physical state	Long yellow prisms
Melting point	85°C
Solubility	Soluble in benzene, ethanol, ether; insoluble in water

27.2 Production and Use
Uses are the same as those of the isomer 4,6-dinitro-*o*-cresol.
27.4 Toxic Effects
No new information was located. The toxicity of 2,6-dinitro-*p*-cresol is reportedly identical to that of the ortho isomer (131). Peripheral neuropathy (dying back) has been reported following exposure (2) but was not definitive.
27.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
28.0 2-Nitroanisole
28.0.1 CAS Number: [*91-23-6*]

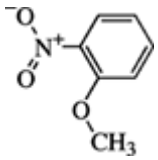
28.0.2 Synonyms: 2-Methoxynitrobenzene, *o*-nitrophenyl methyl ether, 1-methoxy-2-nitrobenzene

28.0.3 Trade Names: NA

28.0.4 Molecular Weight: 153.14

28.0.5 Molecular Formula: $C_7H_7NO_3$

28.0.6 Molecular Structure:



Databases and inventories where listed: CA65, IARC, NTPA, NTPT, WHMI, CANCERLIT, CCRIS, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

28.1 Chemical and Physical Properties (92)

Physical state	Colorless to yellowish liquid
Boiling point	277°C
Melting point	10.5°C
Density	1.254 (20°C/4°C)
Solubility	Soluble in ethanol, ether; moderately soluble in water

28.2 Production and Use

2-Nitroanisole is used as an intermediate in dyestuff and pharmaceutical production.

28.4 Toxic Effects

The oral LD_{50} is 740 mg/kg body weight in rats and 1300 mg/kg in mice. In 14-day studies in F344 rats (583–9330 ppm) and $B6C3F_1$ mice (250–4000 ppm), the male rats showed methemoglobinemia at levels of 1166 ppm or more. Body weights were lower and absolute liver weights higher in both male and female rats. Aside from lower body weights, mice had no treatment-related effects. In 13-week studies at 200, 600, 2000, 6000, or 18,000 mg/kg diet, various manifestations of toxicity were noted, and rats were more susceptible (92). Administration in the diet at levels of 0, 666, 2000, or 6000 mg/kg to male and female $B6C3F_1$ mice for 103 weeks led to significant increases in hepatocellular adenomas and carcinomas in both sexes, in addition to hepatic hemorrhages, Kupffer cell pigmentation, focal necrosis, and cytological alteration. Levels of 0, 222, 666, or 2000 mg/kg to F344 rats for 103 weeks caused increases in mononuclear cell leukemia in both sexes. When F344 rats were fed a 6000 or 18,000 mg/kg diet for 27 weeks and kept on a control diet for 77 weeks more, the incidences of carcinomas of the urinary bladder, adenomatous polyps of the large intestine, and transitional cell tumors of the kidney increased in both sexes (92).

Metabolism studies in rats with labeled 2-nitroanisole showed about 7% excreted in the feces and 70% in the urine after 7 days. Urinary metabolites identified were 2-nitrophenyl sulfate (63%), 2-nitrophenyl glucuronide (11%), 2-nitrophenol (1.5%), and *o*-anisidine (0.6%) (92).

28.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

Aromatic Nitro and Amino Compounds

Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

G. Nitrotoluenes

29.0 2-Nitrotoluene

29.0.1 CAS Number: [*88-72-2*]

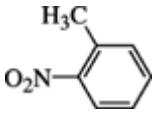
29.0.2 Synonyms: Methylnitrobenzene; 2-methyl-1-nitrobenzene; 1-methyl-2-nitrobenzene; 2-methylnitrobenzene; ONT; 2-nitrotoluol; *o*-nitrophenylmethane; alpha-methylnitrobenzene, *o*-nitrotoluene, 2NT

29.0.3 Trade Names: NA

29.0.4 Molecular Weight: 137.14

29.0.5 Molecular Formula: $C_7H_7NO_2$

29.0.6 Molecular Structure:



Databases and inventories where listed: CGN, DOT, IARC, MA, MPOL, MTL, NTPT, PA, PEL, REL, RQ, TLV, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

29.1 Chemical and Physical Properties (2)

Physical state	Yellow liquid
Density	1.163 (20/4°C)
Melting point	–9.5°C
Boiling point	221.7°C
Vapor pressure	1.6 mmHg (60°C)
Refractive index	1.54739 (20.4°C)
Solubility	Soluble in ethanol, ether, benzene, chloroform; slightly soluble in water

29.2 Production and Use

2-Nitrotoluene is used to produce dyestuff intermediates and in manufacturing agricultural and rubber chemicals.

29.3 Exposure Assessment

NMAM IV ed., Method #2005.

29.4 Toxic Effects

The single oral LD_{50} in male Sprague–Dawley rats is 891 mg/kg, in male Wistar rats 2100 mg/kg, in female Wistars 2100 mg/kg, and in male CF1 mice 2463 mg/kg. In a 13-week subchronic study, male and female F344 rats and male and female B6C3F_1 mice were given diets containing 0, 625, 1250, 2500, 5000 or 10,000 mg/kg (ppm) of 2-NT. Several male rats at the two highest dose levels had mesotheliomas of the tunica vaginalis on the epididymis, an unusual finding (141). Hyaline droplet nephrotoxicity also increased in the male rats; in this respect, 2-NT was the most toxic of the three isomers. In the mice there was degeneration and metaplasia of the olfactory epithelium but no hepatic toxicity. In a 14-day study, 2-NT was given to F344 rats at levels from 625 to 20,000 mg/kg in the diet. Livers of 4/5 male rats at 10,000 ppm showed minimal oval-cell hyperplasia (92). Male and female B6C3F_1 mice in the 14-day study received 2-NT at doses of 388 to 10,000 mg/kg; this led to an increase in relative liver weights of the males on the highest dose. Rats given labeled 2-NT excreted 86% in the urine and nine metabolites were identified. A low percentage was 2-aminobenzoic acid; all other metabolites were nitrobenzyl derivatives conjugated with glutathione, cysteine, sulfate, and glucuronic acid (92). The NTP has done a chronic study of 2-NT in rats and mice, but the report is not yet available.

29.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA and NIOSH REL is 2 ppm (11 mg/m^3) with a skin notation. The OSHA PEL is 5 ppm.

30.0 3-Nitrotoluene

30.0.1 CAS Number: [*99-08-1*]

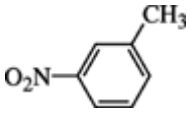
30.0.2 Synonyms: *m*-Nitrotoluol, 1-methyl-3-nitrobenzene; 3-methylnitrobenzene, *m*-nitrophenylmethane, 3-NT

30.0.3 Trade Names: NA

30.0.4 Molecular Weight: 137.14

30.0.5 Molecular Formula: $C_7H_7NO_2$

30.0.6 Molecular Structure:



Databases and inventories where listed. DOT, IARC, MA, MPOL, MTL, NTPT, PA, PEL, REL, RQ, TLV, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

30.1 Chemical and Physical Properties (2)

Physical state	Pale yellow liquid
Density	1.157 (20/4°C)
Melting point	15.5°C
Boiling point	232.6°C
Vapor pressure	1.0 mmHg (60°C)
Refractive index	1.5475 (20°C)
Solubility	Soluble in ethanol, ether, benzene; slightly soluble in water

30.2 Production and Use

3-NT is also used in producing dyestuffs, rubber and agricultural chemicals, explosives, and as a chemical intermediate.

30.3 Exposure Assessment

NMAM IV ed., 1994 Method #2005.

30.4 Toxic Effects

The single dose oral LD_{50} in male Sprague–Dawley rats was 1072 mg/kg, in male Wistars 2200 mg/kg, in female Wistars 2000 mg/kg, and in male CF-1 mice 330 mg/kg (92).

3-NT was given in the diet to male and female F344 rats (625–20,000 mg/kg in the diet) and $B6C3F_1$ mice (388–10,000 mg/kg in the diet) for 14 days. At the 2500-mg level, weight gains of male rats were less than that of controls, and the relative liver weights of mice were increased at 2500 and 5000 ppm 3-NT. In a 13-week study, hyaline droplet nephropathy was noted in male rats. In mice on 3-NT for 13 weeks, no hepatic toxicity was noted, even though liver weight increased. 3-NT decreased testicular function in male rats at the higher dose levels and increased the length of the estrus cycle in females, but there was no adverse effect on reproduction. The exposed mice showed no change in reproductive system evaluations, compared with controls (92, 141). 3-NT at 200–600 mg/kg to female B6C3F1 mice decreased the IgM response and response to *Listeria monocytogenes* but response to other bacteria was not affected (142).

After a dose of labeled 3-NT, male rats excreted 68% in the urine. Eight metabolites were separated; 3-aminobenzoic acid and its acetyl derivative were among them; the other metabolites were nitrobenzyl conjugates (92).

30.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA and NIOSH REL is 2 ppm with a skin notation (11 mg/m^3). The OSHA PEL is 5 ppm.

31.0 4-Nitrotoluene

31.0.1 CAS Number: [*99-99-0*]

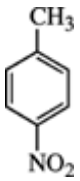
31.0.2 Synonyms: 4-Methylnitrobenzene; 1-methyl-4-nitrobenzene; 4-nitrotoluol; PNT; *p*-nitrophenylmethane, 4-NT

31.0.3 Trade Names: NA

31.0.4 Molecular Weight: 137.14

31.0.5 Molecular Formula: $C_7H_7NO_2$

31.0.6 Molecular Structure:



Databases and inventories where listed: CGN, DOT, IARC, MA, MPOL, MTL, NTPT, PA, PEL, REL, RQ, TLV, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, SUPERLIST.

31.1 Chemical and Physical Properties (2)

Physical state	Yellowish rhombic needles
Density	1.280 (20°C)
Melting point	54.5°C
Boiling point	238.3°C
Vapor density	4.72 (air = 1)
Vapor pressure	1.3 mmHg (65°C)
Refractive index	1.5346 (62.5°C)
Solubility	Soluble in ethanol, benzene, acetone, chloroform, ether; slightly soluble in water

31.2 Production and Use

4-NT is used as a dyestuff intermediate in producing rubber and agricultural chemicals and explosives, and as a chemical intermediate.

31.3 Exposure Assessment

NMAM IV ed., 1994 Method #2005.

31.4 Toxic Effects

The single-dose oral LD_{50} in male Sprague–Dawley rats was 2144 mg/kg, in male Wistar rats 4700 mg/kg, in female Wistars 3200 mg/kg, and in male CF-1 mice 1231 mg/kg (92).

In 14-day studies, male and female F344 rats had doses of 625–20,000 mg/kg in the diet, and $B6C3F_1$ mice had doses of 388–10,000 mg/kg. In male rats, doses over 5000 mg led to decreased body weight gain, but females were less susceptible. Although no treatment-related gross lesions were noted after 4-NT, in male rats liver weights were increased in a dose-related fashion. No hepatic toxicity was seen in mice (92).

A 13-week feeding study in F344 rats (625–10,000 ppm) and B6C3F$_1$ mice led to hyaline droplet nephropathy in male rats and mild enlargement of proximal tubule epithelium in both male and female rats, testicular degeneration in male rats at 10,000 ppm, no discernible estrus cycle in female rats at 10,000 ppm, increased liver weights in mice but no hepatic toxicity or effect on reproductive parameters (92, 141). Administration of 200–600 mg/kg daily for 14 days led to suppression of the IgM response and resistance to *Listeria monocytogenes* but not to other bacteria (143).

After a single dose of ^{14}C-labeled 4-NT to male rats, about 77% was excreted in the urine within 72 h and eight metabolites were separated; 4-nitrobenzoic acid and 4-acetamidobenzoic acid were the chief metabolites (92).

31.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA NIOSH REL is 2 ppm (11 mg/m^3) with a skin notation. The OSHA PEL is 5 ppm.

32.0 Dinitrotoluene Technical Grade

32.0.1 CAS Number: [*25321-14-6*]

32.0.2 Synonyms: DNT; dinitrotoluene (mixed isomers); methyl dinitrobenzene (mixed isomers); dinitrotoluene mixture; dinitrotoluene, all isomers; dinitritoluene (mixed isomers); methyldinitrobenzene; dinitrotoluene (2,4 and 2,6 mix); dinitrophenylmethane; TDNT; toluene, ar,ar-dinitro

32.0.3 Trade Names: NA

32.0.4 Molecular Weight: 182.14

32.0.5 Molecular Formula: $C_7H_6N_2O_4$

Commercial or technical grade dinitrotoluene is a mixture of about 76% of the 2,4- isomer, 19% of the 2,6- compound and 5% is made up of 2,3-, 2,5-, 3,4- and 3,5-dinitrotoluenes (2). The mixture is absorbed through the skin and can cause toxic effects.

32.3 Exposure Assessment

OSHA method #44 uses filter with linax GC tube and GC with thermal energy analyzer detection.

32.5 Standards, Regulations, or Guidelines of Exposure

OSHA PEL and NIOSH REL is 1.5 mg/m^3.

33.0 2,4-Dinitrotoluene

33.0.1 CAS Number: [*121-14-2*]

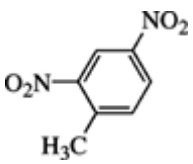
33.0.2 Synonyms: DNT; 2,4-DNT; dinitrotoluol; 1-methyl-2,4-dinitrobenzene; 2,4-dinitrotoluol

33.0.3 Trade Names: NA

33.0.4 Molecular Weight: 182.14

33.0.5 Molecular Formula: $C_7H_6N_2O_4$

33.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, IARC, MA, MTL, NJ, NTPT, PA, RQ, S110, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

33.1 Chemical and Physical Properties (2)

Physical state	Yellow or orange crystals
Boiling point	300°C
Melting point	71°C
Density	1.3208
Solubility	Soluble in ethanol, ether, acetone, benzene

33.2 Production and Use

2,4-Dinitrotoluene is used largely, along with the 2,6-isomer, to make toluene diisocyanate. The DNT mixture is hydrogenated to yield the diamine which is reacted with phosgene to form the diisocyanate which is reacted with polyols to make polyurethane foams (2). DNT is also employed to some extent in manufacturing explosives.

33.4 Toxic Effects

The toxicity of 2,4-DNT was discussed thoroughly in the previous edition (2) and by IARC (92). Although there are conflicting reports on carcinogenicity, depending on the animal model, 2,4-DNT is not a hepatocarcinogen. It can affect testicular function, but the toxicity is half that of the 2,6-isomer.

The various isomers of DNT are considerably less toxic to the mouse, with the possible exception of 2,3-dinitrotoluene, indicating widely differing capacities for metabolism. The oral LD_{50}s for 2,4-dinitrotoluene are 268 (rat) versus 1625 (mouse) (144). 2,4-DNT is reportedly a nonsensitizer (145).

2,4-DNT is rapidly absorbed via skin exposure, and repeated dermal applications to rabbits have produced cyanosis, lipemic plasma, depressed hemoglobin and red blood cells, liver hyperplasia and focal necrosis, bone marrow damage, congested spleen, distended bladder, and brain edema; testicular atrophy and aspermatogenesis were reported in beagles. Adverse neuromuscular effects, tremors, and brain lesions in dogs following oral administration have also been reported (145).

2,4-Dinitrotoluene is also rapidly absorbed after oral administration. Little reduction of dinitrotoluene occurs in isolated perfused liver preparation, in isolated hepatocytes, or in microsomal preparations incubated under air (146). The first step in metabolism in male or female Fischer 344 rats is oxidation at the methyl group to yield dinitrobenzyl alcohols, followed by conjugation with glucuronic acid, preparing the alcohol for bile excretion, which occurs to a much greater degree in male than in female rats (146). Intestinal microflora hydrolyze the glucuronides and reduce one of the nitro groups (to an amino group via nitroso intermediates) (147); the reduced metabolites, aminonitrobenzyl alcohols, are then reabsorbed, whereby, it is postulated, the 2,6 isomer is activated (146). All six dinitrotoluene isomers were metabolized to aminonitrotoluenes by an *Escherichia coli* isolated from human intestinal contents (148), as well as by the intestinal microflora of rats and mice (147). The human urinary metabolites of 2,4-dinitrotoluene in volunteers exposed to dinitrotoluene are 2,4-dinitrobenzoic acid, 2-amino-4-nitrobenzoic acid, 2,4-dinitrobenzyl glucuronide, and 2-(*N*-acetyl)amino-4-nitrobenzoic acid. The first three of these are found in rat urine; the last differs in the position of reduction and acetylation. The most abundant metabolites of dinitrotoluenes in human urine were the dinitrobenzoic acids; in rats the most abundant metabolites were dinitrobenzyl glucuronides. The appearance of a reduced metabolite of 2,4-dinitrotoluene indicates either that human hepatic enzymes are capable of nitro group reduction of dinitrotoluene or that 2,4-dinitrotoluene (or one of its metabolites) gains access to the intestinal microflora (146). The biliary excretion/nitro reduction pathway for bioactivation of 2,6-DNT may occur to a lesser extent in humans than in rats, making an important difference in risk assessment (149).

In a dominant lethal mutation study of 2,4-DNT (60, 180, or 240 mg/kg/day for 5 days, Sprague–Dawley male rats by gavage), lethal mutations were not detected, and no changes were observed in the number of preimplantation losses or implantation sites; however, reproductive performance was adversely affected at the 240 mg dose level (150).

Reproductive toxicity evaluation of 2,4-dinitrotoluene in adult male rats fed 0.1 or 0.2% DNT for 3 weeks demonstrated a marked change in Sertoli cell morphology following 0.2% DNT exposure. Circulating levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were increased in 0.2% DNT-treated animals. Raised serum levels of FSH reportedly are frequently, if not always, associated with Sertoli cell malfunction. Reduced weights of the epididymides and decreased epididymal sperm reserves were also observed. The authors concluded that DNT can induce testicular injury, directly or indirectly disturb pituitary function, and exert a toxic effect at the late stages of spermatogenesis. A direct effect on the hypothalamic-hypophyseal axis was not precluded, according to the authors, because testosterone concentrations remained within the normal range, whereas LH levels were elevated (151).

Exposure to 2,4-DNT reportedly decreased human sperm count and increased spontaneous abortions in the workers' wives (technical-grade dinitrotoluene is assumed) (145); however, in a follow-up epidemiological study, no effect on sperm levels was found in workers (152).

The initial carcinogenicity study in 1978 was conducted by NCI and involved a dietary feeding study of 2,4-DNT continuously for 18 months to male and female F344 rats and B6C3F$_1$ mice at 0.008 or 0.02% (and 0.008 or 0.04%, respectively), followed by a 6-month observation period. Because the incidence of hepatic neoplasms in treated animals and control animals was not significantly different, the NCI bioassay was considered negative for hepatocarcinogenesis in both rats and mice. In this study, 2,4-DNT was the primary component (95% 2,4-DNT, < 5% 2,6-DNT) (153). However, there was an increased incidence of fibroma of the skin and subcutaneous tissue in the high- and low-dose male rats and an increased incidence of mammary gland fibroadenoma in high-dose female rats (153, 154).

A second study evaluated 2,4-DNT (containing approximately 2% 2,6-DNT) in Sprague–Dawley (CD) rats and mice (CD-1) for 2 years (155). The high doses were toxic to both mice and rats, and the life span of mice was shortened by 50%. About half of the high-dose and approximately 25% of the control male rats died by the end of the 20th month. 2,4-DNT was hepatocarcinogenic, resulting in a 21% incidence of hepatocellular carcinomas in male rats of the high-dose (34 mg/kg/day) group dying or killed after 1 year of age. By comparison, high-dose female rats had a 53% incidence of hepatocellular carcinomas (155). The reason for the higher incidence of hepatocellular carcinoma in female rats compared with male rats, the inverse of that observed in a third study, is not clear; differences in strain of rat, the isomeric composition of the DNT, or other unspecified variances in protocols may be the basis for the differences in sex response between these two studies (154).

The results of further study demonstrated that 2,6-DNT is a complete hepatocarcinogen; in contrast, 2,4-DNT was not hepatocarcinogenic when fed at twice the high dose of 2,6-DNT during the same time period. The authors concluded that 2,4-DNT may act as a promoter but cannot initiate carcinogenesis. The hepatocarcinogenicity of technical-grade DNT is mainly due to 2,6-DNT (154, 155).

In an analytically controlled comparative bioassay 2,4-dinitrotoluene was not carcinogenic in male F344 rats (155); the lack of hepatocarcinogenicity of 2,4-DNT was consistent with the conclusion that 2,4-DNT is not a hepatocarcinogen. The difference between these studies could simply be due to strain differences, the greater amount of 2,6-DNT contaminating the 2,4-DNT used, the slightly higher dose of 2,4-DNT used (34 versus 27 mg), or the extended duration of feeding (2 years versus 1 year) (155). The positive response by 2,4-dinitrotoluene in the Ames assay is unclear (115).

IARC, NIOSH, OSHA, and ACGIH have not classified this isomer as a potential carcinogenic risk.

33.5 Standards, Regulations or Guidelines of Exposure

The ACGIH TLV-TWA is 0.2 mg/m^3 with a skin notation and an A3 rating. The actual listing is for the technical grade mixture, but it applies to the components.

34.0 2,6-Dinitrotoluene

34.0.1 CAS Number: [*606-20-2*]

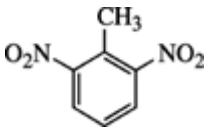
34.0.2 Synonyms: 2-Methyl-1,3-dinitrobenzene; 2,6-DNT; 1,3-dinitro 2-methylbenzene

34.0.3 Trade Name: NA

34.0.4 Molecular Weight: 182.14

34.0.5 Molecular Formula: $C_7H_6N_2O_4$

34.0.6 Molecular Structure:



Databases or inventories where listed: CA65, IARC, MA, NJ, PA, RQ, S110, TRI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

34.1 Chemical and Physical Properties (2)

Physical state	Yellow rhombic crystals
Melting point	64–66°C
Density	1.2833
Solubility	Soluble in ethanol

34.2 Production and Use

2,6-Dinitrotoluene is used primarily, along with the other isomers, in producing toluene diisocyanate; production of the diisocyanate ranges from 100 million to almost a billion pounds each year.

34.4 Toxic Effects

The toxicity and metabolic interactions of 2,6-dinitrotoluene have been reviewed in the previous edition (2) and by IARC (92). In F344 rats, the 2,6-isomer gave four distinct DNA adducts versus three for the 2,4-isomer, and with a much higher level of binding than 2,4-DNT (92, 156). In male B6C3F1 mice, only two such adducts were detected (157). A metabolite, 2-amino-6-nitrotoluene, gave the same adducts as 2,6-DNT, but at 30-fold lower levels (158). Intestinal microflora were important in activating 2,6-DNT to mutagenic metabolites (159), and the genotoxicity was increased by pretreating the rats with the enzyme inducers Aroclor 1254 or creosote (160, 161).

35.0 3,5-Dinitrotoluene

35.0.1 CAS Number: [*618-85-9*]

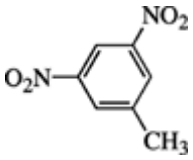
35.0.2 Synonyms: 1-Methyl-3,5-dinitrobenzene

35.0.3 Trade Name: NA

35.0.4 Molecular Weight: 182.14

35.0.5 Molecular Formula: $C_7H_6N_2O_4$

35.0.6 Molecular Structure:



Databases or inventories where listed: IARC, CANCERLIT, DART, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, SUPERLIST.

35.1 Chemical and Physical Properties (92)

Physical state	Yellow rhombic needles
Boiling point	Sublimes
Melting point	93°C
Density	1.2772 (11/4°C)
Solubility	Soluble in benzene, chloroform, ether, ethanol

35.2 Production and Use

3,5-Dinitrotoluene occurs in technical grade dinitrotoluene and has no specific uses by itself.

35.4 Toxic Effects

No specific studies of the toxicity of this isomer were located, although it may contribute to the effects of technical grade dinitrotoluene. The 3,5-isomer was mutagenic in the *Salmonella* test without metabolic activation and in some strains with the rat liver S9 fraction. It was not active in causing mutation in Chinese hamster ovary cells, and it did not induce unscheduled DNA synthesis in rat liver cells in culture (92).

For the remaining dinitrotoluenes, the only data found related to the databases in which they were listed.

36.0 2,3-Dinitrotoluene

36.0.1 CAS Number: [*602-01-7*]

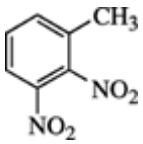
36.0.2 Synonyms: 1-Methyl-2,3-dinitrobenzene

36.0.3 Trade Names: NA

36.0.4 Molecular Weight: 182.14

36.0.5 Molecular Formula: $C_7H_6N_2O_4$

36.0.6 Molecular Structure:



Databases and inventories where listed: CCRIS, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TSCAINV.

37.0 2,5-Dinitrotoluene

37.0.1 CAS Number: [*619-15-8*]

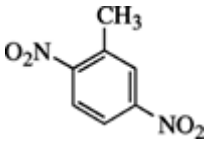
37.0.2 Synonyms: 2-Methyl-1,4-dinitrobenzene

37.0.3 Trade Names: NA

37.0.4 Molecular Weight: 182.14

37.0.5 Molecular Formula: $C_7H_6N_2O_4$

37.0.6 Molecular Structure:



Databases and inventories where listed: CCRIS, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, RTECS, TOXLINE, TSCAINV.

38.0 3,4-Dinitrotoluene

38.0.1 CAS Number: [*610-39-9*]

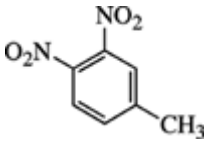
38.0.2 Synonyms: 4-Methyl-1,2-dinitrobenzene; 1,2-dinitro–4-methylbenzene

38.0.3 Trade Names: NA

38.0.4 Molecular Weight: 182.14

38.0.5 Molecular Formula: $C_7H_6N_2O_4$

38.0.6 Molecular Structure:



Databases and inventories where listed: MA, PA, RQ, CANCERLIT, CCRIS, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TSGAINV, SUPERLIST.

39.0 2,4,6-Trinitrotoluene

39.0.1 CAS Number: [*118-96-7*]

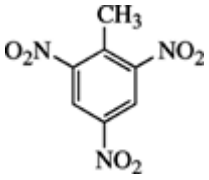
39.0.2 Synonyms: TNT; trinitrotoluol; *sym*-trinitrotoluene; trinitrotoluene; 2-methyl-1,3,5-trinitrobenzene; entsufon; 1-methyl-2,4,6-trinitrobenzene; methyltrinitrobenzene; tolite; trilit; *s*-trinitrotoluene; *s*-trinitrotoluol; trotyl; *sym*-trinitrotoluol; alpha-trinitrotoluol

39.0.3 Trade Names: NA

39.0.4 Molecular Weight: 227.13

39.0.5 Molecular Formula: $C_7H_5N_3O_6$

39.0.6 Molecular Structure:



Databases and inventories where listed: DOT, IARC, IL, MA, NJ, PA, PEL, REL, S110, TLV, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

39.1 Chemical and Physical Properties (2)

Physical state	Colorless to pale yellow crystals or monoclinic prisms
Specific gravity	1.654 (20°C)
Melting point	82°C
Boiling point	240°C (explodes)
Vapor pressure	0.046 mmHg (82°C)
Solubility	Soluble in ether, benzene, chloroform, carbon tetrachloride, toluene, acetone; slightly soluble in water

39.2 Production and Use

TNT has been used in explosives for almost 100 years. It must be exploded by a denonator, but it can be poured into shells when molten.

39.3 Exposure Assessment

OSHA Analytical method # 44 using linax GC tube and analysis by GC with thermal energy analyzer detection with explosives package.

39.4 Toxic Effects

The toxic effects of TNT in exposed workers are well known and include hepatitis, irritation of eyes, nose, throat and skin, methemoglobinemia, and cararacts, in addition to other symptoms (2). Workers exposed to TNT in a packing site, where levels of TNT exceeded 1 mg/m^3 had skin levels after each shift that were threefold those of unexposed workers. This correlated with total blood levels of TNT and the metabolites 4-amino-2,6-dinitrotoluene and 2-amino-4,6-dinitrotoluene (162). Furthermore, the levels of Cu, Zn, Na, Mg, and Se in the semen of these workers were significantly decreased, and sperm viability was less. Sperm malformations increased (162). A county in Germany contaminated with TNT residues from explosives manufacture had a higher risk for leukemia than neighboring counties (92). Thus, biodegradation of TNT residues from military or manufacturing sites is a matter of interest. One study found that reduction to nitroamines (2-amino-4,6-dinitrotoluene, 4-amino-2,6-dinitrotoluene 2,4-diamino-6-nitrotoluene), reduction to 2,4,6-triaminotoluene, and formation of azoxy compounds (2,2', 6,6'-tetranitro-4,4'azoxytoluene and 4,4', 6,6'-tetranitro-2,2'-azoxytoluene) occurred. In addition, *p*-cresol and methylphloroglucinol were identified, indicating removal of the nitrogens (163). Labeled TNT residues in compost from TNT-contaminated soil were not excreted readily in rats and accumulated in the kidneys, indicating that a unique TNT derivative had formed (164). A 6-month oral toxicity study in beagle dogs at levels of 0.5, 2, 8, or 32 mg/kg/day led to anemia, methemoglobinemia, splenomegaly, and effects on the liver, similar to those in exposed workers. Only the highest dose was lethal, despite the toxicity (165). Reportedly a 24-month chronic study in mice and rats led to tumors in female rats but not in mice or male rats (164). The toxicity, mutagenicity, and metabolism of TNT have been covered in a review by IARC (92).

39.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV is 0.1 mg/m^3 with a skin notation. The OSHA PEL is 1.5 mg/m^3 with a skin notation and the NIOSH REL is 0.5 mg/m^3 with a skin notation.

40.0 Tetryl

40.0.1 CAS Number: [*479-45-8*]

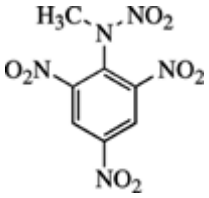
40.0.2 Synonyms: 2,4,6-Trinitrophenylmethylnitramine; *N*-methyl-*N*,2,4,6-tetranitroaniline; nitramine; tetralite; trinitrophenylmethylnitramine; 2,4,6-tetryl

40.0.3 Trade Names: NA

40.0.4 Molecular Weight: 287.15

40.0.5 Molecular Formula: $C_7H_5N_5O_8$

40.0.6 Molecular Structure:



Databases and inventories where listed: DOT, IL, MA, NJ, PA, PEL, REL, TLV, WHMI, CANCERLIT, CCRIS, EINECS, EMIC, EMICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

40.1 Chemical and Physical Properties (2)

Physical state	Yellow monoclinic crystals
Density	1.57 at 19°C
Melting point	130°C
Boiling point	187°C, explodes
Solubility	Soluble in ethanol, ether; insoluble in water

40.2 Production and Use

Tetryl is used in various types of explosive devices.

40.3 Exposure Assessment

NMAM IInd ed., vol 3, 1977 Method #S225.

40.4 Toxic Effects

Tetryl is a sensitizer and causes dermatitis (2). Practically no information on toxicity studies was located, but tetryl reportedly is under study by the U.S. EPA and military groups (115). Plant oxidoreductase enzymes under anaerobic conditions could remove the *N*-nitro group as nitrite, yielding *N*-methyl-trinitroaniline (166).

40.5 Standards, Regulations, or Guidelines of Exposure

The OSHA-PEL, NIOSH REL and ACGIH TLV-TWA are 1.5 mg/m^3 with a note that it causes dermatitis.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

H. Aniline and Derivatives

41.0 Aniline

41.0.1 CAS Number: [*62-53-3*]

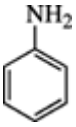
41.0.2 Synonyms: Benzamine; aniline oil; phenylamine; aminobenzene; aniline oil; phenylamine; aminophen; kyanol; benzidam; blue oil; C.I. 76000; C.I. oxidation base 1; cyanol; krystallin; anyvim; arylamine

41.0.3 Trade Names: NA

41.0.4 Molecular Weight: 93.13

41.0.5 Molecular Formula: C_6H_7N

41.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, CGB, DOT, IARC, IL, MA, MI, MTL, NJ, PA, PELS, REL, RQ, S302, TLV, TRI, WHMI, AIDSLINE, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

41.1 Chemical and Physical Properties (2)

Physical state	Oily liquid
Density	1.002 (20/4°C)
Melting point	–6.3°C
Boiling point	184.4–186°C
Vapor density	3.22 (air = 1)
Vapor pressure	15 mm Hg (77°C)
Refractive index	1.5863 (20°C)
Solubility	Soluble in ethanol, ether, benzene, chloroform, carbon tetrachloride, acetone; somewhat soluble in water

41.2 Production and Use

In 1992, more than 900 million pounds were produced, mostly by hydrogenation of nitrobenzene (167). Aniline is used in manufacture of dyestuffs, various intermediates, in rubber accelerators and in antioxidants, pharmaceuticals, photographic chemicals, plastics, isocyanates, hydroquinones, herbicides, fungicides, ion-exchange resins, whitening agents, and as an intermediate for various other chemicals.

41.3 Exposure Assessment

NMAM IVth ed., 1994 Method #2002.

41.4 Toxic Effects

The toxic effects of aniline have been discussed (2); in humans, they include headaches, methemoglobinemia, tremors, narcosis and coma. Although historically bladder cancers in dyestuff workers were called aniline cancers, recent epidemiological studies indicate that *o*-toluidine, a probable contaminant, was more likely the cause of the bladder tumors (168). Although high doses of aniline hydrochloride led to no excess tumors in B6C3F1 mice, levels of 3000 or 6000 ppm in the diet led to hemangiosarcomas or fibrosarcomas of the spleen in rats. Several publications have addressed the mechanism of this effect of aniline. Study of the hematopoietic toxicity of aniline in rats showed that blood methemoglobinemia peaked at 37% in 0.5 h and increased lipid peroxidation occurred in the spleen (169). Tests for up to 90 days with 600 ppm aniline hydrochloride showed that the spleens of test rats had striking histopathological changes and damage to erythrocyte iron was

increased (170). It was surmised that reaction of aniline or a metabolite with erythrocytes led to their accumulation, as well as iron deposition in the spleen (171); thus oxidative stress was responsible for the splenotoxicity of aniline (172). Exposure of rats to an atmosphere of 15,000 ppm aniline for 10 minutes, a situation simulating an industrial accident, also caused an increase in lipid peroxidation in the mitochondrial portions of the cerebellum, brain stem, and brain cortex (173).

Treatment of rats with 10% ethanol in the drinking water for 12 or 36 weeks stimulated the level of P450 and the degree of aniline hydroxylation (127). Human hemoglobin, as well as P450, cause aniline to be metabolized to the 2- and 4-aminophenols (174), but *in vitro*, exclusive 4-hydroxylation of aniline occurred in the presence of singlet oxygen (175). Aniline is readily absorbed through the skin. Thus the various occupational and industrial hygiene "skin" notations are necessary.

41.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA is 2 ppm (7.6 mg/m^3) with A3 and skin notations. The OSHA PEL is 5 ppm. NIOSH considers it a carcinogen.

42.0 **N**-Methylaniline

42.0.1 CAS Number: [*100-61-8*]

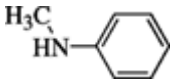
42.0.2 Synonyms: MA, *N*-methylbenzeneamine, monomethylaniline, *N*-methyl-phenylamine, *N*-monomethylaniline, methyl aniline, methylphenylamine, anilinomethane, (methylamino) benzene, *N*-methylaminobenzene, *N*-phenylmethylamine

42.0.3 Trade Names:

42.0.4 Molecular Weight: 107.15

42.0.5 Molecular Formula: C_7H_9N

42.0.6 Molecular Structure:



Databases and inventories where listed: DOT, IL, MA, PA, PEL, REL, TLV, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMICBACK, ETICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

42.1 Chemical and Physical Properties (2)

Physical state	Colorless to slightly yellow liquid; turns brown on exposure to air
Specific gravity	0.989 at 20°C
Melting point	–57°C
Boiling point	194.6–196°C
Flash point	79.4°C (closed cup)
Solubility	Soluble in ethanol, ether; slightly soluble in water

42.2 Production and Use

N-Methylaniline is used as a solvent and an intermediate.

42.3 Exposure Assessment

NMAM IVth ed., 1994, Method #3511.

42.4 Toxic Effects

No new information was located.

42.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA and NIOSH REL is 0.5 ppm with a skin notation. OSHA PEL is 2 ppm.

43.0 **N**,**N**-Dimethylaniline

43.0.1 CAS Number: [*121-69-7*]

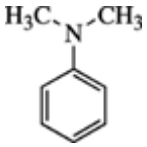
43.0.2 Synonyms: Dimethylaniline, Versneller NL 63/10, *N*,*N*-dimethylbenzenamine; (dimethylamino)benzene, dimethylphenylamine, *N*,*N*-dimethylphenylamine, dimethylphenylamine, DMA

43.0.3 Trade Names: NA

43.0.4 Molecular Weight: 121.18

43.0.5 Molecular Formula: $C_8H_{11}N$

43.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, DOT, IARC, IL, MA, MTL, NJ, NTPT, PA, PEL, REL, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TRI, TSCAINV, SUPERLIST.

43.1 Chemical and Physical Properties (2)

Physical state	Yellow liquid
Density	0.9557 (20/4°C)
Melting point	2.45°C
Boiling point	192.5°C
Vapor density	4.17 (air = 1)
Refractive index	1.55819 (20°C)
Solubility	Soluble in ethanol, ether; slightly soluble in water
Flash point	145°F (closed cup)
	170°C (open cup)

43.2 Production and Use

N,*N*-Dimethylaniline is used in production of dyestuffs, as a solvent, a reagent in methylation reactions, and a hardener in fiberglass reinforced resins.

43.3 Exposure Assessment

NMAM IVth ed., 1994 Method #2002.

43.4 Toxic Effects

The previous edition reported that *N*,*N*-dimethylaniline can undergo both *N*-oxidation and *N*-demethylation (2). Further studies showed that P4502B1 from rats converts this compound to the *N*-oxide or dealkylates it in the ratio of 6 parts *N*-oxide to 1020 parts of dealkylated product, probably by one-electron oxidation (176, 177). In another metabolic system (rabbit liver microsomes), superoxide and P4502B4 were considered the active entities (178); this was reviewed by IARC (179).

43.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA NIOSH REL is 5 ppm with a STEL of 10 ppm and skin and A4 notations. OSHA PEL is also 5 ppm with skin notation.

44.0 **N**-Ethylaniline

44.0.1 CAS Number: [*103-69-5*]

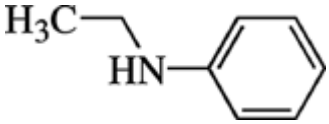
44.0.2 Synonyms: Ethylphenylamine; *N*-ethyl aniline; anilinoethane; *N*-ethylaminobenzene

44.0.3 Trade Names: NA

44.0.4 Molecular Weight: 121.18

44.0.5 Molecular Formula: $C_8H_{11}N$

44.0.6 Molecular Structure:



Databases and inventories where listed: DOT, MA, PA, WHMI, CCRIS, EINECS, EMICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

44.1 Chemical and Physical Properties (2)

Physical state	Colorless liquid, darkens in air
Boiling point	204.5°C
Melting point	–63.5°C
Solubility	Soluble in acetone, benzene; miscible with ethanol, ether; insoluble in water

44.2 Production and Use

N-Ethylaniline is used an an explosive stabilizer and in dyestuff manufacture.

44.4 Toxic Effect

No specific new information located.

44.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

45.0 **N**,**N**-Diethylaniline

45.0.1 CAS Number: [*91-66-7*]

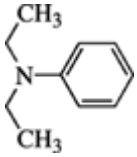
45.0.2 Synonyms: Diethyl aniline, *N*,*N*-diethylbenzenamine, *N*,*N*-diethylaminobenzene, diethylphenylamine,

45.0.3 Trade Name: NA

45.0.4 Molecular Weight: 149.24

45.0.5 Molecular Formula: $C_{10}H_{15}N$

45.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, DOT, MA, PA, WHMI, CCRIS, DSL, EINECS, EMIC, EMICBACK, HSDB, RTECS, TOXLINE, TSCAINV, SUPERLIST.

45.1 Chemical and Physical Properties (2)

Physical state	Colorless or yellow or brown oil (flammable)
Density	0.93507 (20/4°C)
Melting point	–38.8°C
Boiling point	215.5-216°C
Refractive index	1.54105 (22°C)
Solubility	Soluble in ethanol, ether; fairly soluble in water

45.2 Production and Use

Diethylaniline is used as an intermediate in synthesizing of dyestuffs and pharmaceuticals.

45.4 Toxic Effects

During oxidative metabolism, as with *N*,*N*-dimethylaniline, a much greater proportion of the diethylaniline was dealkylated, rather than forming an *N*-oxide (176).

45.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

I. Chlorinated Anilines

46.0 2-Chloroaniline

46.0.1 CAS Number: [*95-51-2*]

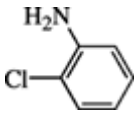
46.0.2 Synonyms: 2-Chlorobenzenamine; 1-amino-2-chlorobenzene; fast yellow gc base; OCA

46.0.3 Trade Name: NA

46.0.4 Molecular Weight: 127.57

46.0.5 Molecular Formula: C_6H_6ClN

46.0.6 Molecular Structure:



Databases and inventories where listed: CCRIS, DSL, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV.

46.1 Chemical and Physical Properties (2)

Physical state	Colorless liquid
Density	1.2125 (20/4°C)
Melting point	a, –14°C; b, –1.9°C
Boiling point	208.8°C
Refractive index	1.5895 (20°C)
Solubility	Soluble in acetone, ether; miscible with ethanol; insoluble in water

46.2 Production and Use

It is reportedly used as an intermediate in dyestuffs (2).

46.4 Toxic Effects
The NTP has done short-term toxicity studies of 2-chloroaniline in rats and mice, but the reports were in peer review. 2-Chloroaniline was the most potent of the isomeric chloroanilines in F344 rats with regard to nephrotoxic and hepatoxic effects (2). In contrast, when the chloroanilines were acetylated, the toxicity was greatly decreased and 2-chloroacetanilide was the least toxic of the isomers (180). Possible metabolites were tested for nephrotoxicity, but they were less potent than the parent chloroaniline (181).
46.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
47.0 3-Chloroaniline
47.0.1 CAS Number: [*108-42-9*]

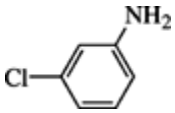
47.0.2 Synonyms: 3-Chlorobenzenamine, MCA, *m*-aminochlorobenzene, 1-amino-3-chlorobenzene, 3-chlorophenylamine, fast orange gc base, orange gc base

47.0.3 Trade Names: NA

47.0.4 Molecular Weight: 127.57

47.0.5 Molecular Formula: C_6H_6ClN

47.0.6 Molecular Structure:



Databases and inventories where listed: WHMI, CCRIS, DART, DSL, EINECS, EMICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.
47.1 Chemical and Physical Properties (2)

Physical state	Colorless liquid
Melting point	–10.3°C
Boiling point	229.8–230.5°C
Refractive index	1.59424 (20°C)
Solubility	Soluble in acetone, benzene, ether; miscible with ethanol; insoluble in water

47.2 Production and Use
Uses are reportedly the same as those of the other isomers.
47.4 Toxic Effects
Although 3-chloroaniline is readily absorbed through the skin and thus can cause the toxicity associated with aromatic amines, in F344 rats, it had the lowest nephrotoxicity of the isomeric chloroanilines. However, the situation was reversed for the acetyl derivatives, and 3-chloroacetanilide was the most toxic (180). The various 3-haloanilines (iodo, bromo, chloro, and fluoro) had different orders of nephrotoxic potential *in vivo* and *in vitro* for unknown reasons. They were not potent nephro- or hepatotoxicants at sublethal doses (182). Tests of possible phenolic metabolites of 3-chloroaniline did not show hepatotoxicity, but 4-amino-2-chlorophenol retained nephrotoxic activity at the highest dose level tested (183).
47.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
48.0 4-Chloroaniline
48.0.1 CAS Number: [*106-47-8*]

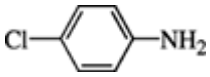
48.0.2 Synonyms: *p*-Chlorophenylamine; 4-chlorobenzenamine, 4-chloro-1-aminobenzene, 1-amino-4-chlorobenzene, *p*-aminochlorobenzene

48.0.3 Trade Names: NA

48.0.4 Molecular Weight: 127.57

48.0.5 Molecular Formula: C_6H_6ClN

48.0.6 Molecular Structure:



Databases and inventories where listed: CA65, IARC, MA, NJ, NTPT, PA, RQ, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

48.1 Chemical and Physical Properties (2)

Physical state	Colorless solid, rhombic crystals
Density	1.427 (19/4°C)
Melting point	72.5°C
Boiling point	231-232°C
Solubility	Soluble in ether; miscible with ethanol; insoluble in water

48.2 Production and Use

4-Chloroaniline is used as a dye intermediate.

48.4 Toxic Effects

The metabolism, excretion pattern, and carcinogenicity of 4-chloroaniline were discussed (2, 179). A patient who was acutely poisoned by 4-chloroaniline excreted conjugates of the parent compound and 2-amino-5-chlorophenol in the urine, indicating that ortho-hydroxylation had occurred, similar to results in other species (179). 4-Chloroaniline was somewhat less toxic to the liver and kidney of F344 rats than 2-chloroaniline, but upon acetylation, it had higher nephrotoxic potential (180). A study of possible phenolic metabolites showed that they had lower renal toxicity than the parent chloroanilines but still retained some toxicity (181, 184). P450 enzymes cause removal of the chlorine to yield 4-aminophenol (185, 186). Contrary to the situation with many halogen-substituted compounds, a fluoro substituent in the 4-position was removed more easily than other halogens (185).

48.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

49.0 2,3-Dichloroaniline

49.0.1 CAS Number: [*608-27-5*]

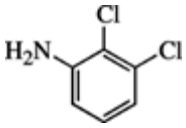
49.0.2 Synonyms: 2,3 Dichlorobenzenamine

49.0.3 Trade Names: NA

49.0.4 Molecular Weight: 162.02

49.0.5 Molecular Formula: $C_6H_5NCl_2$

49.0.6 Molecular Structure:



Data bases and inventories where listed: EINECS, HSDB, RTECS, TOXLINE, TSCAINV.

49.1 Chemical and Physical Properties (2)

Boiling point	252°C
Melting point	24°C
Solubility	Soluble in acetone, ethanol, ether

49.2 Production and Use

No specific uses were located.

49.4 Toxic Effects

2,3-Dichloroaniline was the least nephrotoxic of the dichloroaniline isomers (187).

49.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

50.0 2,4-Dichloroaniline

50.0.1 CAS Number: [*554-00-7*]

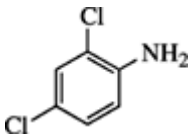
50.0.2 Synonyms: 2,4 -Dichlorobenzenamine, 2,4-dichloroaniline, pract.

50.0.3 Trade Names: NA

50.0.4 Molecular Weight: 162.02

50.0.5 Molecular Formula: $C_6H_5NCl_2$

50.0.6 Molecular Structure:



Data bases and inventories where listed: CCRIS, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TSCAINV.

50.1 Chemical and Physical Properties (2)

Boiling point	245°C
Melting point	63–64°C
Solubility	Soluble in ethanol, ether

50.2 Production and Use

Specific uses not located.

50.4 Toxic Effects

2,4-Dichloroaniline was one of the isomers considered to have low nephrotoxicity, compared with the 3,5-isomer (187). The relative order of toxicity was the same *in vitro* as *in vivo* (188).

50.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

51.0 2,5-Dichloroaniline

51.0.1 CAS Number: [*95-82-9*]

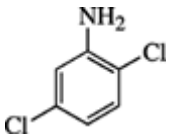
51.0.2 Synonyms: 2,5-Dichlorobenzenamine, amarthol fast scarlet gg base; azoene fast scarlet 2g base; C.I. 37010; C.I. azoic diazo component 3; fast scarlet 2g; scarlet base gg; 1-amino-2, 5-dichlorobenzene; 2-amino-1, 4-dichlorobenzene; 2,5-dichlorobenzamine

51.0.3 Trade Names: NA

51.0.4 Molecular Weight: 162.02

51.0.5 Molecular Formula: $C_6H_5NCl_2$

51.0.6 Molecular Structure:



Databases and inventories where listed: CCRIS, EINECS, EMIC, EMICBACK, HSDB, RTECS, TOXLINE, TSCAINV.

51.1 Chemical and Physical Properties (2)

Boiling point	251°C
Melting point	50°C
Solubility	Soluble in ethanol, ether, benzene

51.2 Production and Use

No specific uses were located.

51.4 Toxic Effects

The nephrotoxicity of 2,5-dichloroaniline in F344 rats was somewhat lower than that of the 3,5-isomer but greater than that of the other isomers (187). A possible metabolite, 2-amino-4-chlorophenol, had low nephrotoxic potential (183).

51.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

52.0 2,6-Dichloroaniline

52.0.1 CAS Number: [*608-31-1*]

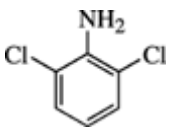
52.0.2 Synonyms: 2,6-Dichlorobenzenamine

52.0.3 Trade Name: NA

52.0.4 Molecular Weight: 162.02

52.0.5 Molecular Formula: $C_6H_5NCl_2$

52.0.6 Molecular Structure:



Databases and inventories where listed: EINECS, TOXLINE, TSCAINV.

52.1 Chemical and Physical Properties (2)

Melting point 39°C

Solubility Soluble in ether

52.2 Production and Uses

No specific uses located.

52.4 Toxic Effects

2,6-Dichloroaniline had moderately low nephrotoxic effects in F344 rats, compared with the 3,5-isomer (187).

52.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

53.0 3,4-Dichloroaniline

53.0.1 CAS Number: [*95-76-1*]

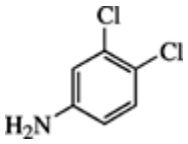
53.0.2 Synonyms: 1-Amino-3, 4-dichlorobenzene, 3,4-dichlorobenzenamine; 3,4-DCA; 4,5-dichloroaniline

53.0.3 Trade Names: NA

53.0.4 Molecular Weight: 162.02

53.0.5 Molecular Formula: $C_6H_5NCl_2$

53.0.6 Molecular Structure:



Databases and inventories where listed: MA, MTL, PA, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

53.1 Chemical and Physical Properties (2)

Melting point 71–72°C

Boiling point 272°C

Solubility Soluble in ethanol, benzene; almost insoluble in water

53.2 Production and Use

It has some use in herbicide production.

53.4 Toxic Effects

3,4-Dichloroaniline causes methemoglobinemia in mice and chloracne in humans (2). However, its nephrotoxic effect was relatively low, compared with that of the 3,5-isomer (187). A possible metabolite had some renal toxicity at a high dose (183).

53.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

54.0 3,5-Dichloroaniline

54.0.1 CAS Number: [*626-43-7*]

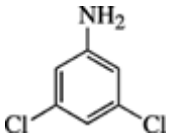
54.0.2 Synonyms: 3,5-Dichlorobenzenamine; *m*-dichloroaniline; BF 352-31

54.0.3 Trade Names: NA

54.0.4 Molecular Weight: 162.02

54.0.5 Molecular Formula: $C_6H_5NCl_2$

54.0.6 Molecular Structure:



Databases and inventories where listed: CCRIS, DART, EINECS, EMICBACK, HSDB, MEDLINE, MESH, TOXLINE, TSCAINV.

54.1 Chemical and Physical Properties (2)

Boiling point	260°C
Melting point	51–53°C
Solubility	Soluble in ethanol, benzene, ether

54.2 Production and Use

No specific uses were located apart from its use in research.

54.4 Toxic Effects

Of all of the dichloroanilines, the 3,5-isomer had the highest nephrotoxic action in F344 rats (187). Further studies examined this effect more throughly. When administered intraperitoneally in dimethyl sulfoxide solution, the rats died within 24 hrs; if given as a solution in saline or sesame oil, no renal toxicity was noted (189). Treatment of rats with various enzyme inducers and inhibitors and then 3,5-dichloroaniline did not cause much change in the renal or hepatic effects of the 3,5-isomer. These results indicated that the parent compound was directly toxic (190). A putative metabolite, 4-amino-2, 6-dichlorophenol, retained the nephrotoxic action of the parent (191). However, another possible metabolite, 3,5-dichlorophenylhydroxylamine, was the most potent inducer of hemoglobin oxidation, the parent 3,5-dichloroaniline was the least active, and 4-amino-2, 6-dichlorophenol was intermediate in activity (192).

54.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

J. Nitroanilines

55.0 2-Nitroaniline

55.0.1 CAS Number: [*88-74-4*]

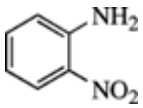
55.0.2 Synonyms: 1-Amino-2-nitrobenzene; 2-nitrobenzenamine; azoene fast orange gr base; azoene fast orange gr salt; azofix orange gr salt; azogene fast orange gr; azoic diazo component 6; brentamine fast orange gr base; brentamine fast orange gr salt; C.I. azoic diazo component 6; devol orange b; diazo fast orange gr; fast orange base gr; fast orange base jr; fast orange gr base; fast orange gr salt; fast orange o base; fast orange o salt; fast orange salt jr; hiltonil fast orange gr base; hiltosal fast orange gr salt; hindasol orange gr salt; natasol fast orange gr salt; *o*-nitraniline; C.I. 37025; orange base ciba ii; orange base irga ii; orange grs salt; orange salt ciba ii; orange salt irga ii

55.0.3 Trade Names: NA

55.0.4 Molecular Weight: 138.13

55.0.5 Molecular Formula: $C_6H_6N_2O_2$

55.0.6 Molecular Structure:



Databases and inventories where listed: DOT, WHMI, CCRIS, DSL, EINECS, EMIC, EMICBACK, HSDB, RTECS, TOXLINE, TSCAINV, SUPERLIST.

55.1 Chemical and Physical Properties (2)

Physical state	Golden yellow to orange rhombic needles
Density	1.442 (20/4°C)
Melting point	69–71.5°C
Boiling point	284.1°C
Solubility	Soluble in ethanol, ether, acetone, benzene; somewhat soluble in water

55.2 Production and Use

2-Nitroaniline is an intermediate for dyestuffs.

55.4 Toxic Effects

Although 2-nitroaniline was not mutagenic in four strains of *Salmonella* (TA97, TA98, TA100, TA102), with or without metabolic activation, it was clastogenic *in vitro* and induced chromosomal aberrations in Chinese hamster ovary cells (193).

55.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

56.0 3-Nitroaniline

56.0.1 CAS Number: [*99-09-2*]

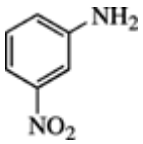
56.0.2 Synonyms: 1-Amino-3-nitrobenzene; 3-nitrobenzenamine; *m*-nitrophenylamine; *m*-nitroaminobenzene; amarthol fast orange r base; *m*-aminonitrobenzene; azobase mna; C.I. 37030; C.I. azoic diazo component 7; daito orange base r; devol orange r; diazo fast orange r; fast orange base r; fast orange m base; fast orange mm base; fast orange r base; hiltonil fast orange r base; naphtoelan orange r base; nitranilin; *m*-nitraniline; orange base irga 1

56.0.3 Trade Names: NA

56.0.4 Molecular Weight: 138.13

56.0.5 Molecular Formula: $C_6H_6N_2O_2$

56.0.6 Molecular Structure:



Databases and inventories where listed: DOT, MTL, WHMI, CCRIS, DSL, EINECS, EMIC, EMICBACK, GENETOX, HSDB, RTECS, TOXLINE, TSCAINV, SUPERLIST.

56.1 Chemical and Physical Properties (2)

Physical state	Yellow rhombic needles
Density	1.430 (20/4°C)
Melting point	114°C
Boiling point	305–307°C
Solubility	Soluble in ethanol, ether; slightly soluble in water

56.2 Production and Use

It is used as an intermediate in the production of dyestuffs.

56.4 Toxic Effects

As reported in the previous edition, 3-nitroaniline causes methemoglobinemia and associated effects; the vapor is toxic, and it is absorbed through the skin (2). A 28-day repeated dose toxicity study in F344 rats has been undertaken (194). Male and female F344 rats received oral doses of 15, 50, or 170 mg/kg/day; lower body weight gain, but no deaths, occurred. Testicular atrophy, reduction in spermatogenesis, hemolytic anemia, and increases in liver, spleen and kidney weight occurred, but ovarian function was not affected. After a 14-day recovery period, the conditions eased or disappeared. The NOEL was less than 15 mg/kg/day.

56.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

57.0 4-Nitroaniline

57.0.1 CAS Number: [*100-01-6*]

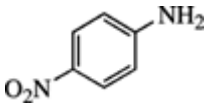
57.0.2 Synonyms: *p*-Aminonitrobenzene; 4-nitrobenzenamine; PNA; C.I. 37035; 1-amino-4-nitrobenzene; *p*-nitrophenylamine; azofix red gg salt; azoic diazo component 37; C.I. developer 17; developer P; devol red gg; diazo fast red gg; fast red base 2j; fast red base gg; fast red 2g base; fast red 2g salt; shinnippon fast red gg base; fast red salt 2j; fast red salt gg; nitrazol cf extra; red 2g base; fast red gg base; fast red mp base; fast red p base; fast red p salt; naphtoelan red gg base; azoamine red 2H; C.I. azoic diazo component 37

57.0.3 Trade Names: NA

57.0.4 Molecular Weight: 138.13

57.0.5 Molecular Formula: $C_6H_6N_2O_2$

57.0.6 Molecular Structure:



Databases and inventories where listed: DOT, IL, MA, MTL, NJ, NTPT, PA, PEL, REL, RQ, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, MESH, MEDLINE, RTECS, TOXLINE, TSCAINV, SUPERLIST.

57.1 Chemical and Physical Properties (2)

Physical state	Pale yellow crystals
Specific gravity	1.442
Melting point	146–149°C
Boiling point	331.7°C
Vapor pressure	<1 torr at 20°C
Flash point	198.9°C (closed cup)

57.2 Production and Use
4-Nitroaniline is used in synthesizing dyes, as a corrosion inhibitor, and in synthesizing of antioxidants.
57.3 Exposure Assessment
NMAM IVth ed., 1994, method #5033 NIOSH for determining human exposure.
57.4 Toxic Effects
4-Nitroaniline was tested in a 2-yr study in B6C3F$_1$ mice using doses of 3, 30, or 100 mg/kg/day in corn oil by gavage. At the two higher dose levels, there was some increase in hepatic hemangiomasarcoma in the male mice, leading NTP to conclude that there was equivocal evidence for carcinogenicity. Female mice showed no increase in tumors (195). In the *Salmonella* test, 4-nitroaniline was positive at high levels in TA98 and TA98NR; it was inactive in TA100 and TA100NR (196). In a series of anilines and phenylenediamines, the nitro group had no specific effect on toxicity (196).
57.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA is 3 mg/m^3 with skin and A4 notations. NIOSH REL is 3 mg/m^3 with skin notation and OSHA PEL is 6 mg/m^3 with skin notation.
58.0 2,6-Dichloro-4-nitroaniline
58.0.1 CAS Number: [*99-30-9*]

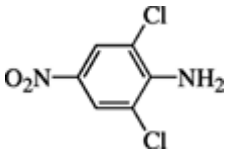
58.0.2 Synonyms: Dicloran; DCNA; Botran 75W; Dichloran; Dicloron; Allisan; ditranil; Kiwi Lustr 277; Resisan; rd-6584; AL-50; U-2069; bortran; CDNA; CNA; Resissan; Botran

58.0.3 Trade Names: NA

58.0.4 Molecular Weight: 207.02

58.0.5 Molecular Formula: $C_6H_4Cl_2N_2O_2$

58.0.6 Molecular Structure:



Databases and inventories where listed: FIFR, NJ, TRI, WHMI, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TSCAINV, SUPERLIST.
58.1 Chemical and Physical Properties (2)

Melting point	191°C
Boiling point	275°C
Solubility	Soluble in ethanol, ether, benzene

58.2 Production and Use
Dichloran is used as an agricultural fungicide.
58.4 Toxic Effects
No new information located.
58.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
59.0 4-Chloro-2-nitroaniline
59.0.1 CAS Number: [*89-63-4*]

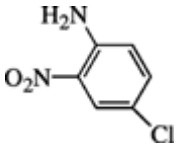
59.0.2 Synonyms: 4-Chloro-2-nitrobenzenamine; azoene fast red 3 gl base; azoene fast red 3 gl salt; azofix red 3 gl salt; azoic diazo component 9; C.I. 37040; C.I. azoic diazo; component 9; daito red base 3 gl; daito red salt 3 gl; devol red f; diazo fast red 3 gl; fast red base 3 gl special; fast red base 3 jl; fast red 3 gl base; fast red ZNC base; fast red 3 gl salt; fast red 3 gl special base; fast red 3 gl special salt; fast red ZNC salt; fast red salt 3 jl; hiltonil fast red 3 gl base; hiltosal fast red 3 gl salt; kayaku fast red 3 gl base; kayaku red salt 3 gl; mitsui red 3 gl base; mitsui red 3 gl salt; naphthanil red 3g base; naphtoelan fast red 3 gl base; naphtoelan fast red 3 gl salt; 2-nitro-4-chloroaniline; PCON; Pcona; red 3 g base; red base ciba vi; red base 3 gl; red base irga vi; Red 3 g salt; red 3 gs salt; red salt ciba vi; red salt irga vi; red salt nbgl; sanyo fast red salt 3 gl; shinnippon fast red 3 gl base; symulon red 3 gl salt; C.I. Azoic Diazo Component No. 9

59.0.3 Trade Names: NA

59.0.4 Molecular Weight: 172.57

59.0.5 Molecular Formula: $C_6H_5ClN_2O_2$

59.0.6 Molecular Structure:



Databases and inventories where listed: CANCERLIT, CCRIS, DSL, EINECS, EMIC, EMICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV.

59.1 Chemical and Physical Properties (2)

Physical state	Dark orange crystals
Melting point	116–117°C
Solubility	Soluble in ethanol, ether

59.2 Production and Use

4-Chloro-2-nitroaniline is an intermediate for synthesizing other compounds.

59.4 Toxic Effects

The NTP apparently has done prechronic studies with this compound, but no toxicity technical report was prepared.

59.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

K. Phenylenediamines

60.0 1,2-Phenylenediamine

60.0.1 CAS Number: [*95-54-5*]

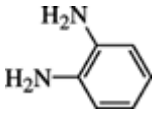
60.0.2 Synonyms: Orthamine; *o*-diaminobenzene; 1,2-diaminobenzene; *o*-phenylenediamine; 1,2-benzenediamine; 2-aminoaniline; C.I. 76010; C.I. oxidation base 16; *o*-phenylendiamine

60.0.3 Trade Names: NA

60.0.4 Molecular Weight: 108.14

60.0.5 Molecular Formula: $C_6H_8N_2$

60.0.6 Molecular Structure:



Databases and inventories where listed: DOT, MA, MTL, NJ, TLV, TRI, WHMI, CANCERLIT, CCRIS, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

60.1 Chemical and Physical Properties (2)

Physical state	Yellow crystals
Melting point	102–104°C
Boiling point	256–258°C
Solubility	Soluble in benzene, ethanol, ether, chloroform; slightly soluble in water

60.2 Production and Use

1,2-Phenylenediamine is used in to synthesize dyes and fungicides and as an oxidative hair and fur dye.

60.4 Toxic Effects

In a plant-based system, 1,2-phenylenediamine had the highest mutagenic activity of the three isomers (197). It is also the only phenylenediamine to show carcinogenic activity.

60.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA is 0.1 mg/m^3 with an A3 notation.

61.0 1,3-Phenylenediamine

61.0.1 CAS Number: [*108-45-2*]

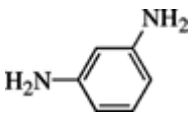
61.0.2 Synonyms: *m*-Diaminobenzene; *meta*-phenylenediamine; Developer C; Developer H; Developer M; Direct Brown GG: Direct Brown BR; 3-aminoaniline; m-benzenediamine; 1,3-benzenediamine; C.I. Developer 11; C.I. 76025; 1,3-diaminobenzene; benzenediamine-1,3; developer 11; apco 2330; MPD

61.0.3 Trade Names: NA

61.0.4 Molecular Weight: 108.14

61.0.5 Molecular Formula: $C_6H_8N_2$

61.0.6 Molecular Structure:



Databases and inventories where listed: DOT, IARC, MA, MTL, NJ, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

61.1 Chemical and Physical Properties (2)

Physical state	White rhombic crystals, turn red with air exposure
Density	1.1389 (5°C); 1.107 (58°C)
Melting point	63–64°C
Boiling point	282–284°C
Refractive index	1.63390 (57.7°C)
Solubility	Soluble in water, methanol, acetone, chloroform, dimethylformamide, dioxane, methyl ethyl ketone: slightly soluble in ether, carbon tetrachloride; less soluble in benzene, toluene, xylene

61.2 Production and Use

1,3-Phenylenediamine is used in to synthesize various dyes, as a curing agent for rubber and epoxy resins, as a corrosion inhibitor and as a photographic chemical, petroleum additive, and reagent.

61.4 Toxic Effects

Although 1,3-phenylenediamine is a sensitizer, it was not a teratogen or carcinogen in animal tests. It was less mutagenic than the 1,2-isomer in a plant system (197).

61.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA is 0.1 mg/m^3 with an A4 notation.

62.0 1,4-Phenylenediamine

62.0.1 CAS Number: [*106-50-3*]

62.0.2 Synonyms: *p*-Diaminobenzene; Pelagol D; Renal PF; Futramine D; Fur Black 41866; C.I. Developer 12; Developer PF; PPD; Peltol D; BASF Ursol D; Tertral D; 4-aminoaniline; 1,4-diaminobenzene; phenylhydrazine; 1,4-benzenediamine; *para*-phenylenediamine; C.I. 76076; Orsin; *p*-aminoaniline; phenylenediamine base; Rodol D; Ursol D; *p*-benzenediamine; benzofur d; C.I. 76060; C.I. developer 13; C.I. oxidation base 10; developer 13; durafur black r; fouramine d; fourrine d; fourrine i; fur black r; fur brown 41866; furro d; fur yellow; Mako h; oxidation base 10; pelagol dr; pelagol grey d; santoflex ic

62.0.3 Trade Names: NA

62.0.4 Molecular Weight: 108.14

62.0.5 Molecular Formula: $C_6H_8N_2$

62.0.6 Molecular Structure:

Databases and inventories where listed: CAA1, DOT IARC, IL, MA, MTL, NJ, PA, PEL, REL, RQ, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

62.1 Chemical and Physical Properties (2)

Physical state White to slightly red monoclinic crystals

Melting point	139.7°C
Boiling point	267°C
Solubility	Soluble in ethanol, chloroform, ether, acetone, benzene; slightly soluble in water

62.2 Production and Use

PPDA is used to synthesize dyes and intermediates, in fur and hairdye formulations, and as a photographic developer.

62.3 Exposure assessment

Monitoring of employee exposure may be evaluated by using OSHA method #87.

62.4 Toxic Effects

As discussed previously (2), PPDA is a sensitizer and has toxic effects in humans, but it was not carcinogenic in rats and mice after dietary administration. It was reported that patients with an allergy to PPDA were more likely to be slow acetylators of aromatic amines; no rapid acetylators were in the sensitive group (198). As with other aromatic amines, acetylation is a detoxication mechanism.

An investigation of the mutagenicity of PPDA and derivatives found that mutagenicity and toxicity did not correlate with the oxidation potential (199). Another study of mutagenicity with numerous PPDA derivatives led to the conclusion that the mutagenicity of substituted PPDAs depends both on the substituent groups and their positions in the molecule (200, 201).

62.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA is 0.1 mg/m^3 with an A4 notation; dermatitis and sensitization are listed as critical effects for the TLV.

63.0 2-Nitro-1,4-phenylenediamine

63.0.1 CAS Number: [*5307-14-2*]

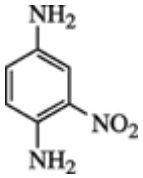
63.0.2 Synonyms: 1,4-Diamino-2-nitrobenzene; *o*-nitro-*p*-phenylenediamine; 4-amino-2-nitroaniline; nitro-*p*-phenylenediamine; 2-nitro-1,4-benzenediamine; 2-nitro-1,4-diaminobenzene; C.I. 76070; durafur brown; C.I. oxidation base 22; durafur brown 2R; Dye gs; fouramine 2R; fourrine 36; fourrine brown 2R; 2-NDB; oxidation base 22; ursol brown rr; zoba brown rr; 2-*n*-*p*-pda; 2-NPPD

63.0.3 Trade Names: NA

63.0.4 Molecular Weight: 153.14

63.0.5 Molecular Formula: $C_6H_7N_3O_2$

63.0.6 Molecular Structure:



Databases and inventories where listed: IARC, MA, NTPT, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

63.1 Chemical and Physical Properties (2, 187)

Physical state	Reddish-brown crystalline powder
Melting point	137–140°C

Solubility Soluble in acetone, ether; slightly soluble in water, ethanol, benzene

63.2 Production and Use

This compound is used in hair and fur dyes.

63.4 Toxic Effects

The oral LD_{50} in an oil/water suspension was 3080 mg/kg body weight in CD rats; the level for i.p. administration in dimethyl sulfoxide was 348 mg/kg body weight; in water, the level was 2100 mg/kg body weight in male Wistar rats. For mice, the i.p. LD_{50} was 214 mg/kg body weight (179).

After an i.p. dose of ^{14}C-labeled compound, 37% of the label was excreted in the urine and 154% in the feces within 24 h.; urinary metabolites identified were N^1, N^4-diacetyl-1,2,4-triaminobenzene (13% of urinary label) and N^4-acetyl-1,4-diamino-2-nitrobenzene (6% of urinary label) (179). This compound was a direct-acting mutagen in the *Salmonella* system (196).

63.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

64.0 4-Nitro-1,2-phenylenediamine

64.0.1 CAS Number: [*99-56-9*]

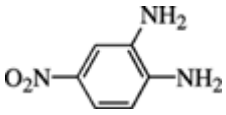
64.0.2 Synonyms: 1,2-Diamino-4-nitrobenzene; 4-nitro-1,2-benzenediamine; 2-amino-4-nitroaniline; 4-nitro-1,2-diaminobenzene; 4-nitro-*o*-phenylenediamine; 3,4-diaminonitrobenzene; 4-NO; 4-NOP; 4-NOPD; 4-*n*-*o*-pda; 4-NDB; C.I. 76020

64.0.3 Trade Name: NA

64.0.4 Molecular Weight: 153.14

64.0.5 Molecular Formula: $C_6H_7N_3O_2$

64.0.6 Molecular Structure:



Databases and inventories where listed: IARC, NTPT, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

64.1 Chemical and Physical Properties (2, 202)

Physical state Dark red needles

Melting point 199–200°C

Solubility Soluble in acetone; slightly soluble in water

64.2 Production and Use

4-Nitro-1,2-phenylenediamine is used in inks, fur and hair dyes, and as a reagent for determining keto acids and ascorbic acid in foods (202).

64.4 Toxic Effects

This compound was not carcinogenic when given in the diet to rats and mice for two years (2), but it was a direct-acting mutagen in *Salmonella* (196), and it induced chromatid breaks and chromosomal aberrations in certain cell lines (202).

64.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

65.0 4-Chloro-1,2-phenylenediamine
65.0.1 CAS Number: [*95-83-0*]

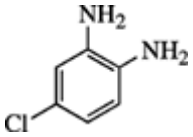
65.0.2 Synonyms: 4-Chloro-*ortho*-phenylenediamine; 4-chloro-1,2-benzenediamine; 1-chloro-3, 4-diaminobenzene; 2-amino-4-chloroaniline; 4-chloro-1,2-diaminobenzene; *p*-chloro-1,2-phenylenediamine; 1,2-diamino-4-chlorobenzene; 3,4-diaminochlorobenzene; 3,4-diamino-1-chlorobenzene; 4-cl-*o*-pd; ursol olive 6 g; C.I. 76015

65.0.3 Trade Names: NA

65.0.4 Molecular Weight: 142.59

65.0.5 Molecular Formula: $C_6H_7ClN_2$

65.0.6 Molecular Structure:



Databases and inventories where listed: CA65, IARC, IL, MA, MI, NTPA, NTPT, PA, CANCERLIT, CCRIS, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.
65.1 Chemical and Physical Properties (2, 209)

Physical state	Brown crystalline solid
Melting point	76°C
Solubility	Soluble in ethanol, ether, benzene, petroleum ether; slightly soluble in water

65.2 Production and Use
The compound has been used in dyes and inks and may have been used to produce a photographic chemical (2).
65.4 Toxic Effects
As discussed in the previous edition, this compound led to tumors in both rats and mice when given in the diet. It also was mutagenic. No new information was located.
65.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
66.0 4-Chloro-1,3-phenylenediamine
66.0.1 CAS Number: [*5131-60-2*]

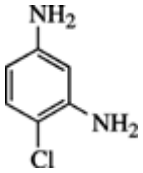
66.0.2 Synonyms: 4-Chloro-1,3-benzenediamine; 1-chloro-2,4-diaminobenzene; 4-chloro-1,3-diaminobenzene; 4-chlorophenyl-1,3-diamine; 4-chloro-*meta*-phenylenediamine; 4-chlorophenylene-1,3-diamine; C.I. 76027; 4-cl-*m*-pd; 4-chlorophenylenediamine

66.0.3 Trade Names:

66.0.4 Molecular Weight: 142.59

66.0.5 Molecular Formula: $C_6H_7ClN_2$

66.0.6 Molecular Structure:



Databases and inventories where listed: IARC, MA, MI, NTPT, CCRIS, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

66.1 Chemical and Physical Properties (2,209)

Physical state	Crystals
Melting point	91°C
Solubility	Soluble in ethanol; slightly soluble in water; insoluble in petroleum ether

66.2 Production and Use

This compound has uses in dye production and in rubber processing.

66.4 Toxic Effects

The effects of 4-chloro-1,3-phenylenediamine have been discussed (2, 203), and no new information was located.

66.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

67.0 2-Chloro-1,4-phenylenediamine

67.0.1 CAS Number: [*615-66-7*]

67.0.2 Synonyms: 2-Chloro-*p*-phenylenediamine; 2-chloro-1-4-benzenediamine

67.0.3 Trade Name: NA

67.0.4 Molecular Weight: 142.06

67.0.5 Molecular Formula: $C_6H_7N_2Cl$

67.0.6 Molecular Structure: NA

Databases and inventories where listed: WHMI, DART, EINECS, EMIC, EMICBACK, ETICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

67.1 Chemical and Physical Properties (2)

67.2 Production and Use

This compound had some uses in hair dye formulations.

67.4 Toxic Effects

The previous edition mentioned that this compound was not carcinogenic in rats or mice in two-year feeding studies. No new information was located.

67.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

68.0 2,6-Dichloro-1,4-phenylenediamine

68.0.1 CAS Number: [*609-20-1*]

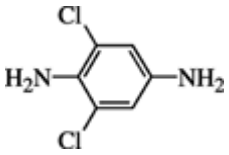
68.0.2 Synonyms: 1,4-Diamino-2,6-dichlorobenzene; 2,6-dichloro-1,4-benzenediamine; 2,5-diamino-1,3-dichlorobenzene; C.I. 37020; daito brown salt rr; fast brown rr salt; 2,6-dichloro-*para*-phenylenediamine

68.0.3 Trade Names: NA

68.0.4 Molecular Weight: 177.03

68.0.5 Molecular Formula: $C_6H_6Cl_2N_2$

68.0.6 Molecular Structure:



Databases and inventories where listed: IARC, NTPT, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

68.1 Chemical and Physical Properties (204)

Physical state	Gray, microcrystalline powder, needles or prisms
Melting point	124–126°C
Solubility	Soluble in acetone, benzene, ethanol, ether

68.2 Production and Use

The compound has been used as an intermediate for dyes, to some extent in preparing certain polyamide fibers, and as a curing agent for polyurethane (204).

68.4 Toxic Effects

No new information on toxicity was located. 2,6-Dichloro-1,4-phenylenediamine is a metabolite of the herbicide/fungicide 2,6-dichloro-4-nitroaniline in humans, monkeys, goats, dogs, mice, rats, and bacteria (204).

68.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

L. Aminophenols

69.0 2-Aminophenol

69.0.1 CAS Number: [*95-55-6*]

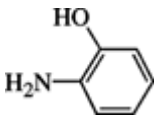
69.0.2 Synonyms: 2-Amino-1-hydroxybenzene; basf ursol 3 ga; benzofur gg; C.I. 76520; C.I. oxidation base 17; fouramine op; *o*-hydroxyaniline; nako yellow 3 ga; paradone olive green b; pelagol 3 ga; pelagol grey gg; zoba 3 ga; 2-aminobenzenol

69.0.3 Trade Name: NA

69.0.4 Molecular Weight: 109.13

69.0.5 Molecular Formula: C_6H_7NO

69.0.6 Molecular Structure:



Databases and inventories where listed: DOT, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

69.1 Chemical and Physical Properties (2)

Physical state	Colorless rhombic needles or plates
Melting point	170–174°C
Boiling point	Sublimes
Solubility	Soluble in ethanol, ether; somewhat soluble in water

69.2 Production and Use

2-Aminophenol is used as a dye intermediate, in fur and hair dyes, and in making cosmetics and drugs.

69.4 Toxic Effects

Compared with 4-aminophenol, 2-aminophenol induced only mild changes in renal function (181). A comprehensive review of the toxicology and biological properties, including absorption, distribution, metabolism, and excretion of the three isomeric aminophenols, has appeared (205).

69.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

70.0 3-Aminophenol

70.0.1 CAS Number: [*591-27-5*]

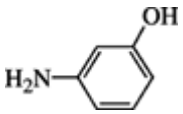
70.0.2 Synonyms: 3-Amino-1-hydroxybenzene; 3-hydroxyaniline; *m*-hydroxyaminobenzene; basf ursol bg; C.I. 76545; C.I. oxidation base 7; fouramine eg; fourrine 65; fourrine eg; furro eg; futramine eg; nako teg; pelagal eg; renal eg; tetral eg; ursol eg; zoba eg; *m*-hydroxyphenylamine

70.0.3 Trade Name: NA

70.0.4 Molecular Weight: 109.13

70.0.5 Molecular Formula: C_6H_7NO

70.0.6 Molecular Structure:



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70.1 Chemical and Physical Properties (2)

Physical state	Colorless prisms
Melting point	122–123°C
Solubility	Soluble in ethanol, ether, water

70.2 Production and Uses

3-Aminophenol is an intermediate in the production of photographic and pharmaceutical chemicals, and in synthesizing dyes. It is also a stabilizer of chlorine-containing thermoplastics (206).

70.4 Toxic Effects

The toxicity of 3-aminophenol has been reviewed (2, 205). It is the least toxic of the three isomers.

Intraperitoneal administration (100 to 200 mg/kg) of *m*-aminophenol to Syrian golden hamsters on day 8 of gestation produced inconsistent results. A teratogenic response was demonstrated, expressed as a percentage of the total number of litters with one or more live fetuses, at a dose of 150 mg/kg in only one (six malformed fetuses) of six litters, and teratogenicity was not evident at a dose of 200 mg/kg (207).

In a follow-up teratology study in which Sprague–Dawley rats were fed a diet of 0.1, 0.25, and 1.0% for 90 days prior to mating, maternal toxicity was demonstrated at the highest dose level, and a significant reduction in body weight was noted in the 0.25% group, but there was no evidence of teratogenic or embryo-fetal toxicity at any dose level tested. Accumulation of iron-positive pigment within the liver, kidneys, and spleen was observed in dams fed a 1% diet, together with significant reduction in red blood cell count and hemoglobin level, as well as an increase in mean corpuscular volume, indicating a hemolytic effect; histomorphologic appearance of the thyroid indicated hyperactive activity (at 0.25 and 1.0% diet) (208). In contrast to *o*- and *p*-aminophenol and their glucuronides, neither *m*-aminophenol nor its conjugate with glucuronic acid forms methemoglobin *in vitro* (2).

70.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

71.0 4-Aminophenol

71.0.1 CAS Number: [*123-30-8*]

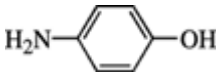
71.0.2 Synonyms: *p*-Hydroxyaniline; 4-amino-1-hydroxybenzene; Azol; Certinal; Citol; Paranol; Rodinal; Unal; Ursol P; paramidophenol; Kodelon; Energol; Freedol; Indianol; Kathol; basf ursol p base; benzofur p; C.I. oxidation base 6a; fouramine p; fourrine 84; PAP; Pelagol grey p base; tertral p base; ursol p base; zoba brown p base; C.I. 76550; durafur brown rb; fourrine p base; furro p base; nako brown r; pelagol p base; renal ac; 4-hydroxyaniline; 4-aminobenzenol

71.0.3 Trade Names: NA

71.0.4 Molecular Weight: 109.13

71.0.5 Molecular Formula: C_6H_7NO

71.0.6 Molecular Structure:



Databases and inventories where listed: DOT, MTL, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

71.1 Chemical and Physical Properties (2)

Physical state	Colorless prisms
Melting point	189.6–190.2°C

71.2 Production and Use

4-Aminophenol is used in preparing dyes and photographic chemicals; the *N*-acetyl derivative is a widely used analgesic.

71.4 Toxic Effects

4-Aminophenol is the most toxic of the three isomers (205, 206) and is the nephrotoxic metabolite of aniline and the medicinal agent acetaminophen (2). Examination of the mechanism of the effect of 4-aminophenol has yielded some conflicting views. Nephrotoxicity has been linked to the 4-

aminophenol 3-*S*-glutathionyl conjugate which was more toxic than the parent 4-aminophenol (209, 210).

These toxicants are formed endogenenously (211). 4-Aminophenol caused selective necrosis to the pars recta of the proximal tubules of the kidney (212), but ascorbic acid decreased the degree of oxidation of the aminophenol and the toxic effect (213). It was postulated that a 4-aminophenoxy free radical formed that was converted to a benzoquinoneimine which binds to cellular macromolecules. However, incubation of renal tubules with 4-aminophenol caused relatively little effect (214), which strengthened the concept that glutathione conjugates rather than autooxidation in the kidney are responsible.

71.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

72.0 2-Amino-5-nitrophenol

72.0.1 CAS Number: [*121-88-0*]

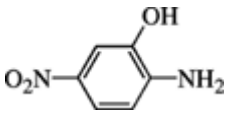
72.0.2 Synonyms: 2-Hydroxy-4-nitroaniline; 5-nitro-2-aminophenol; C.I. 76535; rodol yba; ursol yellow brown a

72.0.3 Trade Names: NA

72.0.4 Molecular Weight: 154.13

72.0.5 Molecular Formula: $C_6H_6N_2O_3$

72.0.6 Molecular Structure:



Databases and inventories where listed: IARC, NTPT, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

72.1 Chemical and Physical Properties

Physical state	Olive-brown to orange crystals
Melting point	207–208°C
Solubility	Soluble in acetone, benzene, ethanol; slightly soluble in water

72.2 Production and Use

2-Amino-5-nitrophenol is used in hair dyes and as an intermediate in preparing azo dyes (187).

72.4 Toxic Effects

The toxicity of 2-amino-5-nitrophenol is relatively low (LD_{50} over 4000 mg/kg orally) (179). The compound has been studied in a two-year test in rats and mice and was not active in mice. Some tumors were noted in male rats but were not convincing (179).

72.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

73.0 2-Amino-4-nitrophenol

73.0.1 CAS Number: [*99-57-0*]

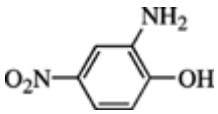
73.0.2 Synonyms: 3-Amino-4-hydroxynitrobenzene; 2-hydroxy-5-nitroaniline; p-nitro-o-aminophenol; C.I. 76530; ursol 4 gl

73.0.3 Trade Names: NA

73.0.4 Molecular Weight: 154.13

73.0.5 Molecular Formula: $C_6H_6N_2O_3$

73.0.6 Molecular Structure:



Databases and inventories where listed: IARC, NTPT, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, SUPERLIST, TOXLINE, TSCAINV.

73.1 Chemical and Physical Properties (179)

Physical state	Yellow-brown to orange prisms
Melting point	143–145°C
Solubility	Soluble in acetone, acetic acid, ethanol, ether; slightly soluble in water

73.2 Production and Use

2-Amino-4-nitrophenol is used in preparing some mordant dyes and in some hair dyes (179).

73.4 Toxicity

This compound was tested (by gavage) at doses up to 250 mg/kg body weight for two years in F344 rats and B6C3F$_1$ mice (179). The incidence of tumors in mice was not increased, but in male rats there was a low but still significant (p = .035) incidence of renal tubular-cell adenomas. Nephropathy was also observed in the male rats. The compound was mutagenic in bacteria, fungi, and cultured mammalian cells. It also led to sister chromatid exchange and chromosomal aberrations in mammalian cells (179).

73.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

M. Toluenediamines

There are six possible toluenediamines formed from nitration of toluene. The commercial mixture contains about 28% of the 2,4-isomer, 18% of the 2,6-isomer with lesser amounts of the others.

74.0 2,3-Toluenediamine

74.0.1 CAS Number: [*2687-25-4*]

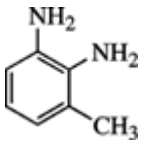
74.0.2 Synonyms: Toluene-2,3-diamine; 2,3-diaminotoluene; 3-methyl-1,2-benzenediamine

74.0.3 Trade Names: NA

74.0.4 Molecular Weight: 122.17

74.0.5 Molecular Formula: $C_7H_{10}N_2$

74.0.6 Molecular Structure:



Databases and inventories where listed: CANCERLIT, CCRIS, EINECS, EMICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV.

74.1 Chemical and Physical Properties (2)

Boiling point	255°C
Melting point	63–64°C
Solubility	Soluble in water, ethanol, ether

74.2 Production and Use

No specific applications were found except for research purposes.

74.4 Toxic Effects

In a series of toluenediamines, the 2,3-isomer was most active as an inducer of CYP 1A (215).

74.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

75.0 2,4-Toluenediamine

75.0.1 CAS Number: [*95-80-7*]

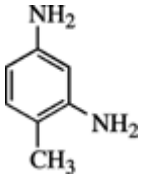
75.0.2 Synonyms: Toluene-2,4-diamine; toluenediamine; 2,4-diaminotoluene; 4-methyl-1,3-benzenediamine; 3-amino-*p*-toluidine; 5-amino-*o*-toluidine; tolylene-2,4-diamine; 1,3-diamino-4-methylbenzene; 2,4-diamino-1-methylbenzene; 2,4-diamino-1-toluene; 2,4-diaminotoluol; 4-methyl-*m*-phenylenediamine; C.I. 76035; C.I. oxidation base; C.I. oxidation base 20; C.I. oxidation base 35; C.I. oxidation base 200; developer 14; developer b; developer db; developer dbj; developer mc; developer mt; developer mt-cf; developer mtd; developer t; azogen developer h; benzofur mt; eucanine gb; fouramine; fouramine j; fourrine 94; fourrine m; MTD; nako tmt; pelagol j; pelagol grey j; pontamine developer tn; renal md; Tertral g; zoba gke; zogen developer h; 4-methylphenylene-1,3-diamine, TDA

75.0.3 Trade Names: NA

75.0.4 Molecular Weight: 122.17

75.0.5 Molecular Formula: $C_7H_{10}N_2$

75.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, CGB, CGN, DOT, IARC, IL, MA, MI, MTL, NJ, NTPA, NTPT, PA, REL, RQ, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

75.1 Chemical and Physical Properties (2)

Physical state	Colorless needles
Melting point	99°C
Boiling point	292°C
Solubility	Soluble in water, ethanol, ether

75.2 Production and Use

The major use of toluenediamine is in producing toluene diisocyanate (TDI), the most important diisocyanate in the flexible polyurethane foam and elastomers industry. The use in hair dye formulations has generally been discontinued, but it is used in some other dyes.

75.3 Exposure Assessment

NMAM IVth ed., 1994 Method #5516.

75.4 Toxic Effects

Overt exposure in humans may lead to methemoglobinemia, especially when red blood cell-reducing mechanisms are impaired, such as in G6PD deficiency which occurs in humans in the absence of glutathione reductase, glutathione, or glutathione peroxidase, eye irritation that may cause corneal damage, and delayed skin irritation.

Reproductive toxicity in the rat has been demonstrated. Reduced fertility, arrested spermatogenesis, and diminished circulating testosterone levels have resulted in rats fed 0.03% 2,4-toluenediamine; electron microscopy revealed degenerative changes in Sertoli cells and a decrease in epididymal sperm reserves; after 3 weeks of 0.06% TDA feeding, sperm counts were further reduced and accompanied by a dramatic increase in testes weight, intense fluid accumulation, and ultrastructural changes in the Sertoli cells (216). In previous studies, testicular atrophy, hormonal effects, and aspermatogenesis were also observed in Sprague–Dawley rats given a 0.1% diet for 9 weeks (217, 218). However, epidemiological studies of workers exposed to commercial mixtures of dinitrotoluene and/or toluenediamine at three chemical plants indicated that the fertility of men had not been reduced significantly and reported no observable effects on the fertility of workers (152, 219).

2,4-Toluenediamine (and 2,6-toluenediamine) is mutagenic in the Ames assay requiring metabolic activation in the presence of S-9; it gave weakly positive results in the micronucleus test; however, this weak effect was detectable only at very toxic doses, and therefore the biological relevance is questionable. Thus the micronucleus test did not discriminate correctly between the carcinogenic 2,4- and the noncarcinogenic 2,6-toluenediamine (220, 221).

When 2,4-toluenediamine was administered in the diet to male and female F344 rats (79 ppm or 170 ppm) or B6C3F_1 mice (100 ppm or 200 ppm), hepatocellular carcinomas were produced in female mice, hepatocellular carcinomas in male rats, and mammary adenomas or carcinomas in female rats, but no carcinomas in the male mice (222). Male Wistar rats also reportedly developed hepatocarcinomas following treatment with 2,4-toluenediamine (223). A skin painting study in Swiss-Webster mice was reportedly noncarcinogenic (224). However, mice are less sensitive than rats; this may be based upon differences in metabolism (225). Biliary tract cancer, although reported in industrial workers was not increased significantly (226).

The IARC working group considered that although there are no human data for evaluation, there are sufficient animal data to classify 2,4-toluenediamine as a Group 2B compound—an agent possibly carcinogenic to humans (227).

2,4-TDA decreased somewhat the immune response of female B6C3F_1 mice given 25–100 mg/kg for 14 days (228). Most of the toxicity studies have attempted to elucidate the differences in mechanism of action between 2,4-TDA and the inactive 2,6 counterpart. In a liver microsomal system, 2,4-TDA was mutagenic, induced CYP 1A, and bound to the Ah receptor, whereas the other isomers were much less active (215). *In vivo*, 2,4-TDA had twice the mutagenic activity of 2,6-TDA,

which showed values like the controls (229).

2,4-TDA formed adducts with poly-d-(G) or poly-d-(C-G) in an *in vitro* assay, indicating that binding of 2,4-TDA to DNA involved guanine (230). Similarly, 2,4-TDA induced 6500 more DNA adducts in rat liver than the noncarcinogen 2,6-TDA (231). Although both of these isomers led to hemoglobin binding in F344 rats, only 2,4-TDA caused DNA adducts (231, 232).

2,4-TDA is the main starting material for TDI which is used in polyurethane foam production. These foams have been crafted into covers for breast implants; thus there is considerable interest in the ultimate fate of TDI and the possible release of 2,4-TDA from the implant. On a comparative basis, rats given labeled 2,4-TDA, either orally or intravenously, excreted 60–70% in the urine, as mono- and diacetyl derivatives, 20–30% in the feces, and only about 2% was retained in the carcass. In contrast, rats that inhaled labeled TDI retained all of the radioactivity from the TDI (233). Rats implanted with a TDI-polyester polyurethane foam did not form DNA adducts in the T lymphocytes, whereas rats fed 2,4-TDA formed DNA adducts in liver or mammary glands (234). In patients who had received breast implants covered with polyurethane, there was a lag period of 20–30 days; after this 2,4-TDA and 2,6-TDA were detected in plasma at levels up to 4 ng/mL and 1.5 ng/mL, respectively, up to two years after the implant (235). This demonstrated that the arylamines can be released slowly from the polyurethane products.

75.5 Standards, Regulations, or Guidelines of Exposure

NIOSH consider 2,4-TDA a carcinogen with lowest feasible exposure.

76.0 2,5-Toluenediamine

76.0.1 CAS Number: [*95-70-5*]

76.0.2 Synonyms: 2,5-Diaminotoluene; 2-methyl-1,4-benzenediamine

76.0.3 Trade Names: NA

76.0.4 Molecular Weight: 122.17

76.0.5 Molecular Formula: $C_7H_{10}N_2$

76.0.6 Molecular Structure: NA

Databases and inventories where listed: IARC, WHMI, CANCERLIT, DART, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

76.1 Chemical and Physical Properties (2)

Physical state	Colorless plates
Boiling point	273–274°C
Melting point	64°C
Solubility	Soluble in water, ethanol, ether, hot benzene

76.2 Production and Use

2,5-Toluenediamine is used in hair and fur dyes.

76.4 Toxic Effects

The sulfate salt of 2,5-toluenediamine was not carcinogenic in rats and mice (2). Likewise, it did not bind to the Ah receptor, induce CYP 1A, or have appreciable mutagenic activity (215).

76.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

77.0 2,6-Toluenediamine

77.0.1 CAS Number: [*823-40-5*]

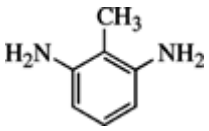
77.0.2 Synonyms: 2-Methyl-1,3-benzenediamine; 2,6-diaminotoluene; 1,3-diamino-2-methylbenzene; 2-methyl-*m*-phenylenediamine; 2,6-tolylenediamine; 2,6-diamino-1-methylbenzene; 2-methyl-1,3-phenylenediamine; 2,6-toluylenediamine; toluene-2,6-diamine

77.0.3 Trade Names: NA

77.0.4 Molecular Weight: 122.17

77.0.5 Molecular Formula: $C_7H_{10}N_2$

77.0.6 Molecular Structure:



Databases and inventories where listed: MA, PA, RQ, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

77.1 Chemical and Physical Properties (2)

Physical state	Colorless prisms
Melting point	106°C
Solubility	Soluble in water, ethanol

77.2 Production and Uses

2,6-Toluenediamine is used primarily for making TDI.

77.4 Toxic Effects

2,6-Toluenediamine induced formation of hemoglobin but not DNA adducts when given to F344 rats (231, 232). Likewise, it did not form DNA adducts in an *in vivo* system using transgenic mice (229). However, in a rat liver microsomal system (induced by Aroclor 1254), 2,6-toluenediamine was a potent mutagen, but it did not induce CYP 1A or bind the Ah receptor (215). An unexplained dichotomy is why 2,6-dinitrotoluene is a carcinogen, but the corresponding diamine is not.

77.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

78.0 3,4-Toluenediamine

78.0.1 CAS Number: [*496-72-0*]

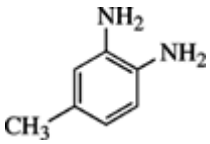
78.0.2 Synonyms: 4-Methyl-1,2-benzenediamine; diaminotoluene; toluene-3,4-diamine; 4-methyl-*o*-phenylenediamine; 3,4-diaminotoluene

78.0.3 Trade Names: NA

78.0.4 Molecular Weight: 122.17

78.0.5 Molecular Formula: $C_7H_{10}N_2$

78.0.6 Molecular Structure:



Databases and inventories where listed: MA, PA, RQ, WHMI, CCRIS, EINECS, EMICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.
78.1 Chemical and Physical Properties (2)

Melting point	89–90°C
Boiling point	265°C (Sublimes)
Solubility	Soluble in water

78.2 Production and Use
No specific applications found.
78.4 Toxic Effects
No information located.
79.0 3,5-Toluenediamine
79.0.1 CAS Number: [*108-71-4*]

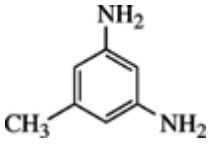
79.0.2 Synonyms: 3,5-Diaminotoluene; 5-methyl-1,3-benzenediamine

79.0.3 Trade Names: NA

79.0.4 Molecular Weight: 122.17

79.0.5 Molecular Structure: $C_7H_{10}N_2$

79.0.6 Molecular Structure:



Databases and inventories where listed: WHMI, EINECS, HSDB, TOXLINE, TSCAINV, SUPERLIST.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

N. Toluidines
80.0 **o**-Toluidine
80.0.1 CAS Number: [*95-53-4*]

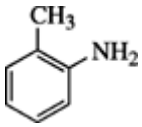
80.0.2 Synonyms: C.I. 37077; *o*-Methylaniline; 2-methyl-1-aminobenzene; 2-methylaniline; 2-methylbenzenamine; 2-aminotoluene; 1-amino-2-methylbenzene; 2-amino-1-methylbenzene; 1-methyl-2-aminobenzene; *o*-tolylamine; methyl-2-aminobenzene

80.0.3 Trade Names: NA

80.0.4 Molecular Weight: 107.15

80.0.5 Molecular Formula: C_7H_9N

80.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, CGB, CGN, DOT, IARC, IL, MA, MI, NJ, NTPA, PA, PEL, REL, RQ, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

80.1 Chemical and Physical Properties (2)

Physical state	Light yellow to reddish brown liquid
Density	0.9984 (20/4°C)
Melting point	–14.7°C
Boiling point	200.2°C
Refractive index	1.57276 (20°C)
Solubility	Soluble in ethanol, ether; slightly soluble in water

80.2 Production and Use

o-Toluidine and the hydrochloride salt are used as intermediates in manufacturing dyes, pharmaceuticals, pesticides, and in vulcanizing rubber.

80.3 Exposure Assessment

NMAM IV ed., 1994 Method #2002.

80.4 Toxic Effects

o-Toluidine was carcinogenic in animals and is suspected as being responsible for bladder cancers in exposed workers (168). However, it has been noted that the workers were also exposed to many other chemicals, and *o*-toluidine could not be identified specifically as the responsible agent (203, 236).

80.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA is 2 ppm with skin and A3 notations. The OSHA PEL is 6 ppm with a skin notation and NIOSH recommends lowest feasible exposure because it considers it a carcinogen.

81.0 **m**-Toluidine

81.0.1 CAS Number: [*108-44-1*]

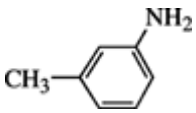
81.0.2 Synonyms: *m*-Tolylamine; 3-methylbenzenamine; 3-aminophenylmethane; 3-methylaniline; *m*-toluamine; *m*-aminotoluene

81.0.3 Trade Names: NA

81.0.4 Molecular Weight: 107.15

81.0.5 Molecular Formula: C_7H_9N

81.0.5 Molecular Structure:



Databases and inventories where listed: DOT, IL, MA, MTL, PA, PELS, TLV, WHMI,

CANCERLIT, CCRIS, DSL, EINECS, EMIC, EMICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

81.1 Chemical and Physical Properties (2)

Melting point	–30°C
Boiling point	203.3°C
Vapor pressure	1 torr at 41°C
Solubility	Soluble in acetone, ethanol, ether, benzene

81.2 Production and Use

m-Toluidine is used in dye production.

81.3 Exposure Assessment

Use NMAM, IVed., 1994 Method #2002.

81.4 Toxic Effects

m-Toluidine causes methemoglobinemia in exposed humans, but it was not carcinogenic in animals, even at high doses (2). No additional data were located.

81.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA is 2 ppm with skin and A4 notations.

82.0 **p**-Toluidine

82.0.1 CAS Number: [*106-49-0*]

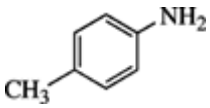
82.0.2 Synonyms: 4-Aminotoluene; 4-methylaniline; naphthol as-kgll; 4-methylbenzenamine

82.0.3 Trade Names: NA

82.0.4 Molecular Weight: 107.15

82.0.5 Molecular Formula: C_7H_9N

82.0.6 Molecular Structure:



Databases and inventories where listed: CA65, DOT, IL, MA, MTL, PA, PELS, REL, RQ, TLV, WHMI, CANCERLIT, CCRIS, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

82.1 Chemical and Physical Properties (2)

Physical state	Leaflets
Melting point	44–45°C
Boiling point	200.5°C
Refractive index	1.55324 (59.1°C)
Density	0.9619 (20/4°C); 0.973 (50/50°C)
Flash point	86°C (closed cup)
Specific gravity	1.046 (20°C)
Vapor pressure	1 torr at 42°C
Solubility	Soluble in ethanol, ether, methanol, carbon disulfide; somewhat soluble in water

82.2 Production and Use

p-Toluidine is used in the synthesis of dyes, as an intermediate, and as a reagent.

82.3 Exposure Assessment

NMAM, IV ed., 1994, Method #2002.
82.4 Toxic Effects
p-Toluidine caused methemoglobinemia and hematuria in exposed humans; it caused liver tumors in mice, but was not effective in rats. No new information was located in the literature.
82.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA is 2 ppm with skin and A3 notations. NIOSH considers it a carcinogen and recommends lowest feasible exposure limit.
83.0 4-Chloro-o-toluidine
83.0.1 CAS Number: [*95-69-2*]

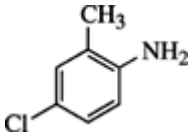
83.0.2 Synonyms: 4-Chloro-2-methylaniline; *para*-chloro-*ortho*-toluidine; 4-chloro-2-methylbenzenamine; 2-amino-5-chlorotoluene; azoene fast red tr base; brentamine fast red tr base, 5-chloro-2-aminotoluene; 4-chloro-6-methylaniline; daito red base tr; deval red k; deval red tr; deazo fast red tra; fast red base tr, fast red 5ci base; fast red tr 11; fast red tr. base; kako red tr base; kambamine red tr; 2-methyl-4-chloroaniline; mitsui red tr base; red base nir; red tr base; sonya fast red tr base; tula base fast red tr

83.0.3 Trade Names: NA

83.0.4 Molecular Weight: 141.60

83.0.5 Molecular Formula: C_7H_8ClN

83.0.6 Molecular Structure:



Databases and inventories where listed: CA65, IARC, MA, NJ, PA, TRI, WHMI, CANCERLIT, CCRIS, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.
83.1 Chemical and Physical Properties

Physical state	Leaflets
Melting point	29–30°C
Boiling point	241°C
Specific gravity	1.14
Solubility	Soluble in ethanol

83.2 Production and Uses
4-Chloro-*o*-toluidine is used to produce dyes and pesticides.
83.4 Toxic Effects
4-Chloro-*o*-toluidine led to hemangiosarcomas when fed to mice as the hydrochloride salt; rats had increases in pituitary and adrenal tumors (237). In workers who had been exposed for many years, there were increases in bladder tumors (237). Testing in *Salmonella*, human lymphocytes, and V79 cells (238) showed little action in mammalian cells, but with microsomal activation, there was activity in *Salmonella*. Apparently, chlorines on the ring system of toluidine led toward increased hydroxylation of the side chain (239).
82.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
84.0 5-Chloro-**o**-toluidine
84.0.1 CAS Number: [*95-79-4*]

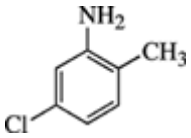
84.0.2 Synonyms: 5-Chloro-2-methylaniline; 5-chloro-2-methylbenzenamine; 2-amino-4-chlorotoluene; 1-amino-3-chloro-6-methylbenzene; 4-chloro-2-aminotoluene; 3-chloro-6-methylaniline; acco fast red kb base; ansibase red kb; azoic diazo component 32; azoene fast red kb base; fast red kb amine; fast red kb base; fast red kb salt; fast red kb salt supra; fast red kbs salt; genazo red kb soln; hiltonil fast red kb base; lake red bk base; metrogen red former kb soln; napthosol fast red kb base; pharmazoid red kb; red kb base; spectrolene red kb; stable red kb base; C.I. azoic diazo component No. 32; C.I. 37090; 2-methyl-5-chloroaniline; 5-chloro-2-methyl-benzamine

84.0.3 Trade Names: NA

84.0.4 Molecular Weight: 141.60

84.0.5 Molecular Formula: C_7H_8ClN

84.0.6 Molecular Structure:



Databases and inventories where listed: MA, MI, NTPT, CCRIS, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

84.1 Chemical and Physical Properties

Physical state	Off-white solid or light brown oil
Melting point	20–22°C
Boiling point	237°C

84.2 Production and Use

The compound is used in synthesizing dyes.

84.4 Toxic Effects

The compound was not carcinogenic in the rats when fed to rats and mice for up to two years, but it led to a positive response in both male and female mice.

84.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

85.0 6-Chloro-**o**-toluidine

85.0.1 CAS Number: [*87-63-8*]

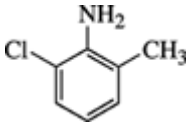
85.0.2 Synonyms: 2-Chloro-6-methylaniline; 2-chloro-6-methylbenzenamine; 2-amino-3-chlorotoluene; 6-chloro-2-methylaniline

85.0.3 Trade Names: NA

85.0.4 Molecular Weight: 141.60

85.0.5 Molecular Formula: C_7H_8ClN

85.0.6 Molecular Structure:



Datebases and inventories where listed: DSL, EINECS, EMICBACK, RTECS, TOXLINE, TSCAINV. No other information on this isomer was located.

86.0 5-Nitro-**o**-toluidine

86.0.1 CAS Number: [*99-55-8*]

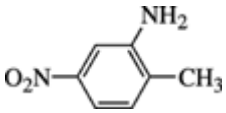
86.0.2 Synonyms: 2-Methyl-5-nitrobenzenamine; 2-methyl-5-nitroaniline; 2-amino-4-nitrotoluene; 1-amino-2-methyl-5-nitrobenzene; 4-nitro-2-aminotoluene; amarthol fast scarlet g base; amarthol fast scarlet g salt; azoene fast scarlet gc base; azoene fast scarlet gc salt; azofix scarlet g salt; azogene fast scarlet g; C.I. 37105; C.I. azoic diazo component 12; dainichi fast scarlet g base; daito scarlet base g; devol scarlet b; devol scarlet g salt; diabase scarlet g; diazo fast scarlet g; fast red sg base; fast scarlet base g; fast scarlet base j; fast scarlet g; fast scarlet g base; fast scarlet gc base; fast scarlet j salt; fast scarlet mN4t base; fast scarlet t base; hiltonil fast scarlet g base; hiltonil fast scarlet gc base; hiltonil fast scarlet g salt; kayaku scarlet g base; lake scarlet g base; lithosol orange r base; mitsui scarlet g base; naphthanil scarlet g base; naphtoelan fast scarlet g base; naphtoelan fast scarlet g salt; PNOT; scarlet base ciba ii; scarlet base irga ii; scarlet base nsp; scarlet g base; sugai fast scarlet g base; symulon scarlet g base; Fast Red G Base

86.0.3 Trade Names: NA

86.0.4 Molecular Weight: 152.15

86.0.5 Molecular Formula: $C_7H_8N_2O_2$

86.0.6 Molecular Structure:



Databases and inventories where listed: IARC, MA, NJ, NTPT, PA, RQ, TRI, WHMI, CANCERLIT, CCRIS, EINECS, EMIC, EMICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

86.1 Chemical and Physical Properties

Physical state	Yellow monoclinic prisms
Melting point	107–108°C
Solubility	Soluble in acetone, benzene, ether, ethanol, chloroform
Solubility in water	1 g/100 mL at 19°C

86.2 Production and Use

5-Nitro-*o*-toluidine is used in the synthesis of numerous dyes.

86.4 Toxic Effects

5-Nitro-*o*-toluidine was carcinogenic in mice and caused liver tumors; in rats there was a weak effect in males (237). The compound was mutagenic in several strains of *Salmonella*.

86.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

O. Anisidines
87.0 **o**-Anisidine
87.0.1 CAS Number: [*90-04-0*]

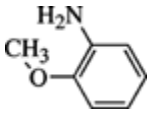
87.0.2 Synonyms: 2-Methoxybenzenamine; *o*-methoxyaniline; 2-anisidine; 2-methoxy-1-aminobenzene; 1-amino-2-methoxybenzene; *o*-anisylamine; *o*-methoxyphenylamine; *o*-aminophenol methyl ether; *o*-aminoanisole

87.0.3 Trade Names: NA

87.0.4 Molecular Weight: 123.15

87.0.5 Molecular Formula: C_7H_9NO

87.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, IARC, IL, MA, MI, MPOL, MTL, NJ, PA, REL, TLV, TRI, WHMI, CANCERLIT, CCRIS, DSL, EINECS, EMIC, EMICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.
87.1 Chemical and Physical Properties (209)

Physical state	Yellowish liquid
Boiling point	224°C
Melting point	6.2°C
Density	1.0923
Refractive index	1.5713
Specific gravity	1.092
Solubility	Soluble in acetone, benzene, ether, ethanol; slightly soluble in water

87.2 Uses
The compound has been used in synthesizing dyes.
87.3 Exposure Assessment
For determining human exposure, the NMAM #2514 in the IV ed. is recommended.
87.4 Toxic Effects
When fed in the diet at levels of 2500 or 5000 mg/kg (as the hydrochloride salt), *o*-anisidine induced carcinomas of the bladder in male and female B6C3F$_1$ mice (203). F344 rats at levels of 5000 or 10,000 mg/kg of the salt showed a high incidence of bladder tumors in both males and females. Males also had an increased incidence of thyroid tumors. However, although *o*-anisidine was mutagenic in *Salmonella* (in the presence of a microsomal activating system), it was not genotoxic in four rat and two mouse strains in such tests as the micronucleus test, unscheduled DNA synthesis, and DNA single-strand breaks (45). Furthermore, even though *o*-anisidine was a bladder carcinogen in transgenic mice, there was no evidence of DNA binding, using two different isotopic labeling systems (240).
87.5 Standards, Regulations, or Guidelines of Exposure

The TLV-TWA is 0.1 ppm with skin and A3 notations. NIOSH considers it a carcinogen with a REL of 0.5 ppm. The OSHA PEL is also 0.5 ppm.

88.0 **p**-Anisidine

88.0.1 CAS Number: [*104-94-9*]

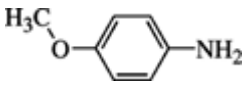
88.0.2 Synonyms: 4-Methoxybenzenamine, *p*-methoxyaniline, *p*-aminoanisole, 1-amino-4-methoxybenzene, *p*-anisylamine, *p*-methoxyphenylamine, 4-methoxy-1-aminobenzene

88.0.3 Trade Names: NA

88.0.4 Molecular Weight: 123.15

88.0.5 Molecular Formula: C_7H_9NO

88.0.6 Molecular Formula:



Databases and inventories where listed: IARC, IL, MA, MTL, NJ, PA, REL, TLV, TRI, WHMI, CANCERLIT, CCRIS, DSL, EINECS, EMIC, EMICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

88.1 Chemical and Physical Properties (209)

Physical state	Crystals
Boiling point	243°C
Melting point	57.2°C
Density	1.071
Solubility	Soluble in acetone, benzene, ether, ethanol, water

88.2 Production and Use

p-Anisidine is used mostly for producing dyes, and some smaller quantities are employed in making pharmaceuticals and liquid crystals (203).

88.3 Exposure assessment

To determine a potential exposure to *p*-anisidine, NIOSH method #2514 found in NMAM IV can be used.

88.4 Toxic Effects

p-Anisidine is not very toxic; the LD_{50} ranged from 810 to 1300 mg/kg body weight in mice, 1400 mg/kg in rats and 2900 mg/kg in rabbits (203). When fed in the diet (as the hydrochloride salt) at levels of 5000 or 10,000 mg/kg for 103 weeks, B6C3F_1 mice showed some depression in body weight gain but no increases in tumor incidence. Under similar conditions at dietary levels of 3000 or 6000 mg/kg, F344 rats also had no increases in tumor incidence, although body weight gain was depressed. Results from tests for mutagenicity in the *Salmonella* system are conflicting (203).

88.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA is 0.1 ppm with A4 and skin notations. NIOSH considers it a carcinogen with a REL of 0.5 ppm. The OSHA PEL is also 0.5 ppm.

89.0 Xylidines

89.0.1 CAS Number: [*1300-73-8*]

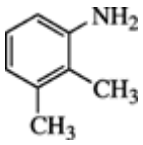
89.0.2 Synonyms: Xylidine isomers; aminodimethylbenzene (mixed isomers); xylidine (mixed isomers); dimethylaminobenzene; dimethylaniline (mixture); benzenamine, ar,ar-dimethyl-; aminodimethylbenzene.

89.0.3 Trade Names: NA

89.0.4 Molecular Weight: 121.18

89.0.5 Molecular Formula: $C_8H_{11}N$

89.0.6 Molecular Structure:



Databases and inventories where listed: DOT, IL, MA, MTL, PA, PEL, REL, TLV, WHMI, EINECS, HSDB, RTECS, TOXLINE, TSCAINV, SUPERLIST.

89.1 Chemical and Physical Properties (Commercial mixture)

Physical state	Pale yellow to brown liquid, with a weak aromatic odor
Boiling point	213–226°C
Vapor pressure	<1 torr at 20°C
Flash point	94.5°C
Density	0.97–0.99
Solubility	Soluble in ether, ethanol; slightly soluble in water

89.2 Production and Use

The mixed isomers that comprise commercial xylidine are mostly the 2,4-, 2,5-, and 2,6-isomers. Xylidine is used to manufacture dyes, pharmaceuticals, and other compounds.

89.3 Exposure Assessment

Human exposure may be monitered by use of NIOSH method #2002 found in NMAM IV.

89.4 Toxic Effects

Xylidine is absorbed through the skin and can cause methemoglobinemia, but it is less active in this regard than aniline. There are species differences in the toxicities of the different isomers, as well as in the metabolic patterns observed.

89.5 Standards, Regulations, or Guidelines of Exposure

The TLV-TWA is 0.5 ppm with skin and A3 notations. The NIOSH REL is 2 ppm and the OSHA PEL is 5 ppm. Both have skin notations as well.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

P. Xylidine Isomers

90.0 2,4-Xylidine

90.0.1 CAS Number: [*95-68-1*]

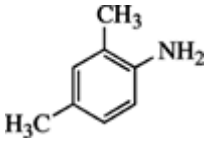
90.0.2 Synonyms: 2,4-Dimethylaniline, 2,4-dimethylaminobenzene; 4-amino-1,3-dimethylbenzene; 1-amino-2,4-dimethylbenzene; 4-amino-3-methyltoluene; 4-amino-1,3-xylene; 2,4-dimethylphenylamine; 2-methyl-*p*-toluidine; 4-methyl-*o*-toluidine; 4-amino-*m*-xylene

90.0.3 Trade Names: NA

90.0.4 Molecular Weight: 121.18

90.0.5 Molecular Formula: $C_8H_{11}N$

90.0.6 Molecular Structure:



Databases and inventories where listed: IARC, WHMI, CANCERLIT, CCRIS, EINECS, EMIC, EMICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

90.1 Physical and Chemical Properties (202)

Physical state	Dark brown liquid
Boiling point	214°C
Melting point	16°C
Density	0.9723
Solubility	Soluble in ethanol, ether, benzene; slightly soluble in water

90.2 Production and Use

2,4-Xylidine, as part of the commercial mixture, has the same uses as xylidine.

90.4 Toxic Effects

The oral LD_{50} in mg/kg body weight for rats ranges from 470–1259; for mice the value is 250 (144). An intravenous dose of 30 mg/kg in cats led to methemoglobin levels almost 10-fold lower than the same dose of aniline. Repeated oral doses for 7 days led to liver damage in rats. The compound was absorbed through the skin of cats, and caused methemoglobinemia and liver damage. Of the three isomers described here, the 2,4- was most active in leading to liver damage and induction of P450 protein. When administered in the diet (as the hydrochloride) for 18 months, 2,4-xylidine was not carcinogenic in male CD rats. A similar study in CD-1 mice showed no increase in tumors in males, but the female mice at the higher dose level had an increase in lung tumors. The major metabolite in rats was 3-methyl-4-aminobenzoic acid (202). Minor amounts of acetyl and sulfate conjugates were also noted.

90.5 Standards, Regulations, or Guidelines of Exposure

As part of commercial xylidine, the ACGIH TLV-TWA is 0.5 ppm with skin and A3 notations; there is no specific standard for the 2,4-isomer.

91.0 2,5-Xylidine

91.0.1 CAS Number: [*95-78-3*]

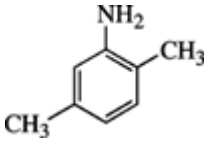
91.0.2 Synonyms: 2,5-Dimethylaniline; 1-amino-2,5-dimethylbenzene; 3-amino-1,4-dimethylbenzene; 2-amino-1,4-xylene; 2,5-dimethylphenylamine; 5-methyl-*o*-toluidine; 6-methyl-*m*-toluidine; *p*-xylidine; 2-amino-*p*-xylene

91.0.3 Trade Names: NA

91.0.4 Molecular Weight: 121.18

91.0.5 Molecular Formula: $C_8H_{11}N$

91.0.6 Molecular Structure:



Databases and inventories where listed: IARC, WHMI, CCRIS, EINECS, EMIC, EMICBACK, ETICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

91.1 Chemical and Physical Properties (202)

Physical state	Colorless to yellow oil
Boiling point	214°C
Melting point	15.5°C
Density	0.9790
Solubility	Soluble in ether; slightly soluble in ethanol and water

91.2 Production and Use

The uses are the same as those of xylidines.

91.3 Exposure Assessment

May use NIOSH method #2002 for determination of potential human exposures (in NMAM IV).

91.4 Toxic Effects

The oral LD_{50} in mg/kg bw was 1300 for rats and 840 for mice (144). 2,5-Xylidine was active as a methemoglobin former but still was much less active than aniline. As with the other isomers, repeated doses caused liver damage. When given in the diet (as the hydrochloride salt) for 18 months, 2,5-xylidine was not carcinogenic in male rats; under a similar protocol, male mice showed an increase in vascular tumors. Rats converted 2,5-xylidine to 4-hydroxy-2,5-dimethylaniline and its conjugates, with minor amounts of 4-methyl-2 and -3-aminobenzoic acids. An oral dose of 200 mg/kg bw inhibited testicular DNA synthesis in male mice. Mutagenicity tests with the *Salmonella* system showed a response after metabolic activation (144).

91.5 Standards, Regulations, or Guidelines of Exposure

There is no specific standard for the 2,5-isomer; the ACGIH TLV-TWA for xylidines is 0.5 ppm.

92.0 2,6-Xylidine

92.0.1 CAS Number: [*87-62-7*]

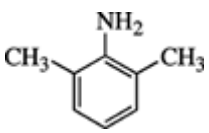
92.0.2 Synonyms: 2,6-Dimethylaniline, *o*-xylidine; DMA; 2-amino-1,3-dimethylbenzene; 1-amino-2,6-dimethylbenzene; xylylamine

92.0.3 Trade Names: NA

92.0.4 Molecular Weight: 121.18

92.0.5 Molecular Formula: $C_8H_{11}N$

92.0.6 Molecular Structure:



Databases and inventories where listed: CA65, CGB, CGN, IARC, MA, NJ, NTPT, PA, TRI, CANCERLIT, HSDB, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

92.1 Chemical and Physical Properties

Physical state	Colorless to reddish yellow liquid
Boiling point	214°C (739 mmHg)
Melting point	8.4°C
Density	0.9842 (20°C)
Solubility	Soluble in ethanol, ether; slightly soluble in water

92.2 Production and Use

2,6-Xylidine is an intermediate in manufacturing pesticides, dyes, antioxidants, pharmaceuticals, resins, fragrances, and other products.

92.3 Exposure Assessment

NIOSH Method #2002 can be used to determine workplace exposures.

92.4 Toxic Effects

The oral LD_{50} in mg/kg body weight ranges from 1050–1250 for rats; for mice the figures are 710–750. The methemoglobin-forming activity of 2,6-xylidine was similar to that of the 2,4-isomer. Male rats given 157 mg/kg body weight for 20 days developed hemosiderosis in the spleen. Continued administration for 30 days led to increased liver weight but no increase in P450 microsomal protein.

CD rats were fed 2,6-xylidine in the diet at levels of 300, 1000, or 3000 ppm; progeny received the same levels for 2 years. Adenomas and carcinomas of the nasal cavity occurred in both males and females, plus subcutaneous fibromas and fibrosarcomas (179).

The major urinary metabolite of 2,6-xylidine in rats was 4-hydroxy-2,6-dimethylaniline, and 3-methyl-2-aminobenzoic acid was a minor metabolite. Other reactive metabolites were tentatively identified (187). In human liver slices, 2,6-xylidine was a metabolite of lidocaine (241). Mutagenicity tests with 2,6-xylidine have given conflicting results.

92.5 Standards, Regulations, or Guidelines of Exposure

There is no specific standard for 2,6-xylidine; the ACGIH TLV-TWA for xylidines is 0.5 ppm with skin and A3 notations.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

Q. Two-Ring Compounds

93.0 Diphenylamine

93.0.1 CAS Number: [*122-39-4*]

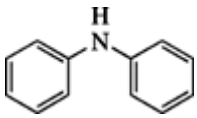
93.0.2 Synonyms: *N*-Phenylbenzenamine; *N*-phenylaniline; DFA; No Scald; DPA; anilinobenzene; (phenylamino)benzene; *N,N*-diphenylamine; big dipper; C.I. 10355; scaldip; phenylbenzenamine

93.0.3 Trade Names: NA

93.0.4 Molecular Weight: 169.23

93.0.5 Molecular Formula: $C_{12}H_{11}N$

93.0.6 Molecular Structure:



Databases and inventories where listed: CGB, CGN, FIFR, IL, INER, MA, MTL, NJ, PA, RQ, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

93.1 Chemical and Physical Properties (2)

Physical state	Colorless monoclinic leaflets
Density	1.159 (20/4°C)
Melting point	53–54°C
Boiling point	302°C
Solubility	Soluble in acetone, benzene, ethanol, ether, methanol; slightly soluble in water

93.2 Production and use

Diphenylamine is used as an antioxidant, fungicide, a prevention against apple scald, as a stabilizer, antihelmintic, and as a reagent.

93.3 Exposure Assessment

Potential exposures to diphenylamine may be measured using OSHA method #78.

93.4 Toxic Effects

Diphenylamine is absorbed through the skin; chronic studies by feeding in the diet of rats and beagle dogs showed some effects on the liver but no increase in tumors. However, dilatation of kidney kidney tubules occurred in rats, related to the impurity *N,N,N*'-triphenyl-*p*-phenylenediamine (2). Further investigation on a relationship between glutathione levels and renal papillary necrosis, using the Syrian hamster model, did not reveal a specific correlation. Within 1 h after a single dose from 200–600 mg/kg body weight there was a dose-dependent decrease in renal cortical glutathione, but significant changes in medullary or papillary glutathione were not seen (242). Ultrastructural studies of the kidney lesions were made (243). Interestingly, dimethyl sulfoxide lessened the incidence of papillary lesions from diphenylamine (244).

93.5 Standards, Regulations, or Guidelines of Exposure

The TLV-TWA is 10 mg/m^3 with an A4 notation. The NIOSH REL is also 10 mg/m^3.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

R. Benzidine and Derivatives

94.0 Benzidine

94.0.1 CAS Number: [*92-87-5*]

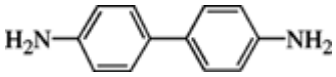
94.0.2 Synonyms: 4,4'-Diaminobiphenyl; 4,4'-diphenylenediamine; 4,4'-biphenyldiamine; 4,4'-bianiline; *p*-diaminodiphenyl; 1,1'-biphenyl-4,4'-diamine, 4,4'-diamino-1,1'-biphenyl; fast corinth base b; *p*-benzidine; benzidine base; C.I. azoic diazo component 112; C.I. 37225, BZ

94.0.3 Trade Names: NA

94.0.4 Molecular Weight: 184.24

94.0.5 Molecular Formula: $C_{12}H_{12}N_2$ or $NH_2C_6H_4C_6H_4NH_2$

94.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, DOT, IARC, IL, MA, NJ, NTPA, PA, PEL, REL, RQ, S110, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

94.1 Chemical and Physical Properties (2)

Physical state	White to slightly reddish powder or crystals
Density	1.250 (20/4°C)
Melting point	116/129°C (isotropic forms)
Boiling point	402°C
Vapor density	6.36
Solubility	Soluble in ether; slightly soluble in ethanol, hot water

94.2 Production and Use

Benzidine has been used as an intermediate for dyes with desirable properties, as a hardener for rubber, in security paper, and in small amounts as a laboratory reagent for blood testing. Because of its carcinogenicity in exposed workers, as well as the carcinogenicity of certain azo dyes derived from benzidine, manufacture for industrial use has been prohibited in the United States.

94.3 Exposure Assessment

Expsoure monitoring by NIOSH method #5509 is recommended (NMAM IV).

94.4 Toxic Effects

Epidemiological studies of exposed workers, which showed a higher risk of bladder cancer, along with the finding that three azo dyes derived from benzidine (BZ), namely, Direct Blue 6, CAS Number: [2602-46-20], Direct Black 38, CAS Number: [*1937-37-7*], and Direct Brown 95, CAS Number: [*1607-86-6*], were more potent carcinogens than BZ, led to a ban on production. However, BZ is still manufactured in some countries which has led to several mechanistic and epidemiological studies of exposed workers, especially in regard to acetyltransferase enzyme expression, *N*-glucuronide formation, and the role of BZ-DNA adducts in carcinogenesis.

Studies of *N*-acetylation of BZ and *N*-acetyl-BZ in human liver slices suggested that *N*-acetyl-BZ is a better substrate for NAT1 than BZ (245, 246). NAT1 and NAT2 catalyzed *N*-acetylation by a binary ping-pong mechanism, but NAT1 was the predominant acetylating enzyme. Another survey found NAT2-associated slow acetylation was not linked to increased risk of bladder cancer in humans and may even exert a protective effect (247). In rat liver slices, *N,N'*-diacetyl-BZ was formed preferentially; in dog liver, no acetylated adducts were found (248). With rat liver microsomes, *N*-acetyl-BZ was oxidized to *N'*-OH-*N*-acetyl-BZ, *N*-OH-*N*-acetyl-BZ, and ring oxidation products, mediated through cytochrome P450 1A1/1A2 (249, 250). The reaction of glutathione with one of the oxidation products, specifically BZ-diimine, led to the formation of 3-(glutathion-*S*-yl)-BZ and prevented complexing with DNA (251).

Formation of *N*-(3'-monophosphodeoxyguanosin-8-yl)-*N'*-acetyl-BZ occured with prostaglandin H synthase (from ram seminal vesicle microsomes) and *N*-acetyl-BZ (252). Levels of this adduct in human peripheral white blood cells correlated with levels in exfoliated urothelial cells from exposed workers (253); it was the only adduct significantly associated with total urinary metabolites of BZ, and it was thought unlikely that interindividual variations in NAT2 function were relevant for BZ-associated cancer (254).

Glutathione-*S*-transferase M1 expression had no apparent impact on bladder cancer from BZ (255), but an acidic urine was associated with higher levels of free BZ in urine and urothelial cell DNA adducts (256).

Glucuronide formation is also important in BZ disposition because splitting of a glucuronide by acidic urine may release free BZ at a susceptible site. However, the *N*-glucuronide of *N*-OH-BZ was stable at an acidic pH (257). Although dog liver slices made an *N*-glucuronide from BZ (258), dog liver did not form such a conjugate from *N*-acetyl-BZ, but human and rat liver did (259). It was noted that liver microsomes from aged rats were more susceptible to the effects of BZ than those from younger animals (260). However, experiments *in vivo* are needed to confirm this.

The disposition of BZ and its activation differ somewhat from that of other carcinogenic amines.

94.5 Standards, Regulations, or Guidelines of Exposure

OSHA does not have a PEL for benzidine. However, it does have a regulation for it: 29CFR1910.10. This regulation states that benzidine and benzidine dyes are potential carcinogens and worker exposures should be reduced to the lowest feasible level. No standard has been set by ACGIH, but BZ is given an Al notation. Persons who use BZ in research should follow guidelines for handling carcinogens.

95.0 3,3'-Dichlorobenzidine

95.0.1 CAS Number: [*91-94-1*]

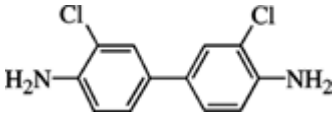
95.0.2 Synonyms: 3,3'-Dichloro-4,4'-biphenyldiamine; *o,o*'-dichlorobenzidine; 4,4'-diamino-3,3'-dichlorobiphenyl; dichlorobenzidine; DCB; 3,3'-dichloro-(1,1-biphenyl)-4,4'-diamine; C.I. 23060; 3,3'-dichlorobiphenyl-4,4'-diamine; 3,3'-dichloro-4,4'-diaminobiphenyl

95.0.3 Trade Names: NA

95.0.4 Molecular Weight: 253.13

95.0.5 Molecular Formula: $C_{12}H_{10}Cl_2N_2$ or $NH_2ClC_6H_3C_6H_3ClNH_2$

95.0.6 Molecular Structure:



Database and inventories where listed: CAA1, CA65, IARC, IL, MA, NJ, NTPA, PA, PEL, REL, RQ, S110, TLV, WHMI, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, IRIS, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

95.1 Physical and Chemical Properties (2)

Physical state	Grayish to purple crystals
Melting point	133°C
Boiling point	368°C
Solubility	Soluble in ethanol, ether, acetic acid; insoluble in water

95.2 Production and use

The compound is used as a curing agent for urethane plastics and for manufacturing yellow dyes.

95.3 Exposure Assessment

NIOSH method #5509 is recommended for determining potential exposures to this chemical (NMAM IV).

95.4 Toxic Effects

The toxicity, metabolism and carcinogenicity of dichlorobenzidine were reviewed by IARC (261). Essentially, the compound is carcinogenic in animals, but epidemiological studies in exposed

workers did not show an excess of tumors. However, the studies were deemed inadequate for a definitive conclusion (261). Of interest is the fact that a dichlorobenzidine-based azo dye, diarylanilide yellow, was fed to animals at 2.5 and 5% of the diet for two years and produced no increase in tumors (262). Presumably, the presence of the chlorine moieties may have interfered with the azo reductase enzyme so that free dichlorobenzidine was not produced.

95.5 Standards, Regulations, or Guidelines of Exposure

There is no TLV-TWA, but ACGIH has skin and an A3 notation for this compound. OSHA considers it a carcinogen and exposures are to be controlled their engineering controls, workpractices and protective equipment.

96.0 3,3'-Dimethoxybenzidine

96.0.1 CAS Number: [*119-90-4*]

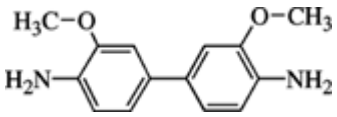
96.0.2 Synonyms: *o*-Dianilidine; Fast Blue; Blue Base; C.I. Disperse Black 6; 3,3'-dimethoxy-1,1'-biphenyl-4,4'-diamine; 4,4'-diamino-3,3'-dimethoxybiphenyl; 3,3'-dimethoxy-4,4'-diaminobiphenyl; 4,4'-diamino-3,3'-biphenyldiol dimethyl ether; dianisidine; *o,o*'-dianisidine; 3,3'-dianisidine; DMOB; acetamine diazo black rd; acetamine diazo navy rd; amacel developed navy sd; azoene fast blue base; azogene fast blue b; blue base irga b; blue base nb; blue bn base; brentamine fast blue b base; cellitazol b; cellitazol bn; C.I. azoic diazo component 48; diacelliton fast grey g; diacel navy dc; diato blue base b; diazo fast blue b; fast blue b base; fast blue dsc base; hiltonil fast blue b base; kayaku blue b base; lake blue b base; meisei teryl diazo blue hr; mitsui blue b base; naphthanil blue b base; neutrosel navy bn; setacyl diazo navy r; spectrolene blue b

96.0.3 Trade Names: NA

96.0.4 Molecular Weight: 244.29

96.0.5 Molecular Formula: $C_{14}H_{16}N_2O_2$

96.0.6 Molecular Structure:



Databases and inventories where listed: CA65, CAA1, IARC, IL, MA, NJ, NTPA, PA, RQ, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, SUPERLIST, TOXLINE, TSCAINV.

96.1 Chemical and Physical Properties (263)

Physical state	Colorless to violet crystals
Molecular weight	244.3
Melting point	171–174.5°C
Solubility	Soluble in ethanol, ether, acetone, benzene, chloroform; only very slightly soluble in water

96.2 Production and Use

This compound has been used in dye production.

96.3 Exposure Assessment

NIOSH method #5013 NMAM IV.

96.4 Toxic Effects

The early data on the carcinogenicity of 3,3'-dimethoxybenzidine were reviewed (263). The NTP has done a chronic study of the dihydrochloride salt given in drinking water at levels of 80, 170, or 330 ppm for 21 months to male and female F344 rats. This treatment led to various types of skin

tumors in males, plus tumors of the Zymbal gland, preputial gland, tongue or palate, and additional tumors of the intestines and liver. Females showed tumors of the clitoral and Zymbal glands, an increase in mammary adenocarcinoma, and various other internal tumors (264). Besides this clear evidence of carcinogenicity, the compound was positive in a *Salmonella* test (TA98) and in a sister chromatid exchange study (264).

96.5 Standards, Regulations, or Guidelines of Exposure

OSHA and NIOSH concluded this chemical may present a cancer risk and exposure should be minimized.

97.0 3,3'-Dimethylbenzidine

97.0.1 CAS Number: [*119-93-7*]

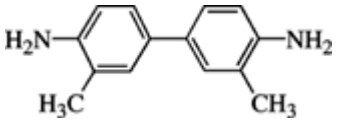
97.0.2 Synonyms: *ortho*-Tolidine; DMB; Fast Dark Blue Base R;3,3'-dimethyl-1, 1'-biphenyl-4, 4'-diamine; 3, 3'-dimethylbiphenyl-4, 4'-diamine; tolidine; dimethyl benzidine; 3, 3'-tolidine; 4, 4'-bi-*o*-toluidine; 4,4'-diamino-3,3'-dimethylbiphenyl; 3,3'-dimethyl-4,4'-biphenyldiamine; diaminoditolyl; bianisidine; *o*, *o*'-tolidine; C. I. 37230; C. I. azoic diazo component 113

97.0.3 Trade Names: NA

97.0.4 Molecular Weight: 212.29

97.0.5 Molecular Formula: $C_{14}H_{16}N_2$

97.0.6 Molecular Structure:



97.1 Chemical and Physical Properties (265)

Physical state	White to reddish crystals or crystalline powder
Melting point	131.5°C
Solubility	Soluble in ethanol, ether; somewhat soluble in chloroform, water

97.2 Production and Use

3,3'-Dimethylbenzidine is a dye intermediate.

97.3 Exposure Assessment

NIOSH method #5013 (NMAM IV).

97.4 Toxic Effects

The NTP did a long-term study of the dihydrochloride of 3,3'-dimethylbenzidine given in the drinking water to F344 rats at 30, 70, or 150 ppm. The study was terminated at 14 months because of the low number of surviving rats. Males had many types of skin tumors, neoplasms of the Zymbal gland, liver, and large intestine, and lower numbers of tumors of the preputial gland, oral cavity, small intestine, and lung. Females had a high incidence of tumors of the Zymbal and clitoral glands, in addition to lower incidences of neoplasms of the skin, liver, intestines, lung, and mammary glands. The compound also tested positive in *Salmonella* (TA98), in sister chromatid exchange, and as an inducer of chromosomal aberrations (266).

97.5 Standards, Regulations, or Guidelines of Exposure

NIOSH and OSHA jointly published a Health Hazard Alert concluding that *o*-tolidine was a potential carcinogen and recommended that worker exposure be reduced to lowest feasible level.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

S. Biphenyls
98.0 2-Nitrobiphenyl
98.0.1 CAS Number: [*86-00-0*]

98.0.2 Synonyms: *o*-Nitrobiphenyl; 2-nitro-1,1'-biphenyl; ONB

98.0.3 Trade Names: NA

98.0.4 Molecular Weight: 199.21

98.0.5 Molecular Formula: $C_{12}H_9NO_2$

Databases and inventories where listed: CCRIS, EINECS, EMIC, EMICBACK, RTECS, TOXLINE.
98.1 Physical and Chemical Properties (2)

Physical State	Colorless Crystals or yellow to reddish liquid
Molecular weight	199.21
Boiling point	320°C
Melting point	37.2°C
Density	1.44
Solubility	Soluble in acetone, ethanol, methanol, carbon tetrachloride, perchloroethylene; slightly soluble in water

98.2 Production and Use
2-Nitrobiphenyl is a plasticizer for resins, a fungicide for textiles, and a wood preservative.
98.4 Toxic Effects
The rat LD_{50} is 1230 mg/kg body weight and it is an irritant.
98.5 Standards, Regulations, or Guidelines of Exposure
None assigned.
99.0 4-Nitrobiphenyl
99.0.1 CAS Number: [*92-93-3*]

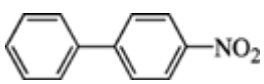
99.0.2 Synonyms: 4-Phenylnitrobenzene; 1-nitro-4-phenylbenzene; 4-nitro-1, 1'-biphenyl

99.0.3 Trade Names: NA

99.0.4 Molecular Weight: 199.21

99.0.5 Molecular Formula: $C_{12}H_9NO_2$

99.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, IARC, IL, MA, NJ, PA, PEL, REL, TLV, TRI, WHMI, CANCERLIT, CCRIS, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.
99.1 Chemical and Physical Properties (2)

Physical state	White to yellow needle-like crystals
Melting point	114–114.5°C
Boiling point	340°C
Solubility	Soluble in hot water, ethanol, ether, insoluble in acetone, benzene

99.2 Production and Use

4-Nitrobiphenyl has some uses as a plasticizer, fungicide, and wood preservative.

99.3 Exposure Assessment

NIOSH method P and CAM #273, (NMAM II(4)).

99.4 Toxic Effects

4-Nitrobiphenyl has produced bladder tumors in dogs and is a carcinogenic risk (227, 267). The oral LD_{50} for rabbits was reported to be 1.97 g/kg and for rats, 2.33 g/kg (144).

The IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Man found no reports on the carcinogenicity of PNB to humans and that the animal data were inadequate to classify the compound as a human carcinogen; consequently IARC assigned 4-nitrobiphenyl to Group 3, not classifiable as to its carcinogenicity to humans (227). However, it is considered an occupational carcinogen by NIOSH and OSHA (267) and a "suspect carcinogen" (or A2) by ACGIH (144).

99.5 Standards, Regulations, or Guidelines of Exposure

None have been assigned, however, OSHA promulgated a standard for this chemical—exposure should be the lowest feasible level and ACGIH has skin and A2 (suspect carcinogen) notations for 4-nitrobiphenyl.

100.0 4-Aminobiphenyl

100.0.1 CAS Number: [*92-67-1*]

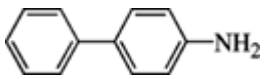
100.0.2 Synonyms: 4-Aminodiphenyl; xenylamine; 4-biphenylamine; [1,1'-biphenyl]-4-amine; *p*-phenylaniline; *p*-xenylamine

100.0.3 Trade Names: NA

100.0.4 Molecular Weight: 169.23

100.0.5 Molecular Formula: $C_{12}H_{11}N$

100.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, IARC, IL, MA, MI, NJ, NTPA, PA, PEL, REL, S110, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

100.1 Chemical and Physical Properties (2)

Physical state	Colorless crystals which turn purple on contact with air; floral odor
Melting point	53-54°C
Boiling point	302°C; 191°C (15 mmHg)
Solubility	Soluble in ethanol, ether, chloroform; slightly soluble in water

100.2 Production and Use

4-Aminobiphenyl was formerly used as a rubber antioxidant and dye intermediate; it is now a research chemical.

100.3 Exposure Assessment

NIOSH method P & CAM #269 (NMAM II(4)).

100.4 Toxic Effects

The carcinogenicity of 4-aminobiphenyl (4-ABP), especially with regard to induct bladder cancer in both animals and humans was discussed in the previous edition (2). In contrast to benzidine, 4-ABP should be a matter of concern for everyone. Although tobacco smoking is the major source of exposure to 4-ABP, there is a baseline exposure level, as indicated by hemoglobin adducts. Nonsmokers had levels of about 20 pg 4-ABP/g hemoglobin; levels in smokers could range from about 140-630 pg 4-ABP/g hemoglobin (268). Even human fetuses had such adducts; in nonsmoking women, fetuses had levels of about 9 pg 4-ABP/g hemoglobin; those from women who smoked had levels from about 75-320 pg 4-ABP/g hemoglobin (269). These data indicate that 4-ABP can cross the placental barrier and bind to fetal hemoglobin (270). The actual source of the 4-ABP in nonsmokers has not been identified; one possibility may be 4-nitrobiphenyl from engine exhausts.

As with other aromatic amine carcinogens, 4-ABP is acetylated and *N*-hydroxylated; the mechanism of its activation to DNA-reactive entities is a matter of much investigation. There have been many efforts to correlate 4-ABP-DNA adduct formation and subsequent induction of cancer. In some cases, adduct formation correlated with eventual tumorigenesis (271–277). But there were other situations where the correlation did not always hold, depending on the tissue and the analytical method (278). Acetylator status played a role with some types of adducts but not with all (279–281). Peroxidase-mediated activation was minor, compared to acetyltransferase effects (282). Acid-labile glucuronide conjugates were studied (283), as well as the possible role of glutathione transferase (284), which did not correlate with adduct levels. 4-ABP, as are other aromatic amines, was oxidized through cytochrome P4501A2 (285) and also through sulfotransferase (286). Even tissue from human fetuses of 14 weeks gestation had a sulfotransferase that activated the *N*-hydroxy derivatives of both 4-ABP and *N*-acetyl-4-ABP (287). The major DNA adduct from *N*-hydroxyacetyl-ABP was 3-(deoxyguanosin-N^2-yl)-4-acetylaminobiphenyl (282, 288). As with other genotoxic compounds, *in vivo* and *in vitro* results from mutagenicity assays did not always agree (289, 290). Even in bladder cancer patients, an important mutation (p53) did not correlate with the cancer stage, and there was no association among 4-ABP adducts, GSTM, and NAT2 genetic polymorphisms (291). Thus, the mechanism for the effects of 4-ABP provides issues for further investigation.

100.5 Standards, Regulations, or Guidelines of Exposure

Although ACGIH has set no TLV for this compound, it has the A1 notation and notes that bladder cancer is the reason for the notation. OSHA regulates this chemical as a carcinogen exposures must be controlled.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

T. Methylenedianilines

101.0 4,4'-Methylenedianiline

101.0.1 CAS Number: [*101-77-9*]

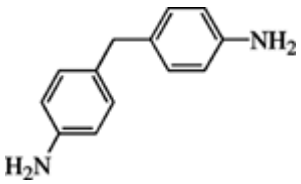
101.0.2 Synonyms: 4,4'-Methylenebisbenzeneamine; Tonox; HT 972; MDA; DDM; 4,4'-diaminodiphenylmethane; methylenebis(aniline); diaminodiphenylmethane; bis (*p*-aminophenyl) methane; DADPM; DAPM; dianilinomethane; 4,4'-diaminoditan; 4-(4-aminobenzyl)aniline; ancamine tl; araldite hardener 972; curithane; 4,4'-diphenylmethanediamine; epicure ddm; epikure ddm; jeffamine ap-20; sumicure M

101.0.3 Trade Names: NA

101.0.4 Molecular Weight: 198.27

101.0.5 Molecular Formula: $C_{13}H_{14}N_2$

101.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, DOT, IARC, MA, MPOL, MTL, NJ, NTPA, PA, REL, TLV, TRI, WHMI, CANCERLIT, CCRIS, DSL, EINECS, EMIC, EMICBACK, ETICBACK, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

101.1 Chemical and Physical Properties (2)

Physical State	Pale yellow crystals (darken on air exposure)
Melting point	91.5–92°C
Boiling point	398°C 768 mmHg
Solubility	Soluble in ethanol, benzene, ether, acetone, methanol; slightly soluble in water, carbon tetrachloride

101.2 Production and Use

Much of the 4,4'-methylenedianiline (MDA) produced is used as an intermediate for producing isocyanates and polyisocyanates, in making polyurethane foams, as a hardening agent for epoxy resins, as a curing agent, an antioxidant, and a fuel additive.

101.3 Exposure Assessment

NIOSH method #5029 (NMAM IV).

101.4 Toxic Effects

The toxicity of MDA has been discussed many times because it was the causative agent in the "Epping" jaundice incident (2, 3). The toxic effects were due to cholestasis, cholangitis, minor liver cell necrosis and hepatitis, but the exposed persons recovered within 7 weeks. After 24 years, a follow-up study of this group revealed one case of biliary tract carcinoma, two cases of retinal pathology, and four cases of recurrent jaundice, indicating long-term effects (292). Other deleterious effects in humans include contact dermatitis from a variety of products which contained MDA (293–296), allergic responses, and an increased risk of bladder cancer. However, a survey of workers who were exposed to MDA through its use as an epoxy curing agent showed no increases in bladder cancer (297). MDA was absorbed to a greater extent through human than through rat skin *in vitro* (298). Absorbed MDA was excreted in the urine as an acetyl-MDA and an unidentified conjugate (299). Workers exposed to MDA or to the diisocyanate of MDA excreted acetyl-MDA in the urine and albumin, and hemoglobin adducts were identified in the blood, indicating hydrolysis of the diisocyanate to MDA (300, 301).

In rats exposed to MDA, there was appreciable liver toxicity (302). It was determined that MDA leads to a cholangiodestructive effect and that the biliary toxicant from MDA is released into the bile (303, 304). As with humans, rats exposed to MDA or MDA diisocyanate excreted MDA and acetyl-MDA in the urine, besides forming hemoglobin adducts (305). In a rabbit liver microsomal system, MDA was metabolized to 4-nitroso-4'-aminodiphenylmethane plus both an azo and an azoxy

compound formed by combination of two MDA molecules after oxidation (306). These results indicate oxidation of MDA through hydroxylamine to a nitroso derivative, followed by condensation.

101.5 Standards, Regulations, or Guidelines of Exposure

The OSHA PEL (29CFR 1910, 1050) is 0.01 ppm with a STEL of 0.1 ppm. The current ACGIH TLV-TWA is 0.1 ppm with an A3 notation and a note that liver toxicity is a critical effect.

102.0 4,4'-Methylenebis(2-methylaniline)

102.0.1 CAS Number: [*838-88-0*]

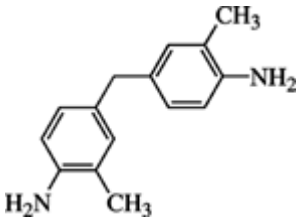
102.0.2 Synonyms: 3,3'-Dimethyl-4, 4'-diaminodiphenylmethane

102.0.3 Trade Names: NA

102.0.4 Molecular Weight: 226.32

102.0.5 Molecular Formula: $C_{15}H_{18}N_2$

102.0.6 Molecular Structure:



Databases and inventories where listed: CA65, IARC, IL, MA, MI, PA, CANCERLIT, CCRIS, EINECS, EMICBACK, GENETOX, MESH, RTECS, SUPERLIST, TOXLINE, TSCAINV.

102.1 Chemical and Physical Properties (263)

Physical state	White powder
Melting point	149°C
Solubility	Soluble in ethanol, hot water

102.2 Production and Use

The compound has been used in dyestuff production.

102.4 Toxic Effects

This compound has been tested by oral administration in rats and dogs (227). It led to high incidences of hepatocellular carcinomas in both species, and there were additional tumors of lung, skin, and mammary gland in rats and lung tumors in dogs. Workers exposed to this compound and others in dye production showed a higher risk of bladder cancer (227).

102.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

103.0 4,4'-Methylenebis(2-chloroaniline)

103.0.1 CAS Number: [*101-14-4*]

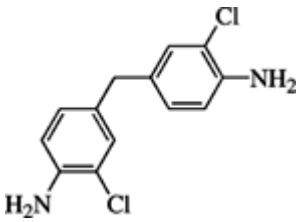
103.0.2 Synonyms: 3,3'-Dichloro-4, 4'-diaminodiphenyl methane; BOCA; bis-amine; Cyanaset; DACPM; MOCA; MBOCA; Curene 442; di(4-amino-3-chlorophenyl)methane; 4, 4'-diamino-3, 3'-dichlorodiphenylmethane; 4, 4'-methylenebis-(2-chlorobenzenamine); *p,p*'-methylenebis(alpha-chloroaniline); methylene-bis-orthochloroaniline; bis-amine A; Cl-mda; curalin M; 4, 4-methylene bis(2-chloroaniline)

103.0.3 Trade Names: NA

103.0.4 Molecular Weight: 267.16

103.0.5 Molecular Formula: $C_{13}H_{12}Cl_2N_2$

103.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, IARC, IL, MA, MI, NJ, NTPA, PA, PELS, REL, RQ, S110, TLV, WHMI, CANCERLIT, CCRIS, DSL, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

103.1 Chemical and Physical Properties (2)

Physical state	Tan solid
Specific gravity	1.44 at 4°C
Melting range	99–110°C
Solubility	Soluble in benzene, ether, ethanol, methyl ethyl ketone, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide; slightly soluble in water

103.2 Production and Use

The major use of 4,4'-methylenebis(2-chloroaniline) (MOCA) is as a curing agent for polyurethane prepolymers where high performance products are required.

103.3 Exposure Assessment

OSHA method #71.

103.4 Toxic Effects

The carcinogenicity of MOCA in animals and its involvement in an increased risk of bladder cancer in humans were reviewed (2, 307). Although MOCA was absorbed through human skin at a level only one-sixth that of MDA, the rate was still sufficient to cause concern (298). As with other aromatic amines, the metabolic process involves acetylation and *N*-hydroxylation (308); then MOCA or a derivative forms DNA adducts (309, 310). Factors such as species, route of administration, and enzyme induction were investigated (310). Use of ^{32}P-postlabeling techniques has facilitated the identification of DNA adducts (311–314). However, in animals, nontarget tissues such as liver often had a higher level of adducts than the target organ (312). The DNA adducts of MOCA differ somewhat from those of analogous amines such as benzidine. The major DNA adduct was identified as *N*-(deoxyadenosin-3',5'-bisphospho-8-yl) 4-amino-3-chlorobenzyl alcohol; the minor one was *N*-(deoxyadenosin–3', 5'-bisphospho-8-yl) 4-amino-3-chlorotoluene. These results indicate that an aromatic ring was cleaved from the molecule with subsequent oxidation to a benzyl alcohol or reduction to a toluene. *N*-OH-MOCA treatment of SV40 immortalized human uroepithelial cells led the cells to convert to a neoplastic form that caused tumors in athymic nude mice (315). It was suggested that an aryl nitrenium ion was the ultimate reactant from MOCA (315).

103.5 Standards, Regulations, or Guidelines Exposure

The current ACGIH TLV-TWA is 0.01 ppm with skin and A2 notations, as a suspect human carcinogen. NIOSH considers it a carcinogen with a REL of 0.003 mg/m^3.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

U. Naphthaleneamines
104.0 1-Naphthylamine
104.0.1 CAS Number: [*134-32-7*]

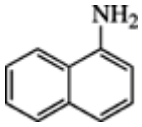
104.0.2 Synonyms: 1-Aminonaphthalene; Fast Garnet B Base; 1-naphthalenamine; alpha-naphthylamine; naphthalidam; naphthalidine; C. I. azoic diazo component 114; fast garnet base b

104.0.3 Trade Names: NA

104.0.4 Molecular Weight: 143.19

104.0.5 Molecular Formula: $C_{10}H_9N$

104.0.6 Molecular Structure:



Databases and inventories where listed: CA65, DOT, IARC, IL, MA, NJ, PA, PEL, REL, RQ, TRI, WHMI, AIDSLINE, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.
104.1 Chemical and Physical Properties (2)

Physical state	White to reddish needles
Density	1.123 (25/25°C)
Melting point	50°C
Boiling point	300.8°C
Vapor density	4.93 (air = 1)
Refractive index	1.6703 (51.2°C)
Solubility	Soluble in ethanol, ether; slightly soluble in hot water

104.2 Production and Use
1-Naphthylamine is used as an intermediate in the synthesis of dyes, antioxidants, herbicides, some drugs, and other chemicals.
104.3 Exposure Assessment
Analytical method NIOSH method 5518 (NMAM IV).
104.4 Toxic Effects
Pure 1-naphthylamine was not carcinogenic in animal tests (2). The commercial material of the past usually contained from 4–10% 2-naphthylamine, a recognized human bladder carcinogen, which accounts for the excess risk of bladder cancer in exposed workers. There has been less research on 1-naphthylamine than some of the other aromatic amines, and most of that has emphasized the formation of glucuronide derivatives. In a rat hepatocyte system, 1-naphthylamine was converted mostly (68%) to the *N*-glucuronide and acetylation occurred to the extent of about 15%. The situation was the reverse for 2-naphthylamine which was mostly acetylated (316). Formation of the

N-glucuronide of 1-naphthylamine by rat and human phenol UDP-glucuronosyltransferase was increased by 3-methylcholanthrene induction (317).

104.5 Standards, Regulations, or Guidelines of Exposure

OSHA in 29CFR 1910.1004 set the level at the lowest feasible level.

105.0 2-Naphthylamine

105.0.1 CAS Number: [*91-59-8*]

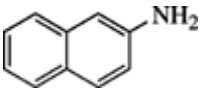
105.0.2 Synonyms: beta-Naphthylamine; NA; BNA; 2-aminonaphthalene; Fast Scarlet Base B; 2-naphthalenamine; 2,6-naphthylamine; C. I. 37270

105.0.3 Trade Names: NA

105.0.4 Molecular Weight: 143.19

105.0.5 Molecular Formula: $C_{10}H_9N$

105.0.6 Molecular Structure:



Databases and inventories where listed: CA65, DOT, IARC, IL, MA, MI, NJ, NTPA, PA, PEL, REL, RQ, TLV, TRI, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, SUPERLIST.

105.1 Chemical and Physical Properties (2)

Physical state	Colorless leaflets (darken)
Density	1.061 (98/4°C)
Melting point	113°C
Boiling point	306.1°C
Refractive index	1.64927 (98.4°C)
Solubility	Soluble in ethanol, ether, benzene; soluble in hot water

105.2 Production and Use

2-Naphthylamine had been used to synthesize dyestuffs and antioxidants. It is now a research chemical.

105.3 Exposure Assessment

NIOSH method #5518 (NMAM IV).

105.4 Toxic Effects

2-Naphthylamine is carcinogenic in animals and is one of the recognized human carcinogens due to its propensity to induce bladder tumors (2, 3, 227). Thus, it is no longer used commercially, but exposure may still occur in some industrial settings. Measurable levels were excreted in the urine by iron foundry workers, possibly through nitronaphthalene formed during foundry processes (318). Immune function in exposed workers was somewhat depressed, as measured according to various types of lymphocytes (319–321).

The *N*-hydroxy derivative of 2-naphthylamine is conjugated with glucuronic acid; the conjugate is transported to the bladder where hydrolysis releases the *N*-hydroxy derivative which is active at the site, probably through an arylnitrenium ion. Research on 2-naphthylamine has emphasized the mechanism of oxidation and glucuronide formation. Oxidation *in vitro* with prostaglandin H synthase indicated two distinct pathways (322). Ring oxygenation can occur by peroxyl radical-mediated attack on the arylamine and by direct transfer of peroxide oxygen from the enzyme to the amine. Horseradish peroxidase yielded polymeric monooxygenated derivatives of 2-naphthylamine

(322). *N*-Glucuronide formation from either the arylamine or the *N*-hydroxy derivative in rat hepatocytes was inducible by 3-methylcholanthrene. In rat hepatocytes, 2-naphthylamine was mostly acetylated; enzyme induction shifted the pattern from *N*-acetylation and some *N*-glucuronide formation to *N*- and C-oxidation (316). As with other aromatic amines, various nucleic adducts have been identified (3). Epidemiologic studies have fully confirmed the carcinogenic effects in humans (323, 324).

105.5 Standards, Regulations, or Guidelines of Exposure

OSHA standard 29CFR 1910.1009 sets the limit at the lowest feasible level, and ACGIH lists the compound as A1, with a note on bladder cancer.

106.0 1,5-Diaminonaphthalene

106.0.1 CAS Number: [*2243-62-1*]

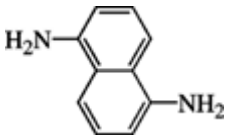
106.0.2 Synonyms: 1,5-Naphthalenediamine

106.0.3 Trade Names: NA

106.0.4 Molecular Weight: 158.20

106.0.5 Molecular Formula: $C_{10}H_{10}N_2$

106.0.6 Molecular Structure:



Databases and inventories where listed: IARC, MA, MI, NTPT, CCRIS, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MESH, RTECS, SUPERLIST, TOXLINE.

106.1 Chemical and Physical Properties (2)

Melting point	190°C
Boiling point	Sublimes
Solubility	Soluble in ethanol, ether, chloroform

106.2 Production and Use

This compound has been used to produce diisocyanates for polyurethane production and some dyes.

106.4 Toxic Effects

An NCI bioassy (1978) in $B6C3F_1$ mice of both sexes, fed diets containing 1000 or 2000 mg/kg for 103 weeks, demonstrated statistically significant increases in *C*-cell carcinomas of the thyroid gland in females, neoplasms of the thyroid gland (follicular cell adenomas and papillary adenomas) in males and females, hepato-cellular carcinomas in females, and alveolar/bronchiolar adenomas and carcinomas in females. In F344 rats of both sexes fed diets containing 500 or 1000 mg/kg for 103 weeks, a statistically significant increase in the incidence of clitoral gland carcinomas was observed (325). 1,5-Naphthalenediamine is also mutagenic to *Salmonella typhimurium* strain TA100 without metabolic activation (204). No further information was located.

Based upon the lack of human data and limited evidence of carcinogenicity in animals, the IARC working group classified 1,5-naphthalenediamine as a Group 3 compound-not classifiable as to its carcinogenicity to humans (227).

106.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

107.0 4,4'-Oxydianiline

107.0.1 CAS Number: [*101-80-4*]

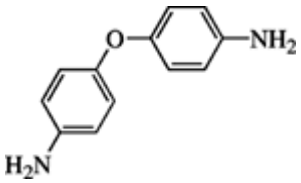
107.0.2 Synonyms: bis (*p*-Aminophenyl) ether; 4-aminophenyl ether; 4,4'-diaminodiphenyloxide; 4,4'-diaminodiphenyl ether; 4,4'-diaminophenyl ether; 4,4'-diaminophenyl oxide; ODA; oxydianiline; oxydi-*p*-phenylenediamine; oxybis(4-aminobenzene); 4,4'-oxydiphenylamine; DADPE; 4,4-dadpe; 4,4'-oxybisbenzenamine

107.0.3 Trade Names: NA

107.0.4 Molecular Weight: 200.24

107.0.5 Molecular Formula: $C_{12}H_{12}N_2O$

107.0.6 Molecular Structure:



Databases and inventories where listed: CA65, IARC, IL, MA, MI, NJ, NTPA, PA, TRI, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, GENETOX, HSDB, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.

107.1 Chemical and Physical Properties (2)

Physical state	Colorless crystals
Melting point	186–187°C
Boiling point	>300°C
Solubility	Soluble in acetone; insoluble in benzene, ethanol, carbon tetrachloride, water

107.2 Production and Use

4,4'-Oxydianiline has been used to produce polyimide resins.

107.4 Toxic Effects

The previous edition outlined the carcinogenic effects noted in rats and mice fed 4,4'-oxydianiline, where the thyroid and liver were target organs (2). Various other smaller scale studies also showed carcinogenic effects (261). 4,4'-Oxydianiline was mutagenic to *Salmonella* strains TA98 and TA100 in the presence of an activating system (261).

107.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

108.0 4-Aminodiphenylamine

108.0.1 CAS Number: [*101-54-2*]

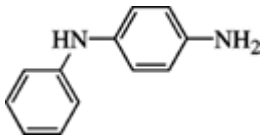
108.0.2 Synonyms: *N*-Phenyl-*p*-phenylenediamine; *p*-anilinoaniline; *N*-phenyl-1, 4-benzenediamine; C. I. azoic diazo component 22; C. I. 37240; acna black df base; azosalt R; C. I. developer 15; C. I. oxidation base 2; C. I. 76085; diphenyl black; fast blue r salt; luxan black R; naphthoelan navy blue; oxy acid black base; peltol br; pelton br ii; *N*-phenyl-*p*-aminoaniline; *p*-semidine; variamine blue salt rt; diphenyl black base P; phenyl 4-aminophenyl amine; *N*-phenyl-1, 4-phenylenediamine; *N*-(4-aminophenyl)aniline

108.0.3 Trade Names: NA

108.0.4 Molecular Weight: 184.24

108.0.5 Molecular Formula: $C_{12}H_{12}N_2$

108.0.6 Molecular Structure:



Databases and inventories where listed: MTL, NTPT, WHMI, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

108.1 Chemical and Physical Properties (2)

Melting point 73–75°C

Boiling point 354°C

108.2 Production and Use

This compound is used as an oxidation dye color in hair dyes (2). It is also promoted as an efficient reagent for oxidase enzymes, including glucose, lactate, xanthine, and lysine oxidases (32).

108.4 Toxic Effects

Alkyl derivatives of 4-aminodiphenylamine sometimes caused sensitization reactions, in keeping with the *p*-phenylenediamine structure.

A bioassay of *N*-phenyl-*p*-phenylenediamine for possible carcinogenicity was conducted by administering the test chemical in the diet to groups of 50 Fischer 344 rats and B6C3F1 mice.

The male and female rats were administered *N*-phenyl-*p*-phenylenediamine at either 600 or 1200 ppm for 78 weeks and were then observed for 26 additional weeks. Groups of 50 mice were initially administered *N*-phenyl-*p*-phenylenediamine at either 2,500 or 5,000 ppm for the males and either 5,000 or 10,00 ppm for the females for 31 weeks. Because of toxicity, the doses were lowered at that time and terminated at 48 weeks and the animals were observed for 43 additional weeks. All surviving mice were killed at 91 weeks.

Mean body weights of the dosed rats were only slightly lower than those of the matched controls during the bioassay but those of the dosed mice were appreciably lower than those of the matched controls. Mortality was high in the dosed groups before reduction of the doses, particularly in the females.

In the male and female rats, the incidences of neoplasms in the groups receiving the test chemical were not significantly different from those in the corresponding control groups.

In the male mice, the incidence of combined hepatocellular adenomas and carcinomas was significantly higher ($p = 0.022$) in the low-dose group than in the controls, but there was no significant dose-related trend and these neoplasms could not be established as being compound related. Unusually extensive hepatic inflammation occurred in large numbers of the dosed males and in lesser numbers of the dosed females. Under the conditions of this bioassay, *N*-phenyl-*p*-phenylenediamine was not carcinogenic for Fischer 344 rats or for B6C3F1 mice (327).

108.5 Standards, Regulations, or Guidelines of Exposure

None assigned.

Aromatic Nitro and Amino Compounds
Elizabeth K. Weisburger, Ph.D., Vera W. Hudson, MS

V. Three-Ring Compounds
109.0 2-Acetylaminofluorene
109.0.1 CAS Number: [*53-96-3*]

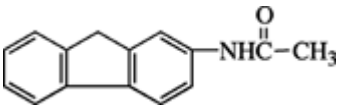
109.0.2 Synonyms: *N*-2-Fluorenylacetamide; N-9H-fluoren-2-yl-acetamide; *N*-acetyl-2-aminofluorene; fluorenylacetamide; *N*-fluoren-2-yl acetamide; 2-acetamidofluorene; 2-acetaminofluorene; 2-fluorenylacetamide; acetoaminofluorene; AAF; 2-AAF; FAA; 2-FAA; acetamidofluorene

109.0.3 Trade Names: NA

109.0.4 Molecular Weight: 223.27

109.0.5 Molecular Formula: $C_{15}H_{13}NO$

109.0.6 Molecular Structure:



Databases and inventories where listed: CAA1, CA65, IL, MA, MI, NJ, NTPA, PA, PEL, REL, RQ, TRI, WHMI, AIDSLINE, CANCERLIT, CCRIS, DART, EINECS, EMIC, EMICBACK, ETICBACK, GENETOX, HSDB, MEDLINE, MESH, RTECS, TOXLINE, TRIFACTS, TSCAINV, SUPERLIST.
109.1 Chemical and Physical Properties (2)

Physical state	White crystals
Melting point	194°C
Solubility	Soluble in ethanol, ether, acetic acid; insoluble in water

109.2 Uses
2-AAF is used as a research chemical.
109.4 Toxic Effects
2-AAF has been the subject of extensive research in many species, has been the basis of structure-activity efforts, and it has been used in model experiments on induction, promotion, and inhibition of chemical carcinogenesis. It also serves as a model compound for investigations in molecular carcinogenesis. Accordingly, any of the recent investigations of acetyltransferases were based on 2-AAF as the model (22–24, 26–28, 328). Similarly, for other transferases (329, 330), DNA adduct formation (331), or other mechanistic aspects of carcinogenesis (332), this compound is the model. Data from the ED_{01} study, where about 25,000 mice were given 2-AAF at various levels have yielded many papers; the data are still being reexamined (333–336). Various reviews on 2-AAF have appeared (34, 337, 338), but realistically the number of papers on 2-AAF and its derivatives (approximately 125 in 5 years) is so large that a review every 5 years or so would be needed to keep research personnel informed.
109.5 Standards, Regulations, or Guidelines of Exposure
Although none have been assigned, 2-AAF was one of the compounds on the original OSHA list of carcinogens in 29CFR1910.1014.
110.0 **N**-Phenyl-2-naphthylamine
110.0.1 CAS Number: [*135-88-6*]

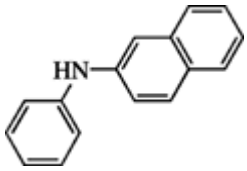
110.0.2 Synonyms: *N*-Phenyl-beta-naphthylamine; *N*-phenyl-2-naphthalenamine; PBNA; phenyl-beta-naphthylamine; Agerite; PBN; aceto pbn; anilinonaphthalene; 2-anilinonaphthalene; antioxidant 116; antioxidant pbn; N-(2-naphthyl)aniline; 2-naphthylphenylamine; beta-naphthylphenylamine; neozon d; neozone; nilox pbna; nonox d; 2-phenyl-aminonaphthalene; phenyl-2-naphthylamine; stabilizator ar; neosone d; vulkanox pbn; nonox dn; *N*-(2-naphthyl)-*N*-phenylamine; stabilizer ar; nocrac d; naftam 2; *N*-beta-naphthyl-*N*-phenylamine; 2-(*N*-phenylamino)naphthalene

110.0.3 Trade Names: NA

110.0.4 Molecular Weight: 219.29

110.0.5 Molecular Formula: $C_{16}H_{13}N$

110.0.6 Molecular Structure:



Databases and inventories where listed: IARC, IL, MA, NTPT, PA, REL, TLV, WHMI, CANCERLIT, CCRIS, DART, DSL, EINECS, EMIC, EMICBACK, ETICBACK, HSDB, MESH, RTECS, TOXLINE, TSCAINV, SUPERLIST.

110.1 Chemical and Physical Properties (202)

Physical state	Gray to tan flakes or powder
Boiling point	395°C
Melting point	108°C
Solubility	Soluble in acetone, benzene, ethanol; insoluble in water

110.2 Production and Use

N-Phenyl-2-naphthylamine has been used as an antioxidant in rubber and other polymers.

110.3 Exposure Assessment

OSHA method #96.

110.4 Toxic Effects

N-Phenyl-2-naphthylamine has been tested for carcinogenicity in various species, including dogs, hamsters, mice, and rats (227). A two-year chronic feeding study in mice and rats, conducted by the NTP, was negative (227), as were other tests in dogs and hamsters. However, this compound remains under a cloud because dogs and humans dephenylated up to 0.03% of a dose to 2-naphthylamine (202, 227). 2-Naphthylamine has induced bladder tumors in animals, is associated with bladder cancer in exposed humans, and was on the original OSHA list of carcinogens.

110.5 Standards, Regulations, or Guidelines of Exposure

None assigned, but ACGIH has an A4 designation for phenyl-2-naphthylamine, with a note on irritation by the compound.

111.0 Triphenylamine

111.0.1 CAS Number: [*603-34-9*]

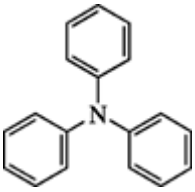
111.0.2 Synonyms: *N*,*N*-Diphenylbenzenamine; triphenyl amine (triphenylene)

111.0.3 Trade Names: NA

111.0.4 Molecular Weight: 245.32

111.0.5 Molecular Formula: $C_{18}H_{15}N$

111.0.6 Molecular Structure:



Databases and inventories where listed: IL, MA, PA, PEL, REL, TLV, WHMI, CCRIS, EINECS, EMICBACK, HSDB, RTECS, TOXLINE, TSCAINV, SUPERLIST.

111.1 Chemical and Physical Properties (2)

Specific gravity	0.774 (0°C)
Melting point	127–129°C
Solubility	Soluble in benzene, ether
Boiling point	348°C

111.2 Production and Use

Triphenylamine is used as a photoconductor on polymer film (2).

111.4 Toxic Effects

The previous edition gave data on acute toxicity which is low; the LD_{50} in rats was 3200–6400 mg/kg; in mice it was 1600–3200 mg/kg.

111.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV and NIOSH REL is 5 mg/m^3; there is no carcinogenicity designation because of the lack of a long-term test. Irritation is noted as the reason for the TLV.

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5 Conclusions

Besides the amino and nitro compounds discussed in the preceding sections, there are still others that are employed in research on mechanisms of various toxic effects.

3,2'-Dimethyl-4-aminobiphenyl leads to colon tumors in rodents; it is being used as a model to study any relationship between acetylator genotype and sequential steps in colon carcinogenesis (339, 340). Still other arylamines are unusual in their actions; 2-anthramine (2-aminoanthracene) is one of few aromatic amines to cause skin tumors when painted on rats or hamsters, but the mechanism of its action has not been elucidated (3). The nitroarenes in engine exhaust are models for investigating structure-activity relationships and the enzyme systems involved in the activation of these compounds (341, 342). However, the diversity of effects attributed to aryl nitro and amino compounds cannot consistently be explained on the basis of structure. Minimal changes often lead to marked differences in response. Furthermore, the correlation between mutagenicity and carcinogenicity is not absolute. And despite having a common moiety, the amino group, activation pathways for some of the carcinogenic arylamines differ.

The reactivity of aryl nitro and amino compounds makes them useful in the preparation of many valuable substances, including drugs, dyes, pesticides, and polymers. Reactivity with constituents of living tissue is also the reason for their toxicity, thus the need to avoid exposure and to observe the

exposure limits set by regulatory and other agencies.

Aromatic Nitro and Amino Compounds

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Aromatic Amino and Nitro–Amino Compounds and their Halogenated Derivatives
Yin-Tak Woo, Ph.D., DABT, David Y. Lai, Ph.D., DABT

General Overview
1.0 Introduction
Aromatic amines are organic compounds that contain at least one amino group attached directly to an aryl moiety. Aromatic amines represent one of the most important classes of industrial and environmental chemicals. Many aromatic amines have been shown to be potent carcinogens and mutagens and/or hemotoxicants capable of inducing methemoglobinemia. Since the introduction of substituted anilines and naphthylamines as intermediates for the manufacture of azo dyes in the mid-1800s, aromatic amines have found numerous uses in various industries. Substantial worker exposure to aromatic amines with subsequent induction of bladder cancer occurred before preventive measures were instituted. Beyond occupational exposure, humans may also be exposed to aromatic amines through environmental sources. At least three carcinogenic aromatic amines (4-aminobiphenyl, 2-naphthylamine, and *o*-toludine) have been detected in cigarette smoke. Many commonly used pharmaceuticals contain or are aromatic amines. Owing to their hazard potential, aromatic amines have been the subject of many biomonitoring studies, making them model compounds in molecular dosimetry and epidemiology studies. Since extensive information is available on the metabolic pathways and, to a lesser extent, the mechanism(s) of action, aromatic amines have also become targets for genetic polymorphism studies with ultimate goals of identifying susceptible subpopulations, and designing of strategies for cancer prevention and intervention. The multifaceted interest in aromatic amines has continued to attract a tremendous amount of scientific studies and attention. Since the publication of the previous edition of Patty's on aromatic amines (1), many reviews and important research articles on aromatic amines have been published (2–102). In this chapter, we present an overview of the aromatic amine class as a whole with emphasis on recent studies, followed by an updated description on individual chemicals grouped into seven subgroups of structurally related compounds.
1.1 Production and Uses
After peaking during the past two decades, recent worldwide production and sales volume for aromatic amines have been growing only at the average rate of expansion of the chemical market as a whole. United States production of many aromatic amines has been declining or even ceased. Table 58.1 summarizes the recent estimates of U.S. production/import volume range of most of the aromatic amines covered in this chapter (103). Estimated worldwide production volumes of individual aromatic amines are also covered under discussion on specific chemicals when the information is available. In general, the supply of many aromatic amines is shifting from United States to East Asian countries along with textile and dye production (104).

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Specific Compounds
The compounds covered in this chapter are grouped into seven subgroups of structurally related

compounds: (1) aniline and derivatives, (2) toluidines and derivatives, (3) aminophenols and nitroaminophenols, (4) phenylenediamines and derivatives, (5) toluenediamines, (6) chlorinated nitrobenzene compounds and (7) bicyclic and tricyclic aromatic amines.

Aromatic Amino and Nitro–Amino Compounds and their Halogenated Derivatives

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A. Aniline and Derivatives

Aniline is the simplest of the aromatic amines with an amino group attached to a benzene. Aniline derivatives that are also widely used in industry as intermediates in chemical synthesis include *N*-alkyl-, *N,N*-dialkyl, nitro-, chloro-, and chloronitro-aniline. Aniline and its derivatives are hematotoxic and have a similar pattern of toxicity. Acute poisoning in humans and animals is manifested by symptoms secondary to methemoglobinemia; several of them have been shown to be potent methemoglobin-forming agents. Animal studies have shown that aniline and its monochloro derivatives are also nephrotoxic and hepatotoxic. In general, alkyl derivatives are less toxic than aniline; however, addition of chloro and nitro groups on the phenyl ring may increase the toxicity of aniline. For instance, a comparative nephrotoxicity study of aniline with its monochloro derivatives, *o-, m-*, and *p*-chloroaniline, has shown that chloro substituents on the phenyl ring of aniline increased the nephrotoxic potential of aniline, the *ortho* substitution producing the greatest enhancement. All three choroaniline isomers are hematotoxic in rodents, with rats being more sensitive than mice and with the relative toxicities following the order *p*- > *m*- > *o*-isomer. In genotoxicity assays, *p*-chloroaniline has been shown to yield positive results in virtually all assays, whereas only mixed results have been obtained on the *o*, and *m*-isomers (154). *m*-Nitro, *o*-chloro-, *m*-chloro, and 2,4-dichloroanilines are also irritants to the skin and mucous membrane. Several dichloro-anilines have been demonstrated to be skin sensitizers. Except for *p*-nitroaniline, there is no evidence that these compounds are reproductive or developmental toxicants. They are inactive in most mutagenicity tests in *Salmonella typhimurium* (except in strain TA98 with a co-mutagen), but have been shown to induce gene mutations and chromosomal aberrations in other genotoxicity assay systems. Although there is limited or equivocal evidence of carcinogenicity in rodent studies, they are considered suspect human carcinogens.

2.0 Aniline

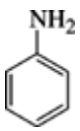
2.0.1 CAS Number: [*62-53-3*]

2.0.2–2.0.3 Synonyms and Trade Names: Benzamine, aniline oil, phenylamine, aminobenzene, phenylamine, aminophen, kyanol, benzidam; blue oil, C.I. 76000, C.I. oxidation base 1, cyanol, krystallin, anyvim, and arylamine

2.0.4 Molecular Weight: 93.128

2.0.5 Molecular Formula: C_6H_7N

2.0.6 Molecular Structure:



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B. Toluidines

Toluidines are aromatic amines with an amino group and a methyl group attached to benzene. There are three toluidine isomers: *o*-, *m*-, and *p*-toluidines, designated with respect to the positions of the amino group and the methyl group. They are used primarily as intermediates in the manufacture of azodyes for the textile industry. Major clinical signs of toxicity observed in humans exposed to toluidines and their chloro and nitro derivatives are methemoglobinemia and hematuria. Toluidines are suspected human carcinogens, with *o*-toluidine being the strongest suspect. An excess of bladder tumors has often been found in workers exposed to varying combinations of dyestuffs containing toluidines. In experimental studies, significant increases of multiple-site tumor incidence have been observed in rats and/or mice on chronic administration of various toluidines in the diet.

22.0 **o**-Toluidine

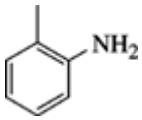
22.0.1 CAS Number: [*95-53-4*]

22.0.2–22.0.3 Synonyms and Trade Names: C.I. 37077, *o*-methylaniline, 2-methyl-1-aminobenzene, 2-methylaniline, 2-methylbenzenamine, 2-aminotoluene, 1-amino-2-methylbenzene, 2-amino-1-methylbenzene, 1-methyl-2-aminobenzene, *o*-tolylamine, and methyl-2-aminobenzene

22.0.4 Molecular Weight: 107.15

22.0.5 Molecular Formula: C_7H_9N

22.0.6 Molecular Structure:



22.1 Chemical and Physical Properties

o-Toluidine is a light yellow to reddish brown liquid. It has a density of 0.9984 (20/4°C), a melting point of –14.7°C, a boiling point of 200.2°C, a refractive index of 1.57276 (20°C), and a flash point of 86°C (closed cup). It is slightly soluble in water and soluble in alcohol and ether (155, 156).

22.2 Production and Use

Commercial production was first reported in the United States in 1922 for *o*-toluidine and in 1956 for *o*-toluidine hydrochloride. In 1983, U.S. production of *o*-toluidine was between 11 and 21 million pounds; 34 companies were identified as suppliers. In 1990, two suppliers of *o*-toluidine and ten suppliers of *o*-toluidine hydrochloride were identified; no production volumes are available (60). *o*-Toluidine and its hydrochloride salt are used primarily as an intermediate in the manufacture of dyes, including azo pigment dyes, triarylmethane dyes, sulfur dyes, and indigo compounds. These dyes are used primarily for printing textiles, in color photography, and as biologic stains. *o*-Toludine is also used as an intermediate for rubber vulcanizing chemicals, pharmaceuticals, and pesticides.

The greatest potential for exposure to *o*-toluidine and its hydrochloride salt are dyemakers and pigment makers through inhalation and dermal contact in the workplace. The National Occupational Hazard Survey estimated that from 1972 to 1974, 13,053 workers were potentially exposed to *o*-toluidine. The National Occupational Exposure Survey conducted from 1981 to 1983 indicated that 5,440 workers were exposed to *o*-toluidine. A total of 54,000 pounds of *o*-toluidine were reported to be released to the environment by 17 industrial facilities in the United States in 1990 (60). *o*-Toluidine is also present in cigarette smoke and is a metabolite of the local anesthetic prilocaine

(177).

22.3 Exposure Assessment

22.3.3 Workplace Methods The recommended method for determining workplace exposures to *o*-toluidine is NIOSH Analytical Method 2002 (111a).

22.3.5 Biomonitoring/Biomarkers An increased level of methemoglobin measured in blood of workers is a nonspecific indicator of exposure to methemoglobin-inducing chemicals, including *o*-toluidine. Investigations regarding other possible biomonitoring methods have recently demonstrated that *o*-toluidine binds to both albumin and hemoglobin and that a linear dose relationship exists for hemoglobin (178). Additionally, the biologic half-lives for the protein adducts are several times that reported for elimination of *o*-toluidine or its metabolites via the urine, thus providing evidence that these proteins may be valuable biomarkers of exposure to *o*-toluidine in the occupational setting (178). The formation of hemoglobin adduct has recently been developed as a biomonitoring method to assess worker exposure to *o*-toluidine in a chemical plant with known bladder cancer excess (93).

22.4 Toxic Effects

The oral LD_{50} in rats is reported to be 900–940 mg/kg; that of the hydrochloride salt, diluted in water, in rats is 2950 mg/kg (179). Oral, dermal, or respiratory tract absorption of *o*-toluidine can result in methemoglobinemia, reticulocytosis, hematuria, skin and eye irritation, and irritation of the epithelium of kidneys and bladder (163, 179).

o-Toluidine was reported to yield positive results in a variety of mutagenicity and related assays, which included Ames *Salmonella*, *in vitro* chromosome aberration, *in vitro* sister chromatid exchange (SCE), mouse lymphoma cell mutation, *in vitro* cell transformation, and *in vitro* unscheduled DNA synthesis tests (100, 116). It also caused somatic mutation in *Drosophila* but was negative in *in vivo* mouse micronucleus test (116).

An IARC working group (111) reported that there were not adequate data to evaluate the carcinogenicity of *o*-toluidine hydrochloride in humans. Although an excess of bladder tumors has often been found in workers exposed to varying combinations of dyestuffs, no population of workers exposed to *o*-toluidine alone has been described, and either the data were insufficient, or insufficient followup time has prevented a clear association being made with the exposure. An excess number of bladder cancers has recently been reported in workers exposed to *o*-toluidine and aniline; the authors concluded that it is more likely that *o*-toluidine is responsible for the observed excess number of cases of bladder cancer, although aniline may have played a role (93, 180).

There is sufficient evidence for the carcinogenicity of *o*-toluidine (as the hydrochloride salt) in experimental animals. When administered in the diet, *o*-toluidine induced various types of tumors in multiple sites, including hepatocellular carcinomas or adenomas in female mice and hemangiosarcomas at multiple sites in male mice of one strain, hemangiosarcomas and hemangiomas of the abdominal viscera in both sexes of another strain, increased incidences of sarcomas of multiple organs in rats of both sexes and mesotheliomas in male rats, and carcinomas of the urinary bladder in female rats (111).

22.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Forty-eight hours after the subcutaneous injection of a single dose of 400 mg/kg body weight *o*-[methy- ^{14}C]-toluidine hydrochloride to male Fischer 344 rats, 83.9% of the ^{14}C appeared in the urine, 3.3% in the feces, and 1.4% was exhaled as $^{14}CO_2$. Various hydroxy- and N-acetyl derivatives were identified as urinary metabolites (111).

22.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV-TWA adopted by ACGIH is 2 ppm with skin notation; the compound is considered a confirmed animal carcinogen with unknown relevance to humans (A3 classification) by the ACGIH (160). The OSHA exposure limit is 5 ppm. NIOSH considers this compound to be an occupational carcinogen (110) and recommends appropriate worker protection. The NIOSH immediately dangerous to life or health concentration (IDLH) is 50 ppm (110).

23.0 **m**-Toluidine
23.0.1 CAS Number: [*108-44-1*]

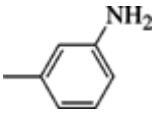
23.0.2 Synonyms: *m*-Tolylamine; 3-methylbenzenamine, 3-aminophenylmethane, 3-methylaniline, *m*-toluamine, and *m*-aminotoluene

23.0.3 Trade Names: NA

23.0.4 Molecular Weight: 107.15

23.0.5 Molecular Formula: C_7H_9N

23.0.6 Molecular Structure:



23.1 Chemical and Physical Properties
m-Toluidine is a liquid. It has a melting point of –30°C, a boiling point of 203.3°C, and a vapor pressure of 1 torr at 41°C. It is slightly soluble in water, soluble in alcohol, ether, acetone, and benzene (155, 156).
23.2 Production and Use
The major uses of *m*-toluidine and its hydrochloride are as intermediates in the manufacture of dyes and other chemicals. Production has been limited because its nonplanar configuration, due to steric hindrance, limits its use in direct dyes. It is used in only 12 dyes; none is of major importance (181).

Exposure to *m*-toluidine is primarily occupationally via inhalation and dermal contact. *m*-Toluidine may be released in wastewater during its production and use in the manufacture of dyes and other chemicals.
23.3 Exposure Assessment
23.3.5 Biomonitoring/Biomarkers An increased level of methemoglobin measured in blood of workers is a nonspecific indicator of exposure to methemoglobin-inducing chemicals including *m*-toluidine.
23.4 Toxic Effects
Clinical signs of intoxication in humans include methemoglobinemia and hematuria; it is absorbed orally, dermally, and via the respiratory tract. There are no epidemiologic studies on workers who have been exposed only to *m*-toluidine. The oral LD_{50} of *m*-toluidine (rats) is reported to be 974 mg/kg (179).

In an 18-mo carcinogenicity diet evaluation in male CD rats (8,000 ppm for 3 mo, then 4,000 ppm for an additional 15 mo; or 16,000 ppm for 3 mo, then 8,000 for an additional 15 mo), and male and female CD-1 mice (16,000 ppm for 5 mo, then 4,000 ppm in males and 8,000 ppm in females for an additional 13 mo; or 32,000 ppm in both sexes for 5 mo and then 8,000 ppm in males and 16,000 ppm in females for additional 13 mo), there was no evidence of a significant increase of incidence of any kind of tumor in the rats, and only a significant increase in liver tumors in male mice (182).
23.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA is 2 ppm, with a skin notation (160).
24.0 **p**-Toluidine
24.0.1 CAS Number: [*106-49-0*]

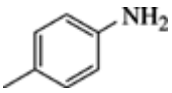
24.0.2–24.0.3 Synonyms and Trade Names: 4-Aminotoluene, 4-methylaniline, naphthol as-kgll, and

4-methylbenzenamine

24.0.4 Molecular Weight: 107.15

24.0.5 Molecular Formula: C_7H_9N

24.0.6 Molecular Structure:



24.1 Chemical and Physical Properties
p-Toluidine occurs in the form of plates or leaflets. It has a melting point of 43°C, a boiling point of 201.5°C, a refractive index of 1.5532 (59.1°C), a flash point of 86°C (closed cup), and a vapor pressure of 1 torr at 42°C. It is slightly soluble in water and soluble in alcohol, ether, acetone, methanol, or carbon disulfide. It has an aromatic, winelike odor and a burning taste (155, 156).
24.2 Production and Use
p-Toluidine and its hydrochloride are used primarily in the synthesis of dyes and in the preparation of ion exchange resins. No information on production volumes is available.

Exposure to *p*-toluidine is primarily occupationally via inhalation and dermal contact. *p*-Toluidine may be released in wastewater during its production and use in the manufacture of dyes and other chemicals. It is also released during the thermal degradation of polyurethane products.
24.3 Exposure Assessment
24.3.3 Biomonitoring/Biomarkers An increased level of methemoglobin measured in blood of workers is a nonspecific indicator of exposure to *p*-toluidine, which is a potent methemoglobin inducer.
24.4 Toxic Effects
Clinical signs of toxicity in humans include anoxic methemoglobinemia and hematuria. It is absorbed orally, dermal, and via the respiratory tract. There are no epidemiologic studies reported on workers who have been exposed only to *p*-toluidine. The oral LD_{50} of *p*-toluidine is 656 mg/kg in rats and 794 mg/kg in mice; its hydrochloride salt in water was 1285 mg/kg in rats; the LD_{50} (rabbit dermal) is 890 mg/kg (179).

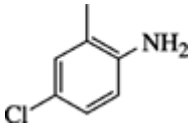
In an 18-mo *p*-toluidine hydrochloride diet carcinogenicity study, male CD rats (1000 and 2000 ppm for 18 mo) did not develop statistically significant increases of tumors; however, CD-1 male and female mice (1000 ppm for 6 mo and then 500 ppm for an additional 12 mo; or 2000 ppm for 6 mo and then 1000 ppm for an additional 12 mo) showed significant increases in liver carcinomas, in males in both dose levels and in females in the high-dose level (182).
24.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV-TWA is 2 ppm (approximately 9 mg/m^3) with skin notation; it is classified as a confirmed animal carcinogen with unknown relevance to humans (A3 classification) by the ACGIH (160).
25.0 4-Chloro-**o**-toluidine
25.0.1 CAS Number: [*95-69-2*]

25.0.2–25.0.3 Synonyms and Trade Names: para-Chloro-ortho-toluidine, 4-chloro-2-methylaniline, 4-chloro-2-methylbenzenamine, 2-amino-5-chlorotoluene, azoene fast red tr base, brentamine fast red tr base, 5-chloro-2-aminotolueue, 4-chloro-6-methylaniline, daiz red base tr, deval red k, deval red tr, deazo fast red tra, fast red base tr, fast red 5ci base, fast red tr 11, fast red tro base, kako red tr base, kambamine red tr, 2-methyl-4-chloroaniline, mitsui red tr base, red base nir, red tr base, sonya fast red tr base, and tula base fast red tr

25.0.4 Molecular Weight: 141.60

25.0.5 Molecular Formula: C_7H_8ClN

25.0.6 Molecular Structure:



25.1 Chemical and Physical Properties
4-Chloro-*o*-toluidine occurs in the form of leaflets. It has a melting point of 27°C and a boiling point of 241°C. It is soluble in alcohol (155, 156).
25.2 Production and Use
Commercial production of 4-chloro-*o*-toluidine was first reported in the United States in 1939. However, production has been stopped since 1979, and all importation was discontinued in 1986. The U.S. International Trade Commission (USITC) reported that 89,753 pounds of 4-chloro-*o*-toluidine and its hydrochloride salt were imported in 1980, 83,098 pounds in 1981, 31,747 pounds in 1982, and 44,147 pounds in 1983 (112). It is used as an azo coupler in the synthesis of azo dyes used in the textile industry and for the manufacture of the insecticide chlordimeform (3, 112).

The greatest potential for exposure to 4-chloro-*o*-toluidine and its hydrochloride salt are dyemakers, pigment makers, and manufacturers of chloridimeform through inhalation and dermal contact in the workplace. The National Occupational Hazard survey, conducted by NIOSH from 1972 to 1974, estimated that 1379 workers were potentially exposed to 4-chloro-*o*-toluidine. The National Occupational Exposure survey (1981–1983) indicated that 1357 workers, including 675 women, were potentially exposed to 4-chloro-*o*-toluidine and 4-chloro-*o*-toluidine hydrochloride. As a decomposition product of chlordimeform, 4-chloro-*o*-toluidine has been identified in field samples of plant materials treated with chlordimeform, a potential source of human exposure to 4-chloro-*o*-toluidine by the ingestion route (112).
25.3 Exposure Assessment
25.3.3 Biomonitoring/Biomarkers An increased level of methemoglobin measured in blood of workers is a nonspecific indicator of exposure to methemoglobin-inducing chemicals, including 4-chloro-*o*-toluidine. Hemoglobin adduct formation has been demonstrated in rats exposed to 4-chloro-*o*-toluidine and may be used as a dosimeter for human exposure to the chemical (73).
25.4 Toxic Effects
The intraperitoneal LD_{50} of 4-chloro-*o*-toluidine hydrochloride was 560–700 mg/kg in rats and 680–720 mg/kg in mice. Hematuria and hemorrhagic cystitis have been reported in workers exposed to 4-chloro-*o*-toluidine (112). 4-Chloro-*o*-toluidine has been demonstrated to be genotoxic in a variety of prokaryotic and mammalian *in vitro* and *in vivo* test systems (112).

According to the IARC working group, limited human evidence and sufficient animal data are available to classify this agent a Group 2A compound and therefore probably carcinogenic to humans (112, 116). Between 1982 and 1990, 7 cases of urinary bladder cancer were detected in a group of 49 workers producing the insecticide chlordimeform from 4-chloro-*o*-toluidine on an irregular basis for an average of 18 years. The incidence of bladder tumors in these workers was significantly higher than that of the cancer registers. In other studies, increased incidences of cancer were also observed in workers exposed to 4-chloro-*o*-toluidine and several other compounds that are known or suspected carcinogens.

In experimental studies, a significant increase in hemangiosarcomas or hemangiomas was observed in both sexes of two strain of mice on chronic administration of 4-chloro-*o*-toluidine hydrochloride

in the diet (112, 116).

25.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Following oral administration of [^{14}C-methyl]-4-chloro-*o*-toluidine to male and female rats, 71% of the administered radioactivity was eliminated in the urine and 24.5% in the faeces within 72 h. 4-Chloro-*o*-toluidine binding to DNA was demonstrated *in vitro* with calf thymus DNA and *in vivo* when it was administrated by intraperitoneal injection to rats (112).

25.5 Standards, Regulations, or Guidelines of Exposure

OSHA regulates 4-chloro-*o*-toluidine and 4-chloro-*o*-toluidine hydrochloride under Hazard Communication Standard. 4-Chloro-*o*-toluidine hydrochloride is regulated as a hazardous constituent of waste under the Resource Conservation and Recovery Act (RCRA) and is subject to reporting/recordkeeping requirements under RCRA and Section 313 of the Emergency Planning and Community Right-to-Know Act of EPA. The Toxic Substances Control Act (TSCA) of the EPA also subjects 4-chloro-*o*-toluidine and its hydrochloride salt to reporting requirements applicable to any significant new use (60).

26.0 5-Chloro-**o**-toluidine

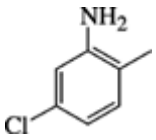
26.0.1 CAS Number: [*95-79-4*]

26.0.2–26.0.3 Synonyms and Trade Names: 5-Chloro-2-methylaniline, 5-chloro-2-methylbenzenamine, 2-amino-4-chlorotoluene, 1-amino-3-chloro-6-methylbenzene, 4-chloro-2-aminotoluene, 3-chloro-6-methylaniline, acco fast red kb base, ansibase red kb, azoic diazo component 32, azoene fast red kb base, fast red kb amine, fast red kb base, fast red kb salt, fast red kb salt supra, fast red kbs salt, genazo red kb soln, hiltonil fast red kb base, lake red bk base, metrogen red former kb soln, naphthosol fast red kb base, pharmazoid red kb, red kb base, spectrolene red kb, stable red kb base, C.I. Azoic Diazo Component No. 32, C.I. 37090, 2-methyl-5-chloroaniline, and 5-chloro-2-methyl-benzamine

26.0.4 Molecular Weight: 141.60

26.0.5 Molecular Formula: C_7H_8ClN

26.0.6 Molecular Structure:



26.1 Chemical and Physical Properties

5-Chloro-*o*-toluidine has a melting point of 22°C and a boiling point of 237°C (155, 156).

26.2 Production and Use

Specific production volumes for 5-chloro-*o*-toluidine are not available. In 1977, the compound and its hydrochloride salt were produced or sold in excess of 1,000 pounds by one U.S. company. In 1974, U.S. imports of 5-chloro-*o*-toluidine amounted to 42,163 pounds. 5-Chloro-*o*-toluidine is used as an azo coupler in the synthesis of azo dyes used in the textile industry (3).

The greatest potential for exposure to 5-chloro-*o*-toluidine is for workers in the chemical and dye manufacturing and textile industries.

26.3 Exposure Assessment

26.3.3 Biomonitoring/Biomarkers Hemoglobin adduct formation has been demonstrated in rats exposed to 5-chloro-*o*-toluidine and may be useful dosimeter for human exposure (73).

26.4 Toxic Effects

No specific acute toxicity data for 5-chloro-*o*-toluidine are available. The compound may induce a similar spectrum of toxicity as other toluidines. The chloro derivatives of toluidines are generally

more potent than toluidines in producing methemoglobinemia and hematuria.

A bioassay for the possible carcinogenicity of 5-chloro-*o*-toluidine was conducted using Fischer 344 rats and B6C3F$_1$ mice. Groups of 50 male and 50 female rats and mice were given 5-chloro-*o*-toluidine in the diet at 2500 or 5000 ppm for rats and 2000 or 4000 ppm for mice. The compound was administered for 78 wk to both rats and mice, followed by an observation period of up to 26 wk for rats and 13 wk for mice. Under the conditions of this bioassay, 5-chloro-*o*-toluidine was carcinogenic to the mice, inducing hemangiosarcomas and hepatocellular carcinomas in both males and females. There was no conclusive evidence of the carcinogenicity of the compound in the rats (183).

26.5 Standards, Regulations or Guidelines of Exposure

No information is available.

27.0 6-Chloro-**o**-toluidine

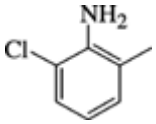
27.0.1 CAS Number: [*87-63-8*]

27.0.2–27.0.3 Synonyms and Trade Names: 6-Chloro-2-methylaniline, 2-chloro-6-methylaniline, 2-chloro-6-methylbenzenamine, 2-amino-3-chlorotoluene, and 6-chloro-2-toluidine

27.0.4 Molecular Weight: 141.60

27.0.5 Molecular Formula: C_7H_8ClN

27.0.6 Molecular Structure:



6-Chloro-*o*-toluidine has a melting point of 2°C, a boiling point of 215°C, and a flash point of 98°C. It is soluble in water and has a specific gravity of 1.152.

28.0 5-Nitro-**o**-toluidine

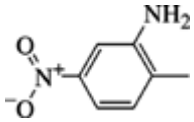
28.0.1 CAS Number: [*99-55-8*]

28.0.2–28.0.3 Synonyms and Trade Names: 2-methyl-5-nitrobenzenamine; 2-methyl-5-nitroaniline; 2-amino-4-nitrotoluene; 1-amino-2-methyl-5-nitrobenzene; 4-nitro-2-aminotoluene; amarthol fast scarlet g base; amarthol fast scarlet g; salt; azoene fast scarlet gc base; azoene fast scarlet gc salt; azofix scarlet g salt; azogene fast scarlet g; C.I. 371.05; C.I. azoic diazo component 12; dainichi fast scarlet g base; daito scarlet base g; devol scarlet b; devol scarlet g salt; diabase scarlet g; diazo fast scarlet g; fast red sg base; fast scarlet base g; fast scarlet base j; fast scarlet g; fast scarlet g base; fast scarlet gc base; fast scarlet j salt; fast scarlet mN4t base; fast scarlet t base; hiltonil fast scarlet g base; hiltonil fast scarlet gc base; hiltonil fast scarlet g salt; kayaku scarlet g base; lake scarlet g base; lithosol orange r base; mitsui scarlet g base; naphthanil scarlet g base; naphtoelan fast scarlet g base; naphtoelan fast scarlet g salt; PNOT; scarlet base ciba ii; scarlet base irga ii; scarlet base nsp; scarlet g base; sugai fast scarlet g base; symulon scarlet g base; Fast Red G Base; C.I. Azoic Diazo Component No. 12.

28.0.4 Molecular Weight: 152.15

28.0.5 Molecular Formula: $C_7H_8N_2O_2$

28.0.6 Molecular Structrure:



28.1 Chemical and Physical Properties
5-Nitro-*o*-toluidine occurs in the form of yellow monclinic prisms. It has a melting point of 107.5°C. It is soluble in acetone, benzene, chloroform, diethyl ether, and ethanol (155, 156).
28.2 Production and Use
Production of 5-nitro-*o*-toluidine in the United States was reported to 180 ton in 1972 and 57 ton in 1975 (112). It has been used as a precursor in the synthesis of a wide varieties of azo dyes. It is also used as a coupling component in the synthesis of organic textile dyes such as Naphthol Red M. The nitro moiety serves as a chromophore (in common with other groups such as nitroso, carbonyl, thiocarbonyl, azo, azoxy, azomethine, and ethenyl, in which the double bonds contribute to the absorption of visible light); the amino group serves as an auxochrome (in common with other groups such as alkylamino, dialkylamine, methoxy, or hydroxy), which functions by intensifying or modifying the color (184).

The greatest potential for exposure to 5-nitro-*o*-toluidine is for workers at dye manufacturing facilities.
28.3 Exposure Assessment
28.3.3 Biomonitoring/Biomarkers An increased level of methemoglobin measured in blood of workers is a nonspecific indi cator of exposure to methemoglobin-inducing chemicals, including 5-nitro-*o*-toluidine.
28.4 Toxic Effects
Methemoglobinemia was induced in guinea pigs and cats after IP injection of the compound (112). It is also the major toxic effect observed in workers following excessive exposure. In addition, upon dermal contact the compound may irritate the skin and cause dermatitis. 5-Nitro-*o*-toluidine has been demonstrated to be genotoxic in a variety of prokaryotic and mammalian *in vitro* and *in vivo* test systems (112). There are no data available for evaluating carcinogenic risk to humans. When 5-nitro-*o*-toluidine was administered as a dietary feeding study to F344 rats (50 or 100 ppm) and B6C3F1 mice (1200 or 2300 ppm) of both sexes, hepatocellular carcinomas were produced in mice but not in rats (185).
28.5 Standards, Regulations, or Guidelines of Exposure
No information is available.

Aromatic Amino and Nitro–Amino Compounds and their Halogenated Derivatives
Yin-Tak Woo, Ph.D., DABT, David Y. Lai, Ph.D., DABT

C. Aminophenols and Nitroaminophenols
Aminophenols and nitroaminophenols are widely used for manufacture of dyes and pharmaceuticals. They are also directly used, along with many other chemicals, as ingredients of hair dyes/colorants and related products and therefore may lead to occupational and consumer exposure. The International Agency for Research on Cancer (37) has extensively reviewed various epidemiological and case-control studies showing excess risk for cancer of the urinary bladder in male hairdressers and barbers and possible excess risk for cancer of the lung and other target sites and concluded that there is evidence, albeit somewhat limited, that occupation as a hairdresser or barber entails exposures that are probably carcinogenic (Group 2A). In contrast to professional exposure, there is inadequate evidence to evaluate the carcinogenic risk of personal use of hair dyes/colorants.

In general, the introduction of the hydrophilic hydroxy group to aromatic amines is expected to decrease its absorption and increase its excretion and therefore may appear to be detoxifying in nature. However, if the hydroxy group is *ortho* or *para* to the amino group, highly reactive and toxic quinoneimine intermediates may be generated after oxidation. The introduction of an additional nitro group to aminophenol may yield an additional amino group via reduction or may confer acute toxicity by acting as an uncoupler of oxidative phosphorylation.

29.0 **o**-Aminophenol

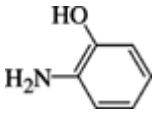
29.0.1 CAS Number: [*95-55-6*]

29.0.2–29.0.3 Synonyms and Trade Names: 2-Aminophenol, 2-amino-1-hydroxybenzene, basf ursol 3ga, benzofur gg, C.I. 76520, C.I. oxidation base 17, fouramine op, *o*-hydroxyaniline, nako yellow 3ga, paradone olive green b, pelagol 3ga, pelagol grey gg, zoba 3ga, and 2-aminobenzenol

29.0.4 Molecular Weight: 109.13

29.0.5 Molecular Formula: C_6H_7NO

29.0.6 Molecular Structure:



29.1 Chemical and Physical Properties

o-Aminophenol occurs as colorless, odorless rhombic needles or plates that readily become grayish or yellowish brown upon exposure to air and light. It has a molecular weight of 109.13, a density of 1.33 g/cm^3 and a melting point of 175°C and is sublimable. It is soluble in water (2 g/100 mL cold water), alcohol (5 g/100 mL), freely soluble in ether, and slightly soluble in benzene (155, 186).

29.2 Production and Use

There is a scarcity of production data on aminophenols because they are often reported as aniline derivatives (186). *o*-Aminophenol is used as an azo and sulfur dye intermediate and for dyeing fur and hair; it is widely used in the cosmetics, dye, and drug industries.

Occupational exposure may occur to hairdressers, barbers, and dye workers. Occasional exposure may also occur through personal use of hair dyes/colorants.

29.3 Exposure Assessment

Biomonitoring data are not available.

29.4 Toxic Effects

o-Aminophenol is not readily absorbed through intact skin but may prove to be a sensitizing agent with resultant contact dermatitis. When inhaled in excessive amounts, it may cause methemoglobinemia as well as bronchial asthma. Intraperitoneal administration (100–200 mg/kg) to Syrian golden hamsters on day 8 of gestation produced a significant teratogenic response similar to that of *p*-aminophenol (see section 31), including neural tube defects (exencephaly, encephalocele, and spina bifida), eye defects, and skeletal defects (129). However, no teratogenicity study by the oral route of administration was found. The compound was reported to be mutagenic in the Ames test (100).

29.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Aminophenols are generally metabolized by *N*-acetylation with the relative rate following the order *p*- > *m*- > *o*- (187). The phenolic group may also be conjugated (e.g., glucuronide) to facilitate excretion. Reactive electrophilic quinoneimine derivatives may be formed by oxidation of *o* or *p* isomer but not the *m* isomer. The oxidation product of *o*-aminophenol has been shown to bind to protein; however, there was no evidence of binding to nucleic acids (188).

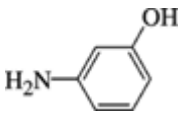
29.5 Standards, Regulations, or Guidelines of Exposure
There is no information on setting of hygienic standards of permissible exposure
30.0 **m**-Aminophenol
30.0.1 CAS Number: [*591-27-5*]

30.0.2–30.0.3 Synonyms and Trade Names: 3-Aminophenol, 3-amino-1-hydroxybenzene, 3-hydroxyaniline, *m*-hydroxyaminobenzene, basf ursol bg, C.I. 76545, C.I. oxidation base 7, fouramine eg, fourrine 65, fourrine eg, furro eg, futramine eg, nako teg, pelagal eg, renal eg, tetral eg, ursol eg, zoba eg, and *m*-hydroxyphenylamine

30.0.4 Molecular Weight: 109.13

30.0.5 Molecular Formula: C_6H_7NO

30.0.6 Molecular Structure:



30.1 Chemical and Physical Properties
m-Aminophenol occurs as colorless, odorless prisms at room temperature and is relatively more stable than its *o* or *p* isomer. It has a melting point of 125°C; it is soluble in cold water (2.5 g/100 mL) and very soluble in alcohol, petroleum ether, and hot water (155, 156, 186).
30.2 Production and Use
m-Aminophenol is used chiefly in the synthesis of dyes and occasionally as a hair dye [red-brown color obtained with *p*-phenylenediamine or light orange with *p*-aminophenol (189)] and in the manufacture of *p*-aminosalicylic acid.

Occupational exposure may occur to hairdressers, barbers, and dye workers. Occasional exposure may also occur through personal use of hair dyes/colorants.
30.3 Exposure Assessment
Biomonitoring data are not available.
30.4 Toxic Effects
Intraperitoneal administration (100–200 mg/kg) of *m*-aminophenol to Syrian golden hamsters on day 8 of gestation produced inconsistent results. A teratogenic response was demonstrated at the mid dose of 150 mg/kg, but not at the high dose of 200 mg/kg (129). In a followup teratology study in which Sprague–Dawley rats were fed a diet of 0.1, 0.25, and 1.0% *m*-aminophenol for 90 d prior to mating, maternal toxicity was demonstrated at the highest dose level, and a significant reduction in body weight was noted in the 0.25% group, but there was no evidence of teratogenic or embryo-fetal toxicity at any dose level tested. Accumulation of iron-positive pigment within the liver, kidneys, and spleen was observed in dams fed a 1% diet, together with significant reduction in red blood cell count and hemoglobin level, as well as an increase in mean corpuscular volume, indicating a hemolytic effect; histomorphologic appearance of the thyroid indicated hyperactive activity (at 0.25 and 1.0% diet) (190). In contrast to *o*- and *p*-aminophenol and their glucuronides, neither *m*-aminophenol nor its conjugate with glucuronic acid has been shown to form methemoblobin *in vitro* (191). The compound was reported to be mutagenic in the Ames test (100).

30.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Aminophenols are generally metabolized by *N*-acetylation, with the relative rate following the order *p*- > *m*- > *o*- (187). The phenolic group may also be conjugated (e.g., glucuronide) to facilitate excretion. Unlike its *o*- or *p*-isomer, *m*-aminophenol does not undergo oxidation to quinone imine derivative.
30.5 Standards, Regulations, or Guidelines of Exposure
Hygienic standards of permissible exposure levels have not been assigned.

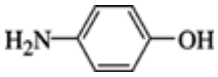
31.0 **p**-Aminophenol
31.0.1 CAS Number: [*123-30-8*]

31.0.2–31.0.3 Synonyms and Trade Names: 4-Aminophenol, *p*-hydroxyaniline, 4-amino-1-hydroxybenzene, Azol, Certinal, Citol, Paranol, Rodinal, Unal, Ursol P, paramidophenol, Kodelon, Energol, Freedol, Indianol, Kathol, basf ursol p base, benzofur p, C.I. oxidation base 6a, fouramine p, fourrine 84, PAP, pelagol grey p base, tertral p base, ursol p base, zoba brown p base C.I. 76550, durafur brown rb, fourrine p base, furro p base, nako brown r, pelagol p base, renal ac, 4-hydroxyaniline, and 4-aminobenzenol

31.0.4 Molecular Weight: 109.13

31.0.5 Molecular Formula: C_6H_7NO

31.0.6 Molecular Structure:



31.1 Chemical and Physical Properties
p-Aminophenol occurs as orthorhombic plates that deteriorate upon exposure to air and light. It has a melting point of 189°C and a boiling point of 284°C, and is sublimable. It is soluble in water (0.39% at 15°C, 0.65% at 24°C, 1.5% at 50°C, 8.5% at 90°C), very soluble in methyl ethyl ketone and absolute ethanol, but practically insoluble in benzene and chloroform (155, 156, 186).
31.2 Production and Use
p-Aminophenol is used in the manufacture of sulfur and azo dyes and in dyeing furs. The hydrochloride salt is used as a photographic developer in conjunction with sodium or potassium carbonates. *p*-Aminophenol was tried as an analgesic because of the belief that acetanilid was ultimately oxidized to *p*-aminophenol; however, it was found to be more toxic than its predecessor, acetanilid (192). Phenacetin, the ethyl ether of *N*-acetyl-*p*-aminophenol, also known as acetophenetidin, has been widely prescribed as an analgesic.

Occupational exposure may occur to hairdressers, barbers, and dye workers. Occasional exposure may also occur through personal use of hair dyes/colorants as well as through the use of OTC drugs that yield *p*-aminophenol as a metabolite.
31.3 Exposure Assessment
Biomonitoring data are not available.
31.4 Toxic Effects
31.4.1 Experimental Studies *p*-Aminophenol is a cytotoxic chemical; one mechanism associated with its cytotoxicity has been attributed to its activity as a tissue respiratory (oxidative phosphorylation) inhibitor (193).

Intraperitoneal administration (100–200 mg/kg) of the compound on day 8 of gestation to Syrian golden hamsters produced a significant teratogenic response including encephalocele and limb, tail, and eye defects; rare malformations observed included ectopic heart, cleft palate, occult cranioschisis, and abnormal genitalia. It was proposed that the mechanism may be related to the formation of a reactive quinone/quinoneimine. In contrast to IP administration, the compound was not teratogenic by the oral route at the same dosages (129).

p-Aminophenol was nonteratogenic in Sprague–Dawley rats fed a diet containing 0.07, 0.2, or 0.7% for up to 6 mo. After 13 wk, 25 females/group were mated to untreated males in a teratology study; after 20 wk, 20 males/group were mated to untreated virgin females in a dominant lethal mutagenicity study. Dose-related nephrosis was seen in both sexes after 13 and 27 wk and in the high-dose males that were removed from the test diet for a 7-wk recovery period. The authors noted

an increase in developmental variations associated with maternal toxicity at the mid- and high-dose levels. The dominant lethal study was equivocal (194).

p-Aminophenol has also been demonstrated to be nephrotoxic to rats. Administration of 25–100 mg/kg to male F344 rats resulted in a dose-related proximal nephropathy. The observed increased excretion of enzymes, glucose, and urine total protein, resulting in glycosuria and amino aciduria, indicated functional defects in the proximal tubule and reduced solute reabsorption efficiency (196). The necrosis is apparently restricted to the straight segment of the proximal tubule of the Fischer 344 rat; Sprague–Dawley rats, on the other hand, are more resistant to the nephrotoxicity of acetaminophen and its nephrotoxic metabolite *p*-aminophenol. The authors postulated that the strain differences in *p*-aminophenol-induced nephrotoxicity may be related to differences in the intrarenal activation of *p*-aminophenol (197).

Mutagenicity studies of *p*-aminophenol yielded mixed results: negative in Ames (100), positive in L5178 mouse lymphoma assay, and negative in CHO/HGPRT assay (51). Although a number of derivatives (e.g., phenacetin) of *p*-aminophenol have been reported to be carcinogenic (116, 198), there appears to be no evidence to indicate that *p*-aminophenol is carcinogenic.

31.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Aminophenols are generally metabolized by N-acetylation with the relative rate following the order *p*- > *m*- > *o*- (187). The phenolic group may also be conjugated (e.g., glucuronide) to facilitate excretion. Reactive electrophilic quinone imine derivatives may be formed by oxidation of the *o* or *p* isomer but not the *m* isomer.

31.4.2 Human Experience *p*-Aminophenol is considered a minor nephrotoxic metabolite of acetaminophen in humans. Long-term use of acetaminophen can result in an increased lipofuscin deposition in kidneys. *In vitro* studies have demonstrated that *p*-aminophenol can undergo oxidative polymerization to form melanin, a component of soluble lipofuscin. Hemolysis accompanies this process in whole blood. Long-term excessive use of phenacetin or acetaminophen has been associated with chronic renal disease, hemolytic anemia, and increased solid lipofuscin deposition in tissues (195).

31.5 Standards, Regulations, or Guidelines of Exposure

Hygienic standards of permissible exposures have not been assigned.

32.0 2-Amino-5-nitrophenol

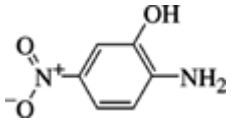
32.0.1 CAS Number: [*121-88-0*]

32.0.2–32.0.3 Synonyms and Trade Names: 2-Hydroxy-4-nitroaniline, 5-nitro-2-aminophenol, C.I. 76535, rodol yba, and ursol yellow brown a

32.0.4 Molecular Weight: 154.13

32.0.5 Molecular Formula: $C_6H_6N_2O_3$

32.0.6 Molecular Structure:



32.1 Chemical and Physical Properties

2-Amino-5-nitrophenol is an orange crystalline solid at room temperature. It has a melting point of 200°C; it is insoluble in water but soluble in alcohol, benzene, and most common organic solvents (155, 199).

32.2 Production and Use

2-Amino-5-nitrophenol is not produced in commercial quantities in the United States. The import volume between 1973 and 1979 was in the order of 13,400 kg per year. It is used as a colorant in semipermanent hair dyes and in the manufacture of azo dye (e.g., C.I. Solvent Red 8) for synthetic resins, lacquers, and wood stains (199).

In view of its widespread use in hair dyes, occupational (hairdressers and barbers) exposure is expected. A National Occupational Hazard Survey conducted by NIOSH in 1981–1983 estimated that a total of 14,512 U.S. workers, including 11,827 women, were potentially exposed to 2-amino-4-nitrophenol in 1339 beauty salons (105). Occasional consumer exposure may also occur through the personal use of hair dye products.

32.3 Exposure Assessment

Biomonitoring studies are not available.

32.4 Toxic Effects

The LD_{50} of 2-amino-5-nitrophenol in rats was reported to be greater than 4 g/kg by oral and 800 mg/kg by intraperitoneal administration (200). Mutagenicity and related genotoxicity studies indicated that the compound is positive in the Ames test with metabolic activation, positive in mouse lymphoma L5178Y assay without metabolic activation, positive in chromosomal aberrations and sister chromatid exchanges assays in CHO cells with and without metabolic activation (199), but negative in dominant lethal mutation in rats (200).

The potential carcinogenicity of 2-amino-5-nitrophenol was tested by NTP (199) by oral administration (gavage) in corn oil to F344/N rats (100 and 200 mg/kg) and $B6C3F_1$ mice (400 and 800 mg/kg) for 2 years. There was some evidence of carcinogenic activity in low-dose male rats, as indicated by increased incidence of acinar cell adenomas of the pancreas. No evidence of carcinogenic activity was found among female rats and the low-dose groups of male and female mice. The poor survival rates in the high-dose male rats and high-dose male and female mice reduced the sensitivity for detecting potential carcinogenic response.

32.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms There is no information on the disposition or metabolism of 2-amino-5-nitrophenol. However, the disposition of the closely related 2-amino-4-nitrophenol has been studied. Up to 1.67% of 2-amino-4-nitrophenol has been shown to be absorbed after dermal application to rats. Absorbed material was excreted in the urine within 24 h. Absorption has also been demonstrated after oral administration. Virtually all absorbed material was excreted in 5 d.

32.5 Standards, Regulations, or Guidelines of Exposure

Hygienic standards of permissible exposure have not been assigned. The use of 2-amino-5-nitrophenol in cosmetic products is prohibited in the European Economic Communities (36).

33.0 4-Amino-2-nitrophenol

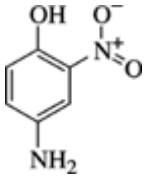
33.0.1 CAS Number: [*119-34-6*]

33.0.2–33.0.3 Synonyms and Trade Names: *p*-Aminonitrophenol, C.I. 76555, fourrine 57, fourrine brown pr, fourrine brown propyl, 4-hydroxy-3-nitroaniline, *o*-nitro-*p*-aminophenol, oxidation base 25, 3-nitro-4-hydroxyaniline, and C.I. oxidation base 25

33.0.4 Molecular Weight: 154.13

33.0.5 Molecular Formula: $C_6H_6N_2O_3$

33.0.6 Molecular Structure:



33.1 Chemical and Physical Properties
4-Amino-2-nitrophenol has a melting point of 131°C (155).
33.2 Production and Use
4-Amino-2-nitrophenol has been used in dyeing human hair and animal fur. The typical concentration in the "semi-permanent" hair dyes was estimated to be in the order of 0.1--1.0% (36).

In view of its use in hair dyes, occupational (hairdressers and barbers) exposure is expected. Occasional consumer exposure may also occur through the personal use of hair dye products.
33.3 Exposure Assessment
Biomonitoring studies are not available.
33.4 Toxic Effects
The LD_{50} of 4-amino-2-nitrophenol in rats was reported to be 3.3 g/kg by oral and 302 mg/kg by intraperitoneal administration (200). The compound was reported to be mutagenic in the Ames test and the mouse lymphoma L5178Y assay (100). The potential carcinogenicity of 4-amino-2-nitrophenol was tested by NCI (201) by dietary administration (1250 or 2500 ppm) to F344/N rats and $B6C3F_1$ mice for 2 years. Under the conditions of the bioassay, the compound was carcinogenic in male rats inducing transitional-cell carcinomas of the urinary bladder (controls 0/15, low dose 0/46, high dose 11/39). The same tumor was also observed in three dosed female rats and may have been associated with the administration of the chemical. No evidence of carcinogenic activity was found in the mice.

33.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms There is no information on the disposition or metabolism of 4-amino-2-nitrophenol. However, the disposition of its isomer 2-amino-4-nitrophenol has been studied. Up to 1.67% of 2-amino-4-nitrophenol has been shown to be absorbed after dermal application to rats. Absorbed material was excreted in the urine within 24 h. Absorption has also been demonstrated after oral administration. Virtually all absorbed material was excreted in 5 d.
33.5 Standards, Regulations, or Guidelines of Exposure
Hygienic standards of permissible exposure have not been assigned.

Aromatic Amino and Nitro–Amino Compounds and their Halogenated Derivatives
Yin-Tak Woo, Ph.D., DABT, David Y. Lai, Ph.D., DABT

D. Phenylenediamines and Derivatives
Phenylenediamines (PDAs) are aromatic amines with two amino groups attached to benzene. There are three possible isomers: *ortho-, meta-*, and *para*-phenylenediamine (*o-, m-*, and *p*-PDA). Their primary uses are in the synthesis of polymers (primarily polyurethanes) and dyestuffs, and as components of hair dye formulations. Several of their nitro and chloro derivatives are also widely used in the hair dye industry.

Phenylenediamines are methemoglobin-forming agents and skin sensitizers. Among the three isomers, *m*-PDA is the most potent methemoglobin-forming agent and *p*-PDA is more toxic and a stronger skin sensitizer than *o*- and *m*-PDA. 2-Nitro-*p*-PDA was reported to cause developmental toxicity in mice. All three isomers of PDA and a number of their nitro and chloro derivatives have

been shown to induce gene mutagen in bacteria and/or cultured mammalian cells. Many of them also induced chromosomal aberrations, sister chromatid exchange, and cell transformation in cultured mammalian cells. The *m* and *p* isomers of PDA did not show any carcinogenic effects in limited carcinogenicity studies in rodents. However, there is sufficient evidence of carcinogenicity in long-term animal studies for *o*-PDA, 2-nitro-*p*-PDA, 4-chloro-*o*-PDA, 4-chloro-*m*-PDA, and 2,6-dichloro-*p*-PDA. Addition of chlorine atom(s) in the phenyl ring appeared to increase the carcinogenicity of phenylenediamines.

Aromatic Amino and Nitro–Amino Compounds and their Halogenated Derivatives
Yin-Tak Woo, Ph.D., DABT, David Y. Lai, Ph.D., DABT

E. Toluenediamines
There are six possible isomers of toluenediamines (TDA), or diaminotoluenes. They are usually synthesized commercially by dinitration of toluene, yielding a mixture of approximately 76% 2,4-TDA, 19% 2,6-TDA, 2.5% 3,4-TDA, 1.5% 2,3-TDA, 0.7% 2,5-TDA, and traces of 3,5-TDA (85). Among these isomers, 2,4-TDA and 2,6-TDA (both also known as *m*-TDA) are the most widely used diamines principally as chemical intermediates for the manufacture of toluene diisocyante (TDI), the predominant diisocyanate in the flexible foam and elastomer industries. In addition, TDA isomers are also used in hair dyes and a variety of other uses.

Four isomers (2,4-, 2,5-, 2,6-, and 3,4-) of TDA have been shown to be mutagenic in the Ames assay. In addition, both 2,4-TDA and 2,6-TDA yielded positive results in *in vitro* chromosome aberration and sister chromatid exchange assays (100). In contrast to genotoxicity assays, differential results have been observed in carcinogenicity studies. Whereas several studies indicated 2,4-TDA to be clearly carcinogenic in rats and mice, bioassays of 2,5-TDA and 2,6-TDA gave negative results. Mechanistic studies (83) showed that although both 2,4-TDA and 2,6-TDA are capable of binding to DNA, 2,4-TDA is about 6500 times more effective than 2,6-TDA. In addition, 2,4-TDA has been shown to induce hepatocellular proliferation (227) and exhibit tumorigenesis-promoting activity inducing liver foci from diethylnitrosamine-initiated hepatocytes (83), whereas 2,6-TDA lacks such activities indicating that genotoxicity alone is insufficient to induce complete carcinogenesis.

NIOSH Analytical Method 5516 is recommended for determining workplace exposure for all toluenediamine isomers (111a).
44.0 2,3-Toluenediamine
44.0.1 CAS Number: [*2687-25-4*]

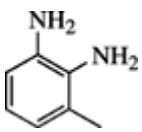
44.0.2 Synonyms: 3-Methyl-1,2-benzenediamine, toluene-2,3-diamine, and 2,3-diaminotoluene, and *o*-TDA

44.0.3 Trade Names: NA

44.0.4 Molecular Weight: 122.17

44.0.5 Molecular Formula: $C_7H_{10}N_2$

44.0.6 Molecular Structure:



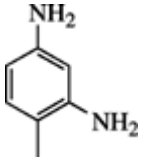
47.1 General
2,3-Toluenediamine has a boiling point of 255°C and a melting point of 63 to 64°C; it is soluble in water, alcohol, and ether. The most significant commercial use of *o*-TDA is in the manufacture of tolyltriazoles, which are used as corrosion inhibitors, photographic chemicals, and catalysts. It is also used as a chemical intermediate in the synthesis of polyols and antioxidants (85). No toxicology information was located in the literature. No hygienic standards of permissible exposure have been assigned. In the absence of data, NIOSH considers all TDA isomers as possible occupational carcinogens.
45.0 2,4-Toluenediamine
45.0.1 CAS Number: [*95-80-7*]

45.0.2–45.0.3 Synonyms and Trade Names: Toluene-2,4-diamine, toluenediamine, 2,4-diaminotoluene, 4-methyl-1,3-benzenediamine, 3-amino-*p*-toluidine, 5-amino-*o*-toluidine, tolylene-2,4-diamine, 1,3-diamino-4-methylbenzene, 2,4-diamino-1-methylbenzene, 2,4-diamino-1-toluene, 2,4-diaminotoluol, 4-methyl-*m*-phenylenediamine, C.I. 76035, C.I. oxidation base, C.I. oxidation base 20; C.I. oxidation base 35; C.I. oxidation base 200, developer 14, developer b, developer db, developer dbj, developer mc, developer mt, developer mt-cf, developer mtd, developer, azogen developer h, benzofur mt, eucanine gb, fouramine, fouramine j, fourrine 94, fourrine m, MTD, nako tmt, pelagol j, pelagol grey j, pontamine developer tn, renal md, Tertral g, zoba gke, zogen developer h, 4-methylphenylene-1,3-diamine, and 2,4-TDA

45.0.4 Molecular Weight: 122.17

45.0.5 Molecular Formula: $C_7H_{10}N_2$

45.0.6 Molecular Structure:



45.1 Chemical and Physical Properties
2,4-Toluenediamine has a boiling point of 292°C and melting point of 99°C; it is soluble in water, alcohol, and ether. It is a colorless to brown, needle-shaped crystal or powder that tends to darken on storage (85, 155).
45.2 Production and Use
2,4-Toluenediamine is a widely used industrial chemical intermediate. It is produced in very large volumes with worldwide production estimated to be 6.9×10^5 metric tons in 1991 (85). The major use for 2,4-TDA is in the manufacture of toluene diisocyanate (TDI), the predominant isocyanate in the flexible polyurethane foams and elastomers industry. It is also used as an intermediate for the synthesis of dyes and pigments and was used in hair dye formulations until 1971 (36).

Human exposure to 2,4-TDA may occur indirectly via exposure to 2,4-toluene diisocyanate, which is known to hydrolyze to 2,4-TDA rapidly upon contact with water. Workers in some plastics and elastomers industries may be exposed to atmospheres containing TDI (228). Direct exposure to 2,4-TDA *per se* could also occur to hairdressers and barbers through the use of hair dye formulations.
45.3 Exposure Assessment
Biomonitoring methods to measure hemoglobin adducts of 2,4-TDA as a dosimeter of exposure have been developed (95, 102). Immunoassays to measure DNA adducts with 2,4-TDA have also been developed (21).
45.4 Toxic Effects
Clinical effects in humans include methemoglobinemia, especially when red blood cell-reducing

mechanisms are impaired, such as in G6PD deficiency, which occurs in humans in the absence of glutathione reductase, glutathione, or glutathione peroxidase. It is an eye irritant that may cause corneal damage, and delayed skin irritation reportedly occurs, which can result in blistering (1).

45.4.1 Experimental Studies Reproductive toxicity in the rat has been demonstrated. Reduced fertility, arrested spermatogenesis, and diminished circulating testosterone levels have resulted in rats fed 0.03% 2,4-TDA; electron microscopy revealed degenerative changes in Sertoli cells and a decrease in epididymal sperm reserves; after 3 wk of 0.06% TDA feeding, sperm counts were further reduced and accompanied by a dramatic increase in testes weights, intense fluid accumulation, and ultrastructural changes in Sertoli cells (130). In previous studies testicular atrophy, hormonal effects, and aspermatogenesis were also observed in Sprague–Dawley rats given a 0.1% diet for 9 wk (131, 132).

2,4-TDA is mutagenic in the Ames assay with metabolic activation in the presence of S-9; it gave weakly positive results in the micronucleus test at near toxic doses (231, 232). *In vitro* chromosome aberration and sister chromatid exchange assays were reported to be positive (100). Its *in vivo* genotoxic activity has recently been demonstrated using the Big Blue transgenic mouse mutation assay (81).

When 2,4-TDA was administered in the diet to male and female F344 rats (79 or 170 ppm) or $B6C3F_1$ mice (100 or 200 ppm), hepatocellular carcinomas were produced in female mice, hepatocellular carcinomas in male rats, and mammary adenomas or carcinomas in female rats, but no carcinomas in the male mice (233). Also male Wistar rats have reportedly been shown to develop hepatocarcinomas following treatment with 2,4-TDA (234). A skin painting study in Swiss–Webster mice was reportedly noncarcinogenic (235). However, it has also been observed that mice appear to be less sensitive than rats; this difference may be based upon differences in metabolism (236).

45.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Metabolism studies (16, 21, 232, 236) indicated that 2,4-TDA is metabolically activated by N-hydroxylation followed by N-acetylation to yield the N-acetoxy derivative as the ultimate DNA reactive and mutagenic intermediate. Based on analysis of the DNA adducts, the 4-amino group appears to be the preferential (80%) site of metabolic activation (21). At an equimolar dose of 250 mg/kg, 2,4-TDA was shown to be 6500 times more active in binding to DNA in rats liver than its 2,6-isomer (83). In addition, 2,4-TDA has been shown to induce hepatocellular proliferation (227) and exhibit tumorigenesis-promoting activity inducing liver foci from diethylnitrosamine-initiated hepatocytes (83). In contrast, the mutagenic but noncarcinogenic 2,6-TDA lacks such tumorigenesis-promoting activities indicating that genotoxicity alone is insufficient to induce complete carcinogenesis.

45.4.2 Human Experience However, epidemiological studies of workers exposed to commercial mixtures of dinitrotoluene and/or toluenediamine at three chemical plants indicated that the fertility of men had not been reduced significantly and reported no observable effects on the fertility of workers (229, 230). However, other reports have suggested that human exposure may disrupt spermatogenesis and cause an excess of miscarriages (131, 132). Biliary tract cancer has been reported in industrial workers (237); however, it could not be determined whether 2,4-TDA played a significant role.

An IARC working group concluded that, despite the lack of human data, there are sufficient animal data to classify 2,4-TDA a Group 2B compound, an agent possibly carcinogenic to humans (116).
45.5 Standards, Regulations, or Guidelines of Exposure
NIOSH recommends that 2,4-TDA be treated as a possible occupational carcinogen.
46.0 2,5-Toluenediamine
46.0.1 CAS Number: [*95-70-5*]

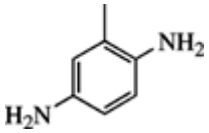
46.0.2–46.0.3 Synonyms and Trade Names: 2,5-Diaminotoluene, toluene-2,5-diamine, 2-methyl-1,4-

benzenediamine and 2,5-TDA

46.0.4 Molecular Weight: 122.17

46.0.5 Molecular Formula: $C_7H_{10}N_2$

46.0.6 Molecular Structure:



46.1 Chemical and Physical Properties
2,5-Toluenediamine has a boiling point of 273 to 274°C and a melting point of 64°C; it is soluble in water, alcohol, and ether (85, 155).
46.2 Production and Use
2,5-Toluenediamine is used primarily in hair dye formulations as one of the major oxidation dye precursors (36). It is also used in the synthesis of saframine, a family of dyes used as biological stain and may be present in indelible ink, antifreeze, and nail polish (238).

As may be expected from its use in hair dye formulations, hairdressers and barbers may be exposed to 2,5-TDA (36). Workers in the dye manufacturing industry may also be exposed.
46.3 Exposure Assessment
No biomonitoring data or studies are available.
46.4 Toxic Effects
2,5-Toluenediamine is toxic following oral, inhalation, and dermal exposure causing hepatotoxicity and hemolytic anemia. The compound is considered highly irritating to skin and eye (239). Myotoxicity (to both cardiac and skeletal muscle) has also been observed in rats exposed to 2,5-TDA; a number of more highly ring-methylated analogs (2,3,5,6-tetramethyl-, 2,5-dimethyl- and 2,6-dimetyl-*p*-phenylenediamine) are even more myotoxic (240). Ames test showed positive mutagenicity with metabolic activation (100).

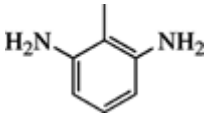
The possible carcinogenicity of 2,5-TDA (as sulfate salt, CAS # [*6369-59-1*]) was tested by the National Cancer Institute in a dietary feeding study (238). Groups of 50 male and female F344 rats (600 or 2000 ppm) and B6C3F_1 mice (600 or 1000 ppm) were given diets containing 2,5-TDA for 78 wk and then observed for an additional period of 28–31 wk for rats and 16–19 wk for mice. The only statistically significant increased incidence was in lung tumors in high-dose female mice, but the evidence was not convincing enough to be attributed to 2,5-TDA. Overall, the compound was considered noncarcinogenic (238).
46.5 Standards, Regulations, or Guidelines of Exposure
No hygienic standards of permissible exposure have been assigned.
47.0 2,6-Toluenediamine
47.0.1 CAS Number: [*823-40-5*]

47.0.2–47.0.3 Synonyms and Trade Names: Toluene-2,6-diamine, 2-methyl-1,3-benzenediamine, 2,6-diaminotoluene, 1,3-diamino-2-methylbenzene, 2,methyl-*m*-phenylenediamine, 2,6-diamino-1-methylbenzene, 2-methyl-1,3-phenylenediamine, 2,6-toluylenediamine, and 2,6-toluenediamine and 2,6-TDA

47.0.4 Molecular Weight: 122.17

47.0.5 Molecular Formula: $C_7H_{10}N_2$

47.0.6 Molecular Structure:



47.1 Chemical and Physical Properties
2,6-Toluenediamine has a melting point of 106°C; it is soluble in water and alcohol. The dihydrochloride of 2,6-TDA is usually more stable than the free amine (85, 155).
47.2 Production and Use
2,6-Toluenediamine is usually produced as a byproduct with 2,4-TDA in mixtures containing 20% 2,6- and 80% 2,4-isomer. It is used primarily in the manufacture of toluene diisocyanate (TDI), the predominant isocyanate in the flexible polyurethane foams and elastomers industry (228).

Human exposure to 2,6-TDA may occur indirectly via exposure to toluene diisocyanate mixture containing 2,6-toluenediisocyanate, which is known to hydrolyze to 2,6-TDA rapidly upon contact with water. Workers in some plastics and elastomers industries may be exposed to atmosphere containing TDI (228).
47.3 Exposure Assessment
Biomonitoring methods to measure hemoglobin adducts of 2,6-TDA as a dosimeter of exposure have been developed (102).
47.4 Toxic Effects
2,6-Toluenediamine is positive in the Ames test, *in vitro* chromosome aberration, and sister chromatid exchange assays (100). Long-term bioassay of 2,6-TDA (as dihydrochloride salt, CAS [*15481-70-6*]) in an NCI feeding study using male and female F344 rats (250 or 500 ppm) and B6C3F$_1$ mice (50 or 100 ppm) showed no evidence of carcinogenicity (241), although the doses used in the mosue study did not reach the maximum tolerated dose.

47.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Metabolism and mechanistic studies (83, 229, 242) showed that 2,6-TDA is metabolically activated to a mutagenic and reactive intermediate capable of binding to DNA. However, unlike its hepatocarcinogenic 2,4-isomer, 2,6-TDA lacks tumorigenesis promoting activities as indicated by its failure to induce hepatocellular proliferation (227) and promote development of liver foci from diethylnitrosamine-initiated hepatocytes (83). Thus the genotoxicity of 2,6-TDA alone is insufficient to confer complete carcinogenic activity.
47.5 Standards, Regulation, or Guidelines of Exposure
No hygienic standards of permissible exposure have been assigned.
48.0 3,4-Toluenediamine
48.0.1 CAS Number: [*496-72-0*]

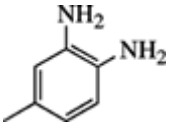
48.0.2 Synonyms: 3,4-Diaminotoluene, 4-methyl-1,2-benzenediamine, diaminotoluene, toluene-3,4-diamine, and 4-methyl-*o*-phenylenediamine

48.0.3 Trade Names: NA

48.0.4 Molecular Weight: 122.17

48.0.5 Molecular Formula: $C_7H_{10}N_2$

48.0.6 Molecular Structure:



3,4-Toluenediamine has a melting point of 88°C and a boiling point of 265°C (sublimes); it is soluble in water. The most significant commercial use of *o*-TDA is in the manufacture of tolyltriazoles, which are used as corrosion inhibitors, photographic chemicals, and catalysts. It is also used as chemical intermediate in the synthesis of polyols and antioxidants (85). The compound was reported to be mutagenic in the Ames test in one study (100), but negative in another (243). No hygienic standards of permissible exposure have been assigned. In the absence of data, NIOSH considers all TDA isomers as possible occupational carcinogens.

49.0 3,5-Toluenediamine

49.0.1 CAS Number: [*108-71-4*]

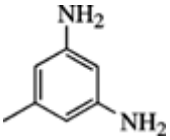
49.0.2 Synonyms: 5-Methyl-1,3-benzenediamine and 3,5-diaminotoluene

49.0.3 Trade Names: NA

49.0.4 Molecular Weight: 122.17

49.0.5 Molecular Formula: $C_7H_{10}N_2$

49.0.6 Molecular Structure:



There is no information available on this isomer in the open literature.

Aromatic Amino and Nitro–Amino Compounds and their Halogenated Derivatives
Yin-Tak Woo, Ph.D., DABT, David Y. Lai, Ph.D., DABT

F. Chlorinated Nitrobenzene Compounds

Chlorinated nitrobenzene compounds are important chemical intermediates for the synthesis of dyes, rubber, agricultural and pharmaceutical chemicals, as well as for some explosives. The chemical reactivity and toxicity of chlorinated nitrobenzene compounds depend on the number of chloro and nitro groups on the ring *and* their relative position. The ring nitro group(s) may contribute to toxicity either by reduction to aromatic amines or by activating the chloro group to become a leaving group, thereby yielding a direct-acting arylating agent. To yield an arylating agent, the electron-withdrawing nitro group(s) must be situated *ortho* or *para* to the chloro group. The strongest arylating agents are 1-fluoro-2,4-dinitrobenzene and 1-chloro-2,4-dinitrobenzene. There is good evidence that the mutagenicity of halogenated nitrobenzene compounds may be correlated to their arylating activity. A comparative mutagencity study (244), using Ames assay, of 21 chloro-/fluoronitrobenzene and 9 chloro-/fluorobenzene compounds indicated that mutagenicity (base-pair substitution only) was exhibited by all compounds having a chloro or fluoro group at the *ortho* or *para* position in the nitrobenzene nucleus. Chlorinated nitrobenzene compounds are also notorious as inducers of methemoglobinemia; this activity is less dependent on the relative positions of chloro

and nitro groups. All three isomers (*o-, m-, p-*) of chloronitrobenzene have been shown to be potent inducers of methemoglobinemia.

50.0 **o**-Chloronitrobenzene

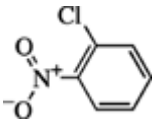
50.0.1 CAS Number: [*88-73-3*]

50.0.2–50.0.3 Synonyms and Trade Names: 1-Chloro-2-nitrobenzene, 2-chloro-1-nitrobenzene, Oncb, 2-nitrochlorobenzene, 2-CNB, and *o*-CNB

50.0.4 Molecular Weight: 157.56

50.0.5 Molecular Formula: $C_6H_4ClNO_2$

50.0.6 Molecular Structure:



50.1 Chemical and Physical Properties

o-Chloronitrobenzene usually occurs as oily yellow crystals at room temperature. It has a melting point of 34°C and a boiling point of 246°C; it is soluble in alcohol, benzene, ether, and acetone but insoluble in water. At room temperature, its vapor pressure is sufficiently high to lead to significant volatilization (62). As an aromatic nitro compound, it is easily reducible to corresponding aromatic amino compounds (26). The chlorine atom can be easily replaced by OH, OCH_3 OC_6H_5, etc., by nucleophilic attack.

50.2 Production and Use

The annual production of *o*-CNB in the United States in 1993 was 19,000 metric tons (2) and on the order of 50,000–70,000 metric tons in Germany (26). It is used as a chemical intermediate for the synthesis of *o*-aminophenol, which is used as a photographic developer. It is also used in the preparation of dyes, corrosion inhibitors, and agricultural chemicals.

Human exposure may occur to dyestuff workers but the extent is uncertain because of its use as a chemical intermediate. *o*-Chloronitrobenzene has been detected in the surface water of the Rhine River in a concentration range of 0.1–0.5 mg/L (26). Concentration levels of up to 1 mg/kg were reportedly found in fish in Europe (26).

50.3 Exposure Assessment

No biomonitoring studies are available.

50.4 Toxic Effects

o-Chloronitrobenzene has been reported to cause a variety of toxic effects, which include skin, eye, and respiratory tract irritation, pulmonary edema, methemoglobinemia, neurotoxicity, dermatitis, skin sensitization, and hepatic, pancreatic, and renal disorders (163, 245). Toxicity studies by NTP (62) showed that *o*-CNB is mutagenic in the Ames test, positive in the sister chromatid exchange assay, and capable of inducing chromosomal aberrations in Chinese hamster ovary cells but negative in sex-linked recessive lethal mutation assays in *Drosophila melanogaster*. Inhalation exposure of rats and mice to *o*-CNB resulted in methemoglobin formation and oxidative damage to red blood cells, leading to a regenerative anemia and a spectrum of tissue damage secondary to erythrocyte injury. Hyperplasia of the respiratory epithelium was also observed in rats exposed to *o*-CNB. The increase in methemoglobin occurred in rats exposed to as low as 1.1 ppm *o*-CNB. The NOAEL was 6 ppm for mice in a 13-wk inhalation study. Reproductive toxicity study indicated evidence of decreased spermatogenesis in rats exposed to *o*-CNB. A planned carcinogenicity study by NTP was cancelled.

50.4.1.3 Pharmacokinetics, Metabolism, amd Mechansims *o*-Chloronitrobenzene can be readily

absorbed by oral, dermal, and inhalation routes (62). It has been reported to be metabolized to *o*-chloroaniline, indicating nitroreduction, and conjugated with GSH to *S*-(2-nitrophenyl)glutathione, indicating the arylating activity (1).

50.5 Standards, Regulations, or Guidelines of Exposure

No hygienic standards of permissible exposure have been assigned. In Germany, this compound has been considered a substance suspected of having carcinogenic potential (246).

51.0 **m**-Chloronitrobenzene

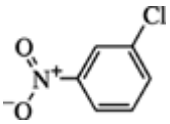
51.0.1 CAS Number: [*121-73-3*]

51.0.2–51.0.3 Synonyms and Trade Names: 3-Nitrochlorobenzene, 1-chloro-3-nitrobenzene; MNCB, nitrochlorobenzene, and *m*-CNB

51.0.4 Molecular Weight: 157.56

51.0.5 Molecular Formula: $C_6H_4ClNO_2$

51.0.6 Molecular Structure:



51.1 Chemical and Physical Properties

m-Chloronitrobenzene has a melting point of 43°C and a boiling point of 236°C. It is soluble in hot alcohol, chloroform, ether, carbon disulfide, and benzene, but relatively insoluble in water (2). Unlike the *o*- and *p*-isomers, the chlorine atom in *m*-CNB is not activated for nucleophilic substitution.

51.2 Production and Use

m-Chloronitrobenzene is of lesser economic importance than its *ortho* and *para* isomers, with no U.S. production reported (2). The annual production in Germany was reported to be in the order of 1000–3000 metric tons. It has limited use in the manufacturing of dyes and agricultural chemicals.

There is no information on potential exposure. Chloronitrobenzene has been detected in the surface water of the Rhine River with concentrations between 20 and 500 ng/L and in fish at levels of up to 1 mg/kg (26).

51.4 Toxic Effects

The main toxicological concern for *m*-CNB is the induction of methemoglobinemia, which could be observed in rats given dermal administration of 800–2000 mg/kg of the compound. Cats are substantially more susceptible to the methemoglobin-forming activity of *m*-CNB. A single IP dose of 5–10 mg *m*-CNB/kg body weight was sufficient to generate methemoglobinemia with the greatest effect observed 10 h after the administration (26). In contrast its *o* and *p* isomers, *m*-CNB has been basically shown to be nonmutagenic in the Ames test, sister chromatid exchange, and chromosome aberration assays (26, 100, 247).

51.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Absorption studies indicated that *m*-CNB may be absorbed via oral, dermal, and inhalation routes. Metabolism studies in rabbit showed *m*-chloroaniline and its phenolic derivatives as the major metabolites. There is no evidence of GSH conjugation indicating the lack of arylating activity. There is evidence that the mode of action of methemoglobinemia is most likely caused by the formation of hydroxylamine derivative during metabolism (26).

51.5 Standards, Regulations, or Guidelines of Exposure

No hygienic standards of permissible exposure have been assigned.

52.0 **p**-Chloronitrobenzene

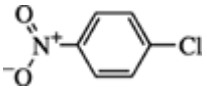
52.0.1 CAS Number: [*100-00-5*]

52.0.2–52.0.3 Synonyms and Trade Names: 4-Chloronitrobenzene, PNCB, nitrochlorobenzene, 1-chloro-4-nitrobenzene, 1,4-chloronitrobenzene, 4-nitrochlorobenzene, 4-chloro-1-nitrobenzene, *p*-nitrochlorobenzene, 1-chloro-4-nitrobenzene, and *p*-CNB

52.0.4 Molecular Weight: 157.56

52.0.5 Molecular Formula: $C_6H_4ClNO_2$

52.0.6 Molecular Structure:



52.1 Chemical and Physical Properties

p-Chloronitrobenzene occurs as yellow crystals at room temperature. It has a melting point of 83.6°C and a boiling point of 242°C; it is soluble in alcohol, benzene, ether, and acetone, but insoluble in water. At room temperature, its vapor pressure (0.009 torr at 25°C) is sufficiently high to lead to significant volatilization (62). As an aromatic nitro compound, it is easily reducible to the corresponding aromatic amino compound (26). The chlorine atom can be easily replaced by OH, OCH_3, OC_6H_5, etc. by nucleophilic attack.

52.2 Production and Use

The annual production of *p*-CNB in the United States in 1993 was 35,000 metric tons (2) and on the order of 50,000–70,000 metric tons in Germany (26). It is used as an intermediate in the manufacture of dyes, rubber, and agricultural chemicals.

Human exposure may occur to dyestuff workers but the extent is uncertain because of its use as a chemical intermediate. *p*-Chloronitrobenzene has been detected in the surface water of the Rhine River at a concentration range of 0.1–6.38 mg/L (26).

52.3 Exposure Assessment

52.3.3 Workplace Methods NIOSH Analytical Method 2005 is recommended for determining workplace exposures to *p*-CNB (111a)

The measurement of blood methemoglobin level has been used as a nonspecific indicator of biological exposure to *p*-CNB.

52.4 Toxic Effects

The most significant toxicity is methemoglobinemia, which may occur after oral, dermal, or inhalation exposure. Symptoms of methemoglobinemia, which include headache, dizziness, vomiting, weakness, cyanosis, and anemia, have been observed in workers exposed to *p*-CNB via skin contact or inhalation. Skin penetration is rapid, and *p*-CNB is more potent than aniline in terms of potential to produce cyanosis and anemia (26). Animal studies also indicated the methemoglobinemia-inducing capability of *p*-CNB (26). A recent NTP subchronic inhalation toxicity study showed evidence of methemoglobinemia in F344/N rats exposed to as low as 1.5 ppm *p*-CNB. No NOAEL could be achieved for rats in this study while a NOAEL of 6 ppm was established for B6C3F_1 mice (62). Mutagenicity studies by NTP (62) showed that *p*-CNB is mutagenic in the Ames test, positive in the sister chromatid exchange assay, and capable of inducing chromosomal aberrations in Chinese hamster ovary cells but negative in sex-linked recessive lethal mutation assay in *Drosophila melanogaster*.

A teratogenicity study of *p*-CNB was conducted in groups of Sprague–Dawley rats administered 5, 15, or 45 mg/kg/d by gavage on days 6 to 19 of gestation and in New Zealand rabbits dosed with 5, 15, or 40 mg/kg/d on gestation days 7 to 19 by gavage (168). In the rat study, there was evidence of

embryotoxicity (increased resorptions) and teratogenicity (increased incidences of skeletal anomalies) only at the high-dose group, which is slightly maternally toxic. In the rabbit study, the high dose was highly toxic to the dams, whereas the mid- and low-doses caused small increases in the incidences of skeletal malformations that were not statistically significant (168).

p-CNB was reported to be noncarcinogenic in Sprague–Dawley rats and equivocal in HaM/ICR mice given maximally tolerated dietary doses (rats: initially 4000 ppm, reduced to 500 ppm after 3 mo and then raised to 1000 ppm after 2 mo; mice: 6000 ppm) and half of those doses for 18 mo followed by 6 mo (rats) or 3 mo (mice) observation (182). In another long-term bioassay in which rats were given *p*-CNB orally at 0.1, 0.7, or 5.0 mg/kg/d, the only predominant adverse effect was apparently significant methemoglobinemia observed at mid- and high-dose levels (1). In view of the uncertainties, NTP originally planned a carcinogenicity bioassay but subsequently decided to discontinue after the subchronic toxicity studies.

52.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Absorption studies indicated that *p*-CNB can be readily absorbed by all routes of exposure (62). *In vitro* studies have demonstrated that *p*-CNB can be reduced to *p*-chloroacetanilide as well as *p*-chloroaniline, and that cytosolic GSH transferase is involved in the conjugation with GSH to form *S*-(4-nitrophenyl)glutathione. Urinary metabolites of male Sprague–Dawley rats following a single IP dose of 100 mg/kg of *p*-CNB diluted in olive oil included trace amounts of unchanged *p*-CNB, *p*-chloroaniline, 2,4-dichloroaniline, *p*-nitrothiophenol, 2-chloro-5-nitrophenol, 2-amino-5-chlorophenol, 4-chloro-2-hydroxyacetanilide, and a small amount of *p*-chloroacetanilide (248).

52.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV–TWA is 0.64 mg/m^3 (0.1 ppm) with skin notation. The ACGIH also considers *p*-CNB a confirmed animal carcinogen with unknown relevance to humans (160). NIOSH considers *p*-CNB as a potential occupational carcinogen. The current OSHA PEL is 1 mg/m^3 with skin notation. The NIOSH immediately dangerous to life or health concentration (IDLH) is 100 mg/m^3 (110). In Germany, *p*-CNB is considered a suspect carcinogen (246) and subject to a variety of legal regulations and orders with a maximum workplace concentration of 1 mg/m^3 assigned (26).

53.0 1-Chloro-2,4-dinitrobenzene

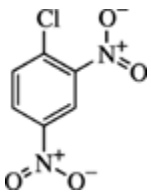
53.0.1 CAS Number: [*97-00-7*]

53.0.2–53.0.3 Synonyms and Trade Names: 2,4-Dinitro-1-chlorobenzene, 2,4-dinitrochlorobenzene, 1,3-dinitro-4-chlorobenzene, dinitrochlorobenzene, chlorodinitrobenzene, DNCB, and 4-chloro-1,3-dinitrobenzene

53.0.4 Molecular Weight: 202.55

53.0.5 Molecular Formula: $C_6H_3ClN_2O_4$

53.0.6 Molecular Structure:



53.1 Chemical and Physical Properties

1-Chloro-2,4-dinitrobenzene occurs as yellow crystals at room temperature. It has a melting point of 53–54°C (for a form) or 43°C (for b form) and a boiling point of 315°C; it is insoluble in water but readily soluble in ether, benzene, or hot alcohol. With two electron-withdrawing nitro groups situated at *ortho* and *para* positions, the chlorine is activated to become a good leaving group, thus

making the compound a good arylating agent (155, 156).
53.2 Production and Use
1-Chloro-2,4-dinitrobenzene is the best-known chlorodinitrobenzene isomer. It has been used in the manufacture of dyes, as a reagent for the detection of pyridine compounds, as an algicide in coolant water of air conditioning systems, and as a positive control in sensitization experiments.

Incidents of occupational exposure have been reported. The highly potent sensitizing activity of DNCB has limited its uses to closed systems.
53.4 Toxic Effects
Although not known to be a potent systemic toxicant with rat oral LD_{50} reported to be 1.07 g/kg (155), this chemical is a notoriously potent sensitizer. Dermal exposure can result in contact urticaria and yellow discoloration of the skin, as well as violent dermatitis (211). Adams et al. (249) reported a case in which DNCB had been used as an algicide in the coolant water of air conditioning systems. Four repairmen working on these systems suffered severe contact dermatitis that was very difficult to treat. The conclusion was that because DNCB is extremely allergenic and should be used only in closed systems that afford no human contact (167). In fact, DNCB has been used since 1927 for experimental induction of contact sensitivity and in allergenic cross-sensitization screening programs (137). A detailed review of the use of DNCB in experimental sensitization studies, including dose–response relationships and species differences, has been published (25).

1-Chloro-2,4-dinitrobenzene has been shown to be mutagenic in the Ames test without metabolic activation (244, 250). The presence of glutathione may reduce the direct-acting mutagenicity of DNCB by forming glutathione conjugate; however, the glutathione conjugate may be further activated by nitroreduction (250). A preliminary carcinogenicity study of DNCB in Charles River rats and Ham/ICR mice by dietary administration for 12–13 months was reported to be negative (182); however, in view of its being a direct-acting arylating agent, testing by dermal and inhalation routes may be more appropriate.

53.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Metabolism studies have demonstrated that DNCB depletes hepatic GSH levels by the biotransformation displacement of chlorine to yield 1-SG-2,4-dinitrobenzene (251). A reactive intermediate may be involved, for further studies have also demonstrated that DNCB was less mutagenic in a GSH-deficient derivative of *Salmonella typhimurium* TA100 (TA100/GSH-) than in TA100 itself, suggesting that the mutagenicity depends on GSH. Further investigations indicated that halogenated aromatics may react with bacterial DNA and produce premutagenic alterations according to two mechanisms: direct attack on the DNA through nucleophilic substitution (S_N2) of the halogen atoms, or activation through GSH conjugation and subsequent nitroreduction of the conjugate or its metabolic products to more reactive intermediates (250).
53.5 Standards, Regulations, or Guidelines of Exposure
1-Chloro-2,4-dinitroenzene is on OSHA's List of Highly Hazardous Chemicals. The highly potent sensitizing activity of DNCB has limited its uses to closed systems.
54.0 1-Chloro-2,5-dinitrobenzene
54.0.1 CAS Number: [*619-16-9*]

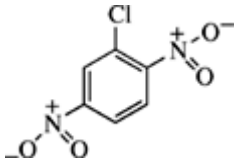
54.0.2 Synonyms: 2-Chloro-1,4-dinitrobenzene

54.0.3 Trade Names: NA

54.0.4 Molecular Weight: 202.55

54.0.5 Molecular Formula: $ClC_6H_3(NO_2)_2$

54.0.6 Molecular Structure:



1-chloro-2,5-dinitrobenzene occurs as light yellow crystals at room temperature, has a melting point of 64°C, and is soluble in alcohol, and ether (155). There is no specific information on its production. Its uses are reported to be identical with those of 1-chloro-2,4-dinitrobenzene, and its toxicity is assumed to be also similar. Information on exposure and regulations is not available.

55.0 1-Chloro-2,6-Dinitrobenzene

55.0.1 CAS Number: [*606-21-3*]

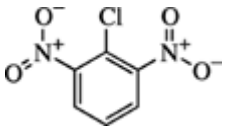
55.0.2 Synonyms: 2-Chloro-1,3-dinitrobenzene

55.0.3 Trade Names: NA

55.0.4 Molecular Weight: 202.55

55.0.5 Molecular Formula: $C_6H_3ClN_2O_4$

55.0.6 Molecular Structure:



1-Chloro-2,6-dinitrobenzene occurs as yellow crystals at room temperature; it has a melting point of 86–87°C and a boiling point of 315°C and is soluble in alcohol, ether, and toluene. With both nitro groups *ortho* to the chlorine, this compound is expected to be a good arylating agent. There is no specific information on its production and uses, although chlorodinitrobenzene isomers and mixtures have been used in the manufacture of dyestuffs, other dye intermediates, and certain explosives (167). Information on exposure, toxicology, and regulation is not available.

56.0 1-Chloro-2,3-dinitrobenzene

56.0.1 CAS Number: [*602-02-8*]

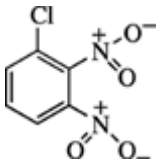
56.0.2 Synonyms: 3-Chloro-1,2-dinitrobenzene

56.0.3 Trade Names: NA

56.0.4 Molecular Weight: 202.55

56.0.5 Molecular Formula: $ClC_6H_3(NO_2)_2$

56.0.6 Molecular Structure:



1-chloro-2,3-dinitrobenzene has a melting point of 78°C and a boiling point of 315°C, is insoluble in water, and is soluble in alcohol and ether. There is no specific information on its production and uses, although chlorodinitrobenzene isomers and mixtures have been used in the manufacture of dyestuffs, other dye intemediates, and cartain explosives (167). Information on exposure, toxicology, and regulation is no available.

57.0 1-Chloro-3,4-dinitrobenzene

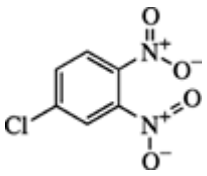
57.0.1 CAS Number: [*610-40-2*]

57.0.2–57.0.3 Synonyms and Trade Names: 1,2-Dinitro-4-chlorobenzene and 3,4-dinitrochlorobenzene

57.0.4 Molecular Weight: 202.55

57.0.5 Molecular Formula: $C_6H_3ClN_2O_4$

57.0.6 Molecular Structure:



1-chloro-3,4-dinitrobenzene occurs as monoclinic prisms and needles at room temperature, has melting points of 36°C (a form), 37°C (b form), 40–41°C (g form), a boiling point of 16° at 4 mm Hg; it is insoluble in water, but soluble in ether, benzene, carbon disulfide, and hot alcohol. There is no specific information on its production and uses, although chlorodinitrobenzene isomers and mixtures have been used in the manufacture of dyestuffs, other dye intermediates, and certain explosives (167). The compound was reported to be a skin sensitizer, causing contact dermatitis ranging from a few itching, vesicular papules to a generalized exfoliative dermatisis (167). Information on exposure and regulation is not available.

58.0 1-Chloro-3,5-dinitrobenzene

58.0.1 CAS Number: [*618-86-0*]

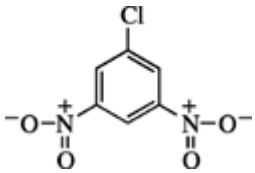
58.0.2 Synonyms: 1-Chloro-3,5-dinitrobenzene

58.0.3 Trade Names: NA

58.0.4 Molecular Weight: 202.55

58.0.5 Molecular Formula: $ClC_6H_3(NO_2)_2$

58.0.6 Molecular Structure:



1-chloro-3,5-dinitrobenzene occurs at colorless needles at room temperature; it has a melting point of 59°C, is insoluble is water, but is soluble in alcohol and ether. There is no specific information on its production and uses, although chlorodinitrobenzene isomers and mixtures have been used in

manufacture of dyestuffs, other dye intermediates, and certain explosives (167). Information on exposure, toxicology, and regulation is not available.

59.0 Pentachloronitrobenzene

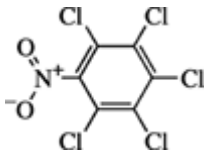
59.0.1 CAS Number: [*82-68-8*]

59.0.2–59.0.3 Synonyms and Trade Names: Avical, Eorthcicle, Fortox, Kobu, Marison Forte, Pkhnb, Terrafun, Tri PCNB, PCNB, Quintozine, quintobenzene, Terrachlor, Terraclor, Avicol, Botrilex, Earthcide, Kobutol, Pentagen, Tilcarex, SA Terraclor 2E, SA Terraclor, nitropentachlorobenzene, brassicol, quintocene, batrilex, fartox, formac 2, fungiclor, gc 3944-3-4, KP 2, olpisan, quintozen, saniclor 30, and tritisan

59.0.4 Molecular Weight: 295.34

59.0.5 Molecular Formula: $C_6Cl_5NO_2$

59.0.6 Molecular Structure:



59.1 Chemical and Physical Properties

Pentachloronitrobenzene is a colorless solid at room temperature. It has a melting point of 144°C (technical grade) and a boiling point of 328°C; it is slightly soluble in water (0.044 mg/L at 20°C; 2 mg/L at 25°C) and freely soluble in carbon disulfide, benzene, and chloroform. Technical-grade PCNB often contains impurities, which include hexachlorobenzene, pentachlorobenzene, and tetrachlorbenzene (155, 156, 252).

59.2 Production and Use

Approximately 2 million pounds of PCNB are used annually in the United States for agricultural purposes. It has been used as a soil or seed fungicide for the control of Botrytis disease, club root of crucifers, scab of potato, and Rhizoctonia damping-off disease of seedlings (253). It is also used as a turf fungicide to prevent root rotting.

As may be expected from its agricultural uses, occupational exposure may occur during its production and direct application as a soil fungicide. The general population may also be exposed through occasional consumer use or through ingestion of foods or drinking water containing PCNB residues.

59.3 Exposure Assessment

Biomonitoring data are not available.

59.4 Toxic Effects

Exposure to PCNB can induce contact sensitization (211). Methemoglobinemia has been demonstrated in cats, which have an unusually high sensitivity due to the low rate of methemoglobin reductase activity, following a single high oral dose of 1.6 g/kg (254). The reported oral LD_{50} for male rats (in corn oil) is 1.74 g/kg, and the LD_{50} (dermal) for rabbits was found to be >4 g/kg (255). The reported LC_{50} values are 1.4 g/m^3 for rats and 2.0 g/m^3 for mice (179).

Subchronic toxicity studies of PCNB by NTP (256) in rodents exposed to diets containing 33, 100, 333, 1000, or 2000 ppm of the compound indicated hyaline droplet nephropathy in male rats exposed to the two highest doses, minimal thyroid follicular cell hypertrophy in rats, and centrolobular hepatocellular hypertrophy in both rats and mice. The no-observed effect levels (NOELs) for histologic lesions were 33 ppm for male rats, 333 ppm for female rats, 100 ppm for female mice; no

NOEL could be determined for male mice in this study.

No adverse effects were reported in a three-generation reproductive study in which CD rats were administered a diet of PCNB at concentrations of 0, 5, 50, or 500 ppm (255). A followup teratogenic study in Charles River strain albino rats, administered PCNB at dosages of 100–1563 ppm in corn oil, did not demonstrate any treatment-related developmental effects (257). Nonteratogenicity was also confirmed in Wistar rats following oral administration (258). In a comparative study using contaminated PCNB (11% hexachlorobenzene) and purified PCNB (<20 ppm hexachlorobenzene), contaminated PCNB produced renal agenesis and cleft palates in C57B1/6 mice and cleft palates in CD-1 mice. Purified PCNB produced fewer cleft palates and no kidney malformations. Neither sample produced teratogenesis in CD rats (259).

Mutagenicity and related tests of PCNB showed that the compound is negative in most tests which include Ames, *E. coli* WP2, sister chromatid exchange, unscheduled DNA synthesis, and dominant lethal test in rats; there was only one report of induction of chromosome aberration in CHO cells both with and without metabolic activation (252).

A two-year dietary feeding study in four beagle dogs of each sex, at dietary levels of 0, 5, 30, 180, or 1080 ppm, demonstrated no treatment-related effect; 30 ppm was identified as the NOEL, and cholestatic hepatitis with secondary bile nephrosis was observed at 180 and 1080 ppm (255).

In a number of carcinogenesis assays, PCNB has not demonstrated carcinogenicity at 25, 100, 300, 1000, or 2500 ppm (diet of a commercial mixture of 20% PCNB) (260). A preliminary study showed that PCNB, (purity not specified) generated liver tumors in male B6AKF1 mice and female $B6C3F_1$ mice (261). A skin painting tumor initiation–promotion (croton oil) study in mice (purity not given) generated squamous cell carcinomas (262). An NCI bioassay on technical-grade PCNB (97% pure with 1% hexachlorobenzene) administered in the diet to Osborne–Mendel rats (5417 or 10,064 ppm for males, 7875 or 14,635 ppm for females) and $B6C3F_1$ mice (2606 or 5213 ppm for males, 4093 or 8187 for females) showed no evidence of carcinogenicity (253). In a second NCI/NTP study (252) in which $B6C3F_1$ male and female mice were fed diets containing 2500 and 5000 ppm, PCNB was also noncarcinogenic; however, infection in female mice may have reduced the sensitivity of the bioassay because of poor survival. In a recent industry-sponsored study submitted to the Office of Pesticide Program, PCNB was reported to induce slight but statistically significant increases in the incidences of follicular cell tumors in Charles River CD rats (263).

59.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Metabolism studies in a variety of animal species indicated that PCNB can be metabolized to (1) sulfur-containing metabolites after glutathione-*S*-transferase-catalyzed conjugation with glutathione, (2) pentachloroaniline after reduction, and (3) pentachlorophenol via denitration (252, 255). No information is available on mechanistic studies.

59.5 Standards, Regulations, or Guidelines of Exposure

A ACGH TLV–TWA is 0.5 mg/m^3 with A4 designation indicating that it is not classifiable as a human carcinogen (160). There are some restrictions on tolerance levels of this pesticide on peanuts and a variety of vegetables and fruits.

Aromatic Amino and Nitro–Amino Compounds and their Halogenated Derivatives

Yin-Tak Woo, Ph.D., DABT, David Y. Lai, Ph.D., DABT

G. Bicyclic and Tricyclic Aromatic Amines

Many bicyclic and tricyclic aromatic amines are potent carcinogens, with three of them (2-

naphthylamine, 4-aminobiphenyl, and benzidine) unequivocally shown to be human carcinogens and many of them considered occupational carcinogens (see Section 1.3.1) Compared to monocyclic aromatic amines, the additional aromatic ring(s) in the bicyclic and tricyclic aromatic amines confer greater capability for resonance stabilization of the metabolically activated reactive intermediate to allow more time to travel from the site of activation to reach DNA binding sites to initiate carcinogenesis. The structure–activity relationships of carcinogenic bicyclic and tricyclic aromatic amines have been extensively studied (44, 98, 198). The following structural features have been consistently observed across aromatic amines with various bicyclic and tricyclic aryl moieties: (1) aromatic amines with amino group(s) occupying the terminal end(s) (e.g., 2-position of naphthalene or aminofluorene, 4,4'-positions of biphenyl or diphenylmethane) of the longest conjugated chain of the aryl moiety are the most active carcinogens, (2) N-substitution with alkyl group(s) higher than methyl tends to be inhibitory especially if branched, (3) ring substitution with bulky group(s) tends to be inhibitory especially if flanking the amino group, (4) ring substitution with highly hydrophilic group(s) such as sulfonic acid tends to be inhibitory, and (5) ring substitution that distorts molecular planarity [e.g., at the 2-, 2'-, 6-, 6'-position(s) of biphenyl] may decrease or abolish activity. The structural formulas of the bicyclic and tricyclic aromatic amines covered in this chapter are depicted in Fig. 58.2 to provide an overview as well as under description of specific compound.

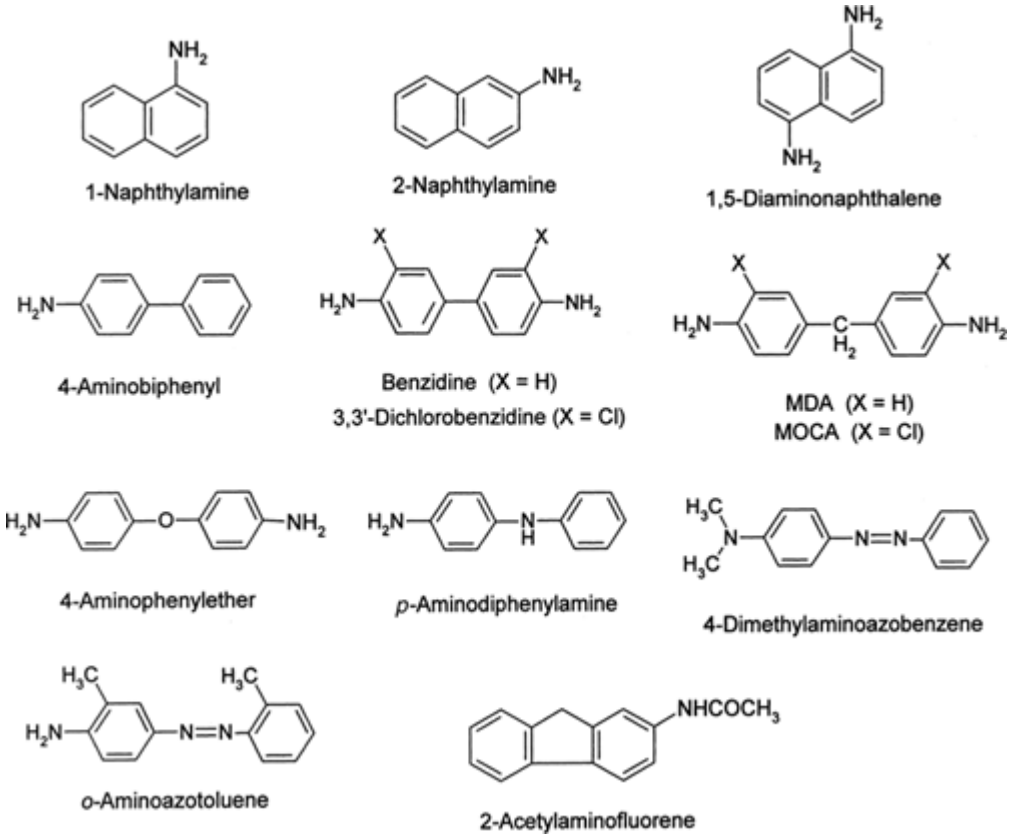


Figure 58.2. Overview of structural formulas of bicyclic and tricyclic aromatic amines.

Aromatic Amino and Nitro–Amino Compounds and their Halogenated Derivatives

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Aliphatic and Aromatic Nitrogen Compounds

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1.0 Ethyleneimine

1.0.1 CAS Number:

[*151-56-4*]

1.0.2-1.0.3 Synonyms and Trade Names:

Aziridine; dimethyleneimine; azocyclopropane; azirane; dihydroazirine; EI; amenoethylene; ethyleneimine; and ethylimine

1.0.4 Molecular Weight:

43.8

1.0.5 Molecular Formula:

C_2H_5N

1.0.6 Molecular Structure:

1.1 Chemical and Physical Properties

1.1.1 General

Physical Form:	mobile, colorless liquid, very volatile fluid
Boiling Point	55–56°C
Freezing Point	–78°C
Specific Gravity	0.8321 (24°C)
Vapor Pressure	160 mmHg at 20°C
Flammability	
Flash Point	–11°C
Explosive Limits IEL	3.6%
UEL	46%
Ignition Temperature (auto)	320°C
Solubility	infinitely soluble in water; soluble in alkali, alcohol

1.1.2 Odor and Warning Properties Ethyleneimine (EI) is a volatile liquid at room temperature and has an ammonia-like odor that is detectable at 2 ppm (v/v). Although it is highly volatile, the liquid is rapidly absorbed through the skin, and it is considered to have poor warning properties.

1.2 Production and Use

Ethyleneimine is used to manufacture triethylenemelamine and is used in its polymeric form in paper and textile chemicals, adhesive binders, petroleum refining chemicals, fuels and lubricants, coating resins, varnishes, lacquers, agricultural chemicals, cosmetics, ion-exchange resins, photographic chemicals, colloid flocculants, and surfactants (1).

One producer of EI in the United States has estimated annual capacity of 2.2 million kg. There are other producers of ethyleneimine in Germany, Japan, and probably the former Soviet Union (2, 3).

1.3 Exposure Assessment

Several analytical methods have been described (2–4). Environmental atmospheres that may contain EI are sampled by drawing air through a Folin's reagent bubbler, extracting with chloroform, and analyzing by high-performance liquid chromatography (HPLC) with an ultraviolet (UV) detector; the range is 0.16 to 20 mg/m^3. NIOSH Analytical Method 3514(14a).

1.4 Toxic Effects

1.4.2 Experimental Studies Ethyleneimine is highly toxic on an acute basis by all routes of administration. It is treated as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans) by the International Agency for Research on Cancer (2, 3), as an A3 carcinogen (confirmed animal carcinogen with unknown relevance to humans) (5), a cancer-suspect agent (Group 3) by the Occupational Safety and Health Administration (OSHA), and is regulated when present in materials at concentrations of 1% or more (6). The National Institute for Occupational Safety of Health (NIOSH) also regards EI as a “potential human carcinogen” (7).

1.4.1.1 Acute Toxicity Ethylenimine on an acute basis is highly toxic by all routes of administration (Table 59.1) (8–10). Its oral LD_{50} in rats is only 15 mg/kg, and the free imine is also a potent skin irritant and vesicant (8). Application of 0.005 mL of the imine as the pure material or 0.5 mL of a 15% aqueous solution caused severe corneal damage (10).

Table 59.1. Acute Toxicity Response to Ethyleneimine–Animals

Species	Dose	Route	Response	Ref.

Rat	15 mg/kg	Oral	LD_{50}	8
Rat	100 mg/m^3 (~56 ppm)	Inhalation	2-hr LC_{50}	9
Rabbit	100 mg/m^3	Inhalation	2-hr LC_{50}	9
Mouse	400 mg/m^3 (~222 ppm)	Inhalation	2-hr LC_{50}	9
Guinea pig	25 ppm	Inhalation	8-h LC_{LO}	8
Guinea pig	0.014 mL/kg	Skin	LD_{50}, necrosis	8
Rabbit	13 mg/kg	Skin	LD_{50}	10
Rabbit	0.005 mL	Eye	Severe corneal damage	10
Rabbit	0.5 mL (15% aqueous)	Eye	Severe corneal damage	10

In a series of acute inhalation exposures for varying periods of time (5 to 480 min), the 8-h LC_{50} in guinea pigs was 25 ppm, a concentration that also produced one death out of six rats. Death was delayed, and both rats and guinea pigs showed extreme respiratory difficulty at concentrations higher than 10 ppm; evidence of eye and nose irritation occurred at 100 ppm and higher (8).

Cause of death from massive overexposure is due to central nervous system (CNS) effects. Clinical signs of toxicity include eye and respiratory irritation, vomiting, and CNS effects including convulsions.

1.4.1.2 Subchronic and Chronic Toxicity Based on repeated exposure, 7-h exposures to 1.65 ppm for several months caused essentially no effects in several species. However, similar exposures to 3.5 ppm caused illness and death.

Inhalation of ethyleneimine results in delayed lung damage, including congestion, edema, and hemorrhage. Kidney damage has also been observed. Proteinuria, hematuria, increased blood urea nitrogen, and a depression of all blood elements have also been seen following inhalation. Histopathological examination has shown necrotic degeneration of renal tubular epithelium (4).

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Specific data on the absorption of EI by various routes of exposure were not found. However, based on toxicity test results in animals, EI is readily absorbed by all routes.

Ethyleneimine injected intraperitoneally into rats was distributed widely through the body and slightly accumulated in the liver, spleen, kidneys, intestine, and cecum.

Ethyleneimine apparently undergoes oxidation, because recovered radiolabeled CO_2 appears in the expired air of rats dosed intraperitoneally. Several urinary metabolites were also reported but were not identified. Some of the intraperitoneal dose was not metabolized but was eliminated unchanged in the urine and expired air. Urinary excretion is the major route of elimination for EI and its metabolites and accounts for about 50% of the administered dose. Pulmonary excretion of CO_2 and unchanged EI accounted for 3 to 5% and 1 to 3% of the administered dose, respectively. Fecal elimination or other minor routes of excretion were not discussed (11).

1.4.1.4 Reproductive and Developmental Except for a limited Soviet study suggesting embryo and maternally toxic effects during a 20-day inhalation exposure at 10 mg/m^3 (12), no developmental toxicity studies or studies to evaluate reproductive performance in mammals have been reported for

EI.

1.4.1.5 Carcinogenesis The carcinogenicity of ethyleneimine was evaluated in two strains of mice, and both gave positive results (13, 14). Groups of 18 male and 18 female mice of $B6C3F_1$ or B6AKR strains were treated orally (initially by gavage, then in the diet) from age 7 days through 77 to 78 weeks. The time-weighted average (TWA) dose was about 1.8 mg/kg/day. The incidence of hepatomas and lung adenomas was significantly elevated in both strains and sexes. In $B6C3F_1$ mice, the incidence of hepatomas and pulmonary adenomas was 15/17 and 15/17 in males and 11/15 and 15/15 females, respectively. In the B6AKR strain, hepatomas and adenomas occurred in 9/16 and 12/16 males and in 2/11 and 10/11 females, respectively. In the control groups, hepatomas were 8/79 and 0/87 in male and female B6C3F1 mice and 5/90 and 1/82 in male and female B6AKR mice. The respective incidence of pulmonary adenomas was 5/79, 3/87, 10/90, and 3/82. The incidence of hepatomas and pulmonary adenomas (reported as combined tumors) was significantly ($p < .01$) elevated (13, 14).

In rats treated by subcutaneous injections, EI was associated with an increase in injection site tumors, but no pulmonary or liver tumors were reported (10). In suckling mice (age 7 days, 4.64 mg/kg body weight), the incidence of tumors was significantly ($p < .01$) greater among males of two strains than in controls (13). Seven of 18 $B6C3F_1$ mice and 6 of 18 B6AKR strain male mice developed tumors of the liver, lungs, or lymphatics. The incidence of tumors in female mice was not different from controls.

On the basis of these carcinogenicity studies and its mutagenic potential, OSHA (6) called EI a "cancer-suspect" agent. The International Agency for Cancer Research (2, 3) placed EI in its Group 3 category (the agent is not classifiable as to its carcinogenicty to humans). ACGIH (5) calls EI an A3 carcinogen (confirmed animal carcinogen with unknown relevance to humans). NIOSH (7) reported it as a "potential human carcinogen."

1.4.1.6 Genetic and Related Cellular Effects Studies Ethyleneimine is an extremely reactive alkylating agent that is very mutagenic in all test systems investigated.

Ethyleneimine induced gene mutation (in microorganisms, such as viruses and *Salmonella typhimurium* bacteria, in plants, and in mammals), mitotic recombination (in fungi), mitotic and/or meiotic chromosomal aberrations (in plants, in *Drosophila melanogaster*, and in mammals), and dominant and recessive lethal mutations (in *Drosophila melanogaster*). It was mutagenic in every investigation except in a few instances where negative results could clearly be attributed to a dosing regimen that was too low (15).

1.4.2 Human Experience Epidemiological studies of worker groups exposed chronically to EI have not been reported. Several case reports are available, however, that describe the effects of acute accidental exposure. When five students were exposed to EI for about 2 h in a poorly ventilated room, the effects of exposure, which were delayed several hours in their onset, included vomiting, persistent eye inflammation (3 months after the exposure), a profound hacking cough with mild obstructive pneumonopathy, and ulceration of the upper respiratory tract (16). Several fatalities resulted from inhalation (or combined inhalation and skin contamination) of EI (17). Death resulted from pneumonia and pulmonary edema within several hours after brief exposures or, in one case, from progressive respiratory obstruction caused by destruction of the tracheobronchial cartilage over a period of 2 months following a 5-min exposure.

An occupational hazard assessment of EI sponsored by the National Cancer Institute (NCI) and centered on its carcinogenic potential was recently reported (18).

1.5 Standards, Regulations, or Guidelines of Exposure

The IARC has classified EI as a Group 3 carcinogen (the agent is not classifiable as to its carcinogenicity to humans). OSHA calls EI a "cancer-suspect agent" (Group 3) and regulates it as an

occupational carcinogen when it is present in formulations at concentrations of 1% or more requiring protective clothing, respiratory protection. NIOSH regards EI as a “potential human carcinogen” and recommends that occupational exposures be limited to the lowest possible concentrations. ACGIH categorizes EI as A3 (confirmed animal carcinogen with unknown relevance to humans).

Ethyleneimine does not have adequate warning properties to avoid overexposure. However, industrial exposure to EI is rigidly controlled by OSHA regulations and, or ACGIH and exhaust fans threshold limit value (TLV) limits its exposure during a 40-h week to an 8-hr TWA of 0.88 mg/m^3 (0.5 ppm), with a “skin” notation to alert against cutaneous absorption (5). Manufacturer recommendations (U.S.) are very explicit and suggest that one should not attempt to handle EI until fully acquainted with the dangers involved (1).

Finally, EPA lists EI as a hazardous air pollutant (HAP) generally known or suspected to cause serious health problems. The Clean Air Act, as amended in 1990, directs the EPA to set standards that require major sources to sharply reduce routine emissions of toxic pollutants. EPA is required to establish and phase-in specific performance-based standards for all air emission sources that emit one or more of the listed pollutants. Ethyleneimine is included in this list (19).

1.6 Studies on Environmental Impact

Ethyleneimine may be released to the environment as emissions or in wastewater from its manufacture and use. It is a reactive molecule, but there are no data on its fate in environmental media. It should react in the atmosphere with hydroxyl radicals (estimated half-life 1.5 days). If released in water, it will hydrolyze at a neutral pH in about 5 months, but it is apt to be lost much faster by evaporation or chemical reactions with metal ions. It should rapidly evaporate from soil, but it may also leach into the soil or complex with metal ions in the soil. It would not be expected to bioconcentrate in fish. No environmental monitoring data could be found for EI. Human exposure would be primarily occupational (20).

Aliphatic and Aromatic Nitrogen Compounds

Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

2.0 Propyleneimine

2.0.1 CAS Number:

[*75-55-8*]

2.0.2–2.0.3 Synonyms and Trade Names:

2-Methylaziridine, PI, and 2-methyleneimine

2.0.4 Molecular Weight:

57.09

2.0.5 Molecular Formula:

C_3H_7N

2.0.6 Molecular Structure:

2.1 Chemical and Physical Properties

2.1.1 General

Physical Form	colorless, oily liquid
Boiling Point	66–67°C

Freezing Point	–65°C
Vapor Density	2.0 (air = 1)
Density	0.802 at 25°C
Refractive Index	1.409 e
Vapor Pressure	112 mmHg at 20°C
Flammability	flammable
Solubility	miscible in water, soluble in ethanol
Stability	polymerizes; hydrolyzes in water or solutions of HCl to give methylethanolamine

2.1.2 Odor and Warning Properties Similar to that of aliphatic amines (fishy).

2.2 Production and Use

Propyleneimine is used in limited quantities as a chemical intermediate in the modification of latex surface-coating resins, polymers in textile and paper industries, dyes, photography, gelatins, oil additives, and organic synthesis. It is also a co-monomer for polymers with methacrylic acid and esters. Propylene imine has been made commercially by combining 1,2-dichloropropane with ammonia at elevated temperatures. It can function chemically as a secondary amine yielding N-substituted PI or as a cyclic amine involving ring opening reactions (2, 3).

2.3 Exposure Assessment

Several analytical methods for PI in air have been described (2, 3). In addition, one recent method that involves HPLC and UV detection should also be considered (21). Because PI is used in limited quantities and is treated as a possible carcinogen by OSHA, the IARC, and ACGIH, its exposure potential would be expected to be very low.

2.4 Toxic Effects

2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity Propyleneimine is highly toxic on an acute basis. However, relative to EI, it was one-fourth to one-eighth as toxic in a very limited acute inhalation study in rats (8). Acute toxicity data for PI are summarized in Table 59.2.

Table 59.2. Acute Toxicity Response to Propyleneimine–Animals (8)

Species	Dose	Route	Response
Rat	19 mg/kg	Oral	~LD_{50}
Guinea pig	0.043 mL/kg	Skin	~LD_{50}
Rabbit	0.005 ml	Eye	~LD_{50}
Rat	500 ppm, 2 hr	Inhalation	0 of 6 died
	500 ppm, 4 hr	Inhalation	5 of 6 died
Guinea pig	500 ppm, ½ hr	Inhalation	0 of 5 died
	500 ppm, 2 hr	Inhalation	3 of 5 died

2.4.1.2 Subchronic and Chronic Toxicity No subchronic or chronic inhalation toxicity studies were found. Repeated oral administration to assess carcinogenicity potential is discussed later.

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms No published studies on the absorption, distribution, metabolism, or excretion of PI were found.

2.4.1.4 Reproductive and Developmental No studies to evaluate PI's potential effects on the pregnant female or male and female reproductive performance were found.

2.4.1.5 Carcinogenesis The carcinogenicity of PI was evaluated in rats. When groups of 26 rats/sex were given oral doses of PI for 28 weeks, 28 of 52 rats dosed at 20 mg/kg and 45 of 52 rats dosed at 10 mg/kg developed tumors. Breast tumors, gliomas, ear duct tumors, leukemias, intestinal tumors, and miscellaneous tumors were reported. Both test groups experienced paralysis after 18 to 30 weeks of dosing, and mortality was high in the 20 mg/kg group. Therefore, this study, originally designed for a 60-week dosing regimen, was terminated after approximately 28 weeks. It was concluded that PI is a powerful carcinogen that affects a wide variety of organs (22).

2.4.1.6 Genetic and Related Cellular Effects Studies Like EI, PI is mutagenic in a variety of *in vitro* assays. It is positive in *Salmonella typhimurium* strains TA98 and TA100 (23) and in strains TA1535 and TA1538 with and without metabolic activation (24). Propyleneimine is also positive in *Saccharomyces cerevisiae* (25) in an unscheduled DNA synthesis (UDS) assay using human diploid fibroblasts (26), and in a rec-assay with *Escherichia coli* (27). In addition, PI was positive in several cell transformation assays (28).

PI was also positive *in vivo* in a rat micronucleus test using either bone marrow or peripheral blood as the target organ (29). It was also positive in the *Drosophila melanogaster* wing spot test (30).

2.4.2 Human Experience There are no human case reports or epidemiology studies available for PI. However, the acute toxic properties of PI are considered similar to those of ethyleneimine—irritation of skin, eye, and upper respiratory tract, nausea, and vomiting. Headache, dizziness, and shortness of breath might also occur.

2.5 Standards, Regulations, or Guidelines of Exposure

PI has been classified by the IARC as a Group 2B carcinogen (the agent is possibly carcinogenic to humans) (2, 3) and meets the criteria for OSHA's medical records rule (31). It has also been classified by the American Conference of Governmental Industrial Hygienists (ACGIH) as Group A3, a confirmed animal carcinogen with unknown relevance to humans (5).

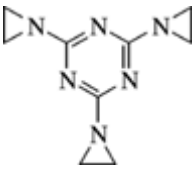
Occupational exposure limits were established for PI by both ACGIH (5) and OSHA (32): 2 ppm (4.7 mg/m^3) as an 8-h TWA, 40-h workweek, with a “skin notation” to alert against cutaneous absorption. In addition, exposure should be minimized due to IARC's classification of PI as a Group 2B carcinogen, ACGIH's classification as an A3 carcinogen, OSHA's medical record rules, and NIOSH's listing as a “potential human carcinogen.” Its occupational exposure limit (8-h TWA, skin notation), is 2 ppm (4.7 mg/m^3) as proposed by both OSHA (32) and the ACGIH (5).

2.6 Studies on Environmental Impact

The major sources of environmental release of propyleneimine are emissions and effluents from plants that manufacture or use this compound for surface coating resins to improve adhesion. If released to the soil, propyleneimine may be removed by chemical hydrolysis (half-life on the order of 17.5 days at neutral pH), ring-opening reactions with naturally occurring chemical species (i.e. humic materials), or fairly rapid volatilization from dry soil surfaces. If released to water, propyleneimine may undergo chemical hydrolysis (half-life 17.5 days at neutral pH), volatilization (half-life greater than or equal to 5 days in water 1 m deep flowing 1 m/s) or undergo ring-opening reactions with naturally occurring chemical species. Propyleneimine is not expected to photolyze, oxidize, or bioaccumulate significantly in aquatic organisms. If released to the atmosphere, propyleneimine, it is predicted, will exist almost entirely in the vapor phase. The primary removal mechanism is expected to be reaction with photochemically generated hydroxyl radicals (half-life on the order of 1.6 days). Human exposure to propyleneimine is probably due mainly to occupational exposure during production and use (20).

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

3.0 Triethylenemelamine
3.0.1 CAS Number:
[*51-18-3*]
3.0.2–3.0.3 Synonyms and Trade Names:
2,4,6-Triethylenimino-1,3,5-triazine; tetramine; TEM; Triamelin
3.0.4 Molecular Weight:
204.23
3.0.5 Molecular Formula:
$C_9H_{12}N_6$
3.0.6 Molecular Structure:



3.1 Chemical and Physical Properties
3.1.1 General

Physical Form	crystalline solid
Melting Point	160°C (decomposes)
Solubility	40% in water (w/w, 26°C) <0.1 g/100 mL at 16°C
Stability	aqueous solutions are stable for 3 months at 4°C; polymerizes at room temperature

3.1.2 Odor and Warning Properties None.
3.2 Production and Use
Triethylenemelamine (TEM) is a potent mutagen (33). It has little, if any, industrial application. TEM is used mainly in medicine as an antineoplastic agent and as a "positive control" in many *in vitro* and *in vivo* mutagenicity assays (34, 35).
3.3 Exposure Assessment
Because TEM has limited, if any, use in industry, no analytical methods have been developed to detect TEM in air, water, soil or biological specimens.
3.4 Toxic Effects
3.4.1 Experimental Studies 3.4.1.1 Acute Toxicity Triethylenemelamine is highly toxic on the basis of acute toxicity. Its oral LD_{50} is 13 mg/kg in the rat and 15 mg/kg in the mouse; in the dog, 1 mg/kg was lethal in 3 to 5 days (36). There are delayed gastrointestinal symptoms, diarrhea, and characteristic damage to lymphatic cells of the intestinal tract and elsewhere; bone marrow damage with depression of all blood elements; weakness, convulsions, respiratory failure, and death (36–38). No acute inhalation toxicity data were found. Acute toxicity responses by the oral and other routes of administration are tabulated in Table 59.3.

Table 59.3. Acute Toxicity of TEM in Animals (36)

Species	Dose (mg/kg)	Exposure Route	Response

Mouse	2.8	i.p.	LD_{50}
	15.0	Oral	LD_{50}
Rat	1.0	i.p.	LD_{50}
	13.0	Oral	LD_{50}
Dog	1.0	Oral	Lethal in 3–5 days
	0.4	i.v.	Lowest lethal dose
Cat	1.0	i.v.	Lethal in 7–12 days

3.4.1.2 Subchronic and Chronic Toxicity Very limited information about the general toxic response of animals to repeated dosing of TEM was found. Lethality occurred when rats and mice were given five daily intraperitoneal doses of TEM at 0.32 mg/kg and 1.1 mg/kg, respectively (36).

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Triethylenemelamine is well absorbed from the gastrointestinal tract and from the peritoneal cavity (36). Absorption through the skin or from the respiratory tract was not studied. In humans, blood levels of TEM fall rapidly after intravenous injection to a level of only 10% of the expected value in 2 min after dosing. No selective uptake by any tissue was reported. Eight percent of the ^{14}C ring-labeled TEM was excreted in the urine within 24 h as cyanuric acid (39). These results were very similar to those seen earlier in mice following intraperitoneal injection of a ^{14}C-labeled compound (40).

3.4.1.4 Reproductive and Developmental Toxicity Although no standard developmental toxicity or reproductive toxicity studies were found, TEM did induce fetal death and malformed offspring when pregnant rats were given intraperitoneal doses as low as 0.3 mg/kg (41). It is also a potent antifertility agent in mice dosed intraperitoneally at 0.25 to 1.0 mg/kg for 5 days (42).

3.4.1.5 Carcinogenesis In several older, limited studies, triethylenemelamine reportedly produced tumors in mice by the dermal and intraperitoneal routes and in rats by subcutaneous and/or intramuscular administration. These data were reviewed and evaluated by the IARC (2, 3) and judged as “limited evidence of carcinogenicity in animals.” As a result of this evaluation of the animal data and a lack of evidence of carcinogenicity in humans, the IARC placed TEM in its Group 3 category (2, 3).

3.4.1.6 Genetic and Related Cellular Effects Studies Triethylenemelamine is a potent mutagen (33). It evokes a positive response in almost every *in vitro* and *in vivo* mutagenicity assay in which it was tested. TEM was mutagenic in *Salmonella typhimurium, Saccharomyces cerevisiae, Neurospora crassa*, and cultured human lymphocytes, and it produced dominant lethal mutations in mice (2, 3, 33). It was also positive in the mouse micronucleus assay (43) and produced alterations in sperm-head morphology, as well as significant impairment of spermatogenesis in mice (42). In addition, it was positive in a recent rat micronucleus study using both bone marrow and peripheral blood as target organs (29) and produced specific locus mutations in *Neurospora crassa* (44). Because of its potent mutagenicity potential, TEM is used as an antineoplastic agent in treating a variety of human cancer types.

3.4.2 Human Experience The signs and symptoms produced in humans from therapeutic administration of TEM are briefly described. There are delayed gastrointestinal symptoms, diarrhea, and characteristic damage to the lymphatic cells of the intestinal tract and elsewhere; bone marrow

damage and depression of all blood elements (pancytopenia); tumor inhibition and cytotoxicity (chromosomal aberrations and inhibition of cell division); and antifertility effects. No injuries have been reported from the earlier, very limited use of TEM in industry (2, 3).

3.5 Standards, Regulations, or Guidelines of Exposure

Based on only limited evidence of carcinogenicity potential in rats and mice, the IARC placed TEM in its Group 3 category (the agent is not classifiable as to its carcinogenicity to humans). Neither OSHA nor NTP has classified TEM as a carcinogen. Because TEM has limited, if any, use in industry, no occupational exposure limits have been set. However, TEM is a highly toxic chemical and a potent mutagen, and exposure should be minimized.

3.6 Studies on Environmental Impact

None.

Aliphatic and Aromatic Nitrogen Compounds

Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

4.0 Chloroethylamines (Nitrogen Mustards)

4.0.1 CAS Number:

[*51-75-2*]

4.0.2–4.0.3 Synonyms and Trade Names:

MBA; Nitrogen Mustard; mechloroethamine; HN-2; Mustine Note; 2,2'-dichloro-*N*-methyldiethylamine; Dichloren; bis(2-chloroethyl)methylamine; 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine; bis(beta-chloroethyl) methylamine; Caryolysine; mechlorethanamine; chlormethine

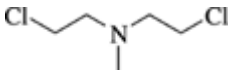
4.0.4 Molecular Weight:

156.05

4.0.5 Molecular Formula:

$C_5H_{11}Cl_2N$

4.0.6 Molecular Structure:



4.1.1 General

The information in this section describes the properties and toxicity of six of the simpler b-chloroethylamines in the following sections.

4.2 Production and Use

The nitrogen mustards are tertiary amines in which the halogen atom and the amine portion have reactivities similar to those of alkyl halides and alkyl amines. They are oily liquids that have limited water solubility but form readily soluble hydrochlorides. They are prepared by the action of thionyl chloride on the appropriate alkanolamine. Many of the actions of the nitrogen mustards resemble those of ethyleneimine derivatives because they are transformed in aqueous solutions into the highly reactive ethylenimonium intermediates: these ions can readily react with a variety of organic compounds *in vitro*, especially with amino, sulfhydro, and carboxyl groups of proteins and phosphate groups in nucleic acid, and therefore can alkylate biologically important macromolecules (36, 45).

The nitrogen mustards are not manufactured in significant commercial quantities in the United States. Some derivatives have been used in medicine as “antineoplastic agents,” and, to an even lesser extent, in treating a variety of nonmalignant diseases. No significant industrial uses of these chemicals in the United States were found.

Three b-chloroethylamine derivatives have been classified by the IARC as carcinogens. Studies of nitrogen mustard [2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine] reported "limited evidence of carcinogenicity in humans" and "sufficient evidence of carcinogenicity in animals," and it is classified by the IARC in Group 2A, (probably carcinogenic to humans). Nitrogen mustard N-oxide [2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine, *N*-oxide] and uracil mustard [5-bis(2-chloroethyl) amino-2,4(1*H*,3*H*)-pyrimidinedione] studies reported "sufficient evidence of carcinogenicity in animals," and they are classified by the IARC as Group 2B carcinogens (2, 3).

4.3 Exposure Assessment

Because there are no significant industrial uses of nitrogen mustards, no specific information to assess human exposure potential was found.

4.4 Toxic Effects

The important characteristic actions of the bis(b-chloroethyl)amines on biological systems are (1) severe local irritation of tissues and vesicant action on the skin and corneal damage in the eye; (2) delayed deaths for doses around the LD_{50}, prominent gastrointestinal effects and diarrhea; (3) cytotoxic effects and inhibition of cell division; (4) bone marrow and lymph node damage and leukopenia; (5) tumor inhibition; (6) antifertility effects, that is, impairment of menses and spermatogenesis; (7) mutagenic activity (*in vitro* and *in vivo*); (8) carcinogenicity or tumor irritation; and (9) pharmacological and neurotoxic activity (large doses). Their proclivity to damage actively proliferating cells (bone marrow, fetal tissue, germinal epithelium, neoplasms) is evident from the effects listed. Because many of these effects resemble those of ionizing radiation, the term "radiomimetic" is frequently used. Not all of the series produce all of these effects to the same degree; however, the differences among the polyfunctional b-chloroethylamines are minimal.

All of the preceding effects that have been observed in animals can presumably occur in humans. Most of these effects have been observed during the therapeutic use of these agents. Nearly all patients developed nausea, vomiting, headache, and diarrhea. A major toxic effect is depression of normal bone marrow function and a decrease in the total number of circulating leukocytes and platelets. Because the b-chloroethylamines have limited specialized use in industry and chemical laboratories and because their high degree of toxicity and serious effects are rather universally recognized, there have been few reports of injury from these sources. No case reports or epidemiology studies of exposure to nitrogen mustards were found.

The chloroethylamines in this group are discussed individually in sections 5.0 through 10.0

Aliphatic and Aromatic Nitrogen Compounds

Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

5.0 Nitrogen Mustard (Hydrochloride)

5.0.1 CAS Number:

[*55-86-7*]

5.0.2–5.0.3 Synonyms and Trade Names:

Ethanamine; 2-chloro-*N*-(2-chloroethyl)-*N*-methyl-(hydrochloride); bis(2-chloroethyl)methylamine (HCl); chlormethine(HCl); Mustine(Hal); and HN_2(HCl) Mechlorethamine hydrochloride; beta, beta'-dichlorodiethyl-*N*-methylamine hydrochloride; Azotoyperite; bis(2-chloroethyl)methylamine hydrochloride; C 6866; Caryolysine hydrochloride; chloramin hydrochloride; chlormethine hydrochloride; Dema; dichloren hydrochloride; dichloromethyldiethylamine hydrochloride; Embichin hydrochloride; Erasol hydrochloride; HN2 hydrochloride; methyl bis(beta-chloroethyl) amine, hydrochloride; methylbis(2-chloroethyl)amine hydrochloride; Mitoxine; Mustargen hydrochloride; Mustine hydrochlor; Mustine hydrochloride; MBA hydrochloride; *N*-methyl-2,2'-dichlorodiethylamine hydrochloride; *N*-methylbis(beta-chlorethyl)amine hydrochloride; *N*-methylbis

(2-chloroethyl)amine hydrochloride; Nitrogranulogen hydrochloride; 1,5-dichloro-3-methyl-3-azapentane hydrochloride; 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine hydrochloride; 2,2'-dichloro-*N*-methyldiethylamine hydrochloride; mustargen; *N*,*N*-bis(2-chloroethyl)methylamine hydrochloride; antimit; chlorethazine; chlormethinum; cloramin; dimitan; embikhine, erasol-ido; kloramin; mebichloramine; merchlorethamine; Nitol; nitol "takeda", Pliva; stickstofflost; zagreb; *N*-bis-(2-chloroethyl)-*N*-methylamine hydrochloride; mechlorethamine Hydrochloride,5%

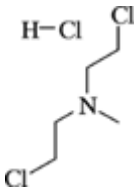
5.0.4 Molecular Weight:

156.05; 192.52 (*HCl)

5.0.5 Molecular Formula:

$C_5H_{12}Cl_3N$

5.0.6 Molecular Structure:



5.1 Chemical and Physical Properties

5.1.1 General

	Nitrogen Mustard	Nitrogen Mustard HCl
Chemical Formula	$C_5H_{11}Cl_2N$	$C_5H_{12}Cl_3N$
Physical State	liquid	white crystals
	none	none
Boiling Point	217°C at 10 mmHg	—
Melting Point	14.45°C	–60°C
Density	1.118 at 25/5°C	—
Solubility	miscible with DMF, CS_2, and CCl_4	soluble in H_2O and ethanol
Stability	reacts with H_2O; decomposes on standing	stable dry; unstable in H_2O

5.1.2 Odor and Warning Properties None.

5.2 Production and Use

See section 4.2.

5.3 Exposure Assessment

See section 4.3.

5.4 Toxic Effects

5.4.1 Experimental Studies

5.4.1.1 Acute Toxicity Nitrogen mustard (and its hydrochloride) is highly toxic on an acute basis and

produces all of the effects previously described. It has an oral LD_{50} of 10 mg/kg in rats and 20 mg/kg in mice (46). By the dermal route, its LD_{50} in rats is 12 mg/kg, indicating that it is readily absorbed (47). By the intravenous route, its LD_{50} was 1.1 mg/kg in rats, 2 mg/kg in mice, 1 mg/kg in dogs, and 1.6 mg/kg in rabbits (46). By inhalation, the only information found was for short exposure periods—a 2-min LC_{50} of 600 mg/m^3 in rats, a 30-min LC_{50} of 1500 mg/m^3 in mice, and a 10-min LC_{50} of 2000 mg/m^3 in dogs (48).

Nitrogen mustard in contact with the eye is reportedly severely damaging and acts similarly to sulfur mustard gas but with more immediate effect and greater tendency to injure deeper ocular structures, particularly the iris and lens (49). Relative to dermal exposure, it is reportedly a potent vesicant and local irritant.

5.4.1.2 Subchronic and Chronic Toxicity No specific repeated exposure studies were found.

5.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Oral absorption of nitrogen mustard and its hydrochloride salt is variable and less complete than absorption from subcutaneous injection, but these materials are readily absorbed dermally and by inhalation. An intravenous dose of 3 mg/kg administered to dogs readily disappeared from the blood: 0.01% was found in urine, low levels were found in various tissues, and bone marrow showed the highest concentration. Approximately 90% was metabolized within 4 min of incubation with whole blood (50). Within 30 sec after intravenous injection of ^{14}C-labeled nitrogen mustard, more than 90% disappeared from the blood in another study (39). The promptness with which these agents are transformed *in vivo* is also evident by their rapid action. Following its *in vivo* administration, nitrogen mustard or its hydrochloride is probably converted to an ethylenimonium ion which then reacts readily with a large number of biologically important macromolecules (36, 45).

5.4.1.4 Reproductive and Developmental Nitrogen mustard is reportedly an active developmental toxin in four species of laboratory animals: mice, rats, rabbits, and ferrets (51). It was also an antifertility agent in rodents (52–54). All of the preceding effects involved intraperitoneal or intravenous doses of less than 1 mg/kg.

5.4.1.5 Carcinogenesis Nitrogen mustard administered mainly as the hydrochloride salt is carcinogenic in mice and rats. Following its subcutaneous, intraperitoneal, or intravenous injection, it produced an increased incidence of lung tumors and thymic lymphomas in mice. It produced a variety of malignant tumors in rats following intravenous injection. On the basis of there studies, its mutagenic potential, and "limited evidence of carcinogenicity in humans," IARC has classified nitrogen mustard in Group 2A (probably carcinogenic to humans) (3).

5.4.1.6 Genetic and Related Cellular Effects Studies Nitrogen mustard, like many antineoplastic agents, is mutagenic in many *in vitro* and *in vivo* test systems. It induced dominant lethal mutations and induced micronuclei in bone marrow cells of mice exposed *in vivo* and alkylated DNA of ascites cells in experimental animals treated *in vivo*. It induced chromosomal aberrations, sister chromatid exchanges, and unscheduled DNA synthesis in human cells *in vitro*. It induced sister chromatid exchanges, chromosomal aberrations, and DNA damage in rodent cells *in vitro*; the latter studies on the induction of mutation were inconclusive. It also transformed mouse C3H10T1/2 cells. Nitrogen mustard induced aneuploidy and somatic mutation and recombination in *Drosophila*, chromosomal aberration in plants, mitotic recombination and mutation in fungi, and mutation and DNA damage in bacteria (3).

5.4.2 Human Experience See section 4.4.

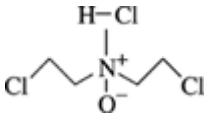
5.5 Standards, Regulations, or Guidelines of Exposure

No workplace limits for industrial air have been proposed for nitrogen mustard (or its hydrochloride)

by OSHA, ACGIH, or AIHA.
5.6 Studies on Environmental Impact
Nitrogen mustard's production and use as an antineoplastic agent and its former production as a gas warfare agent may result in its release to the environment through various waste streams. If released to the atmosphere, nitrogen mustard will mainly exist in the vapor phase in the ambient atmosphere based on an estimated vapor pressure of 65 mmHg at 25°C. Vapor-phase nitrogen mustard is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals whose estimated half-life is about 2 days. An estimated K_{oc} of 74 suggests that nitrogen mustard will have high mobility in soil. Volatilization from dry soil surfaces may be an important fate process based on its vapor pressure; however, nitrogen mustard is not expected to volatilize from moist soil surfaces because of its low Henry's law constant. Nitrogen mustard is expected to hydrolyze rapidly in both moist soil and water. A hydrolysis half-life of 11 hours at 25°C was measured in water; methyldiethanolamine is the expected product from this reaction. Nitrogen mustard is not expected to adsorb to suspended matter in the water column based on its K_{oc} value or to volatilize from water surfaces given an estimated Henry's law constant of 8.5×10^{-8} atm-cu m/mole. Bioconcentration in aquatic organisms should not occur based on an estimated BCF value of 3 (20).

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

6.0 Nitrogen Mustard **N**-Oxide (Hydrochloride)
6.0.1 CAS number:
[*302-70-5*]
6.0.2 Synonyms:
Ethanamine; 2-chloro-*N*-(2-Chloroethyl)-*N*-methyl-,*N*-oxide(hydrochloride); 2,2-dichloro-*N*-methyldiethylamine, oxide (HCl); chlormethine *N*-oxide(HCl); HN2 Oxide Mustard; 2-chloro-*N*-(2-chloroethyl)-*N*-methyl-Ethanamine, *N*-oxide hydrochloride
6.0.3 Trade Names:
None
6.0.4 Molecular Weight:
172; 208.5(*HCl)
6.0.5 Molecular Formula:
$C_5H_{12}Cl_3NO$
6.0.6 Molecular Structure:



6.1 Chemical and Physical Properties
6.1.1 General:

Physical State	colorless, odorless crystals (*HCl)
Melting Point	109°C (*HCl)
Solubility	both forms are soluble in H_2O and ethanol

6.1.2 Odor and Warning Properties None.
6.2 Production and Use

See section 4.2.
6.3 Exposure Assessment
See section 4.3.
6.4 Toxic Effects
6.4.1 Experimental Studies 6.4.1.1 Acute Toxicity Nitrogen mustard N-oxide produces all of the biological effects described previously for this class of compound. Although few acute data were found, the N-oxide form is slightly less toxic than nitrogen mustard itself. Its intravenous LD_{50} in rats is 60 mg/kg (55) compared to 1.1 mg/kg for nitrogen mustard (46). By the oral route, an LD_{50} of 60 mg/kg in rats was reported for the N-oxide (56) compared to a 10 mg/kg LD_{50} for nitrogen mustard (46). No data related to dermal, eye, or inhalation toxicity were found.

6.4.1.2 Subchronic and Chronic Toxicity No specific toxicity studies of repeated exposure were found.

6.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms After intravenous injections of 5 mg/kg of radio-labeled N-oxide into dogs, almost no activity was found in blood after 1 h, suggesting rapid metabolism. The highest level of radioactivity in the urine was found between 5 and 20 min after injection and declined to zero after 4 h (57). No other information on absorption, distribution, or excretion of nitrogen mustard N-oxide in mammals was found.

6.4.1.4 Reproductive and Developmental No specific studies to evaluate developmental toxicity potential in animals were found. However, like other b-chloroethylamines, nitrogen mustard N-oxide has produced antifertility effects in male rats (58) and mice (59).

6.4.1.5 Carcinogenesis Nitrogen mustard N-oxide is reportedly carcinogenic in mice and rats. Following subcutaneous administration in mice, it produced lung tumors, thymic lymphomas, and Harderian gland adenomas. In rats given the material intravenously, it produced mainly lymphoreticular tumors and sarcomas. The preceding data were evaluated by the IARC and considered “sufficient evidence of carcinogenicity in animals.” Based on this evaluation and its mutagenic potential, the IARC classified nitrogen mustard N-oxide as Group 2B (possibly carcinogenic to humans) (3).

6.4.1.6 Genetic and Related Cellular Effects Studies In earlier studies, nitrogen mustard N-oxide was mutagenic in tumor cells and bacteria and also induced dominant lethal mutations in mice (2, 3). In more recent studies, this material was mutagenic in *Salmonella typhimurium, Escherichia coli*, and *Bacillus subtilis* (60). It also induced sister chromatid exchanges in human lymphocytes (61) and unscheduled DNA synthesis in various rat cell types (62).

6.4.2 Human Experience See section 4.4.
6.5 Standards, Regulations, or Guidelines of Exposure
No workplace limits for industrial air have been set by OSHA, ACGIH, or NIOSH for nitrogen mustard *N*-oxide(or its hydrochloride).
6.6 Studies on Environmental Impact
Because the substance is used only as an antineoplastic agent, health professionals (e.g., pharmacists, nurses, and physicians) involved in cancer chemotherapy are the principal personnel who may be exposed. Exposure may occur during drug preparation, administration, or cleanup (63).

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

7.0 Tris(b-chloroethyl)amine (hydrochloride)

7.0.1 CAS Number:
[*555-77-1*]; [*817-09-4*] (*HCl)
7.0.2 Synonyms:
Ethanamine, 2-chloro-*N*, *N*-bis(2-chloroethyl)*(hydrochloride); 2,2',2"-trichlorotriethylamine (*HCl); HN3(*HCl); trimustine(*HCl); trichloromethine- (*HCl)
7.0.3 Trade Name:
None
7.0.4 Molecular Weight:
204.53; 240.99 (*HCl)
7.0.5 Molecular Formula:
$C_6H_{12}NCl_3$
7.0.6 Molecular Structure:
$N(CH_2CH_2Cl)_3$(ĖHCl)
7.1 Chemical and Physical Properties
7.1.1 General

Physical State	liquid; white powder(*HCl)
Boiling Point	144°C at 15 mmHg
Solubility	Very soluble in water
Melting Point	131°C (HCL)

7.1.2 Odor and Warning Properties None.
7.2 Production and Use
See section 4.2.
7.3 Exposure Assessment
See section 4.3.
7.4 Toxic Effects
7.4.1 Experimental Studies 7.4.1.1 Acute Toxicity Tris(b-chloroethyl)amine produces the same biological effects as the preceding nitrogen mustards. This material is highly toxic on an acute basis. It is readily absorbed through the skin as indicated by dermal LD_{50}s of 7, 4.9, 19, and 1 mg/kg body weight, in mice, rats, rabbits, and dogs, respectively (46). By the oral route, a lowest lethal dose (LD_{LO}) of 5 mg/kg for rats (64) and an LD_{50} of 1.1 mg/kg for mice (65) were reported. The LD_{50} after intravenous injection was 0.7 mg/kg for rats and 2.5 mg/kg for rabbits (46).

In dogs, tris(b-chlorethyl)amine caused vomiting, anorexia, and blood in the feces a few hours after a single intravenous dose of 1 mg/kg. Coma preceded death by anoxia as a consequence of peripheral circulatory failure (66). In rabbits (67) injected intravenously and in mice (68) given a subcutaneous dose, the immediate response was a decreased peripheral lymphocyte count. Tris(b-chloroethyl) amine is reportedly a strong vesicant on skin and produces conjunctivitis (2, 3).

7.4.1.2 Subchronic and Chronic Toxicity No specific toxicity studies of repeated exposure were found for tris(b-chloroethyl)amine (or its hydrochloride).

7.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms No specific data on absorption, distribution, excretion, or metabolism were found. However, tris(b-chloroethyl)amine causes cross-links in membrane proteins and hemoglobin in human erythrocytes *in vitro* (69, 70), and it also alkylates nucleic acids *in vitro* (71).

7.4.1.4 Reproductive and Developmental No studies to assess developmental toxicity potential were found. However, like other nitrogen mustards, tris(b-chloroethyl)amine is probably an antifertility agent in male rats (2.4 mg/kg) by the intravenous route (72) and in male mice (1.5 mg/kg) by intraperitoneal administration (73).

7.4.1.5 Carcinogenesis Tris(b-chloroethyl)amine was tested for carcinogenic potential in mice and rats given the material by subcutaneous injection. The study in mice was considered inadequate for evaluation by the IARC. However, in rats, this material induced a high incidence of sarcomas (mostly spindle-cell type) in animals of each sex at the site of injection, as well as a few intestinal adenocarcinomas; neither tumor type was seen in controls. IARC considered the preceding data "sufficient evidence of carcinogenicity in experimental animals." Although no human carcinogenicity data were available, the IARC classified tris(b-chloroethyl)amine in Group 2B (the agent is possibly carcinogenic to humans). This classification was based on these animal studies, its mutagenic potential, and analogy to other nitrogen mustards (74).

7.4.1.6 Genetic and Related Cellular Effects Studies Tris(b-chloroethyl)amine, like other antineoplastic agents, is mutagenic *in vitro* and *in vivo*. It inhibited DNA synthesis and induced mutations at the hprt locus of Chinese hamster V79 cells (75) and produced DNA inhibition in human fibroblast cells (76). A single intraperitoneal treatment at 5 mg/kg also induced dominant lethal mutations in mice (77).

7.4.2 Human Experience See section 4.4.
7.5 Standards, Regulations, or Guidelines of Exposure
No workplace limits have been set by OSHA, ACGIH, or AIHA for tris(b-chloroethyl)amine (or its hydrochloride) in industrial air.
7.6 Studies on Environmental Impact
Tris(2-chloroethyl)amine belongs to the nitrogen mustard group of compounds. It is produced in small quantitities as the hydrochloride and may enter the waste stream as such during the production process. If released to either soil or water, hydrolysis is expected to be a major fate process for tris(2-chloroethyl)amine, especially under weakly alkaline conditions. An estimated Henry's law constant of 3×10^{-7} atm-cu m/mole indicates that this compound is essentially nonvolatile and thus volatilization from water and moist soil will not be an important environmental fate process. An estimated K_{oc} value of 672 suggests that tris(2-chloroethyl)amine has a low to moderate mobility potential through soil. However, as hydrolysis may proceed quickly, mobility of this compound through the soil is not expected to be a major fate process. An estimated BCF value of 30 suggests that this compound will not bioconcentrate in aquatic organisms and hydrolysis should preclude bioconcentration from being a major fate process. If released to the atmosphere, tris(2-chloroethyl) amine is expected to degrade rapidly based on a half-life of five hours. Insufficient data are available to predict the relative importance or rate of biodegradation in soil or water (20).

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

8.0 Dimethyl(b-chloroethyl)amine (hydrochloride)
8.0.1 CAS Number:
[*107-99-3*]; [*4584-46-7*](*HCl)
8.0.2 Synonyms:
Ethanamine, 2-chloro-*N*-*N*-dimethyl(hydrochloride); dimethylalminoethyl chloride; HN1; nitrogen half mustard
8.0.3 Trade Name:
None
8.0.4 Molecular Weight:
107.58; 144.04(*HCl)
8.0.5 Molecular Formula:
$C_4H_{10}NCl$

8.0.6 Molecular Structure:
$(CH_3)_2NCH_2CH_2Cl(\dot{c}HCl)$
8.1 Chemical and Physical Properties
8.1.1 General

Physical State	liquid
Boiling Point	109–110°C at 750 mmHg
Melting Point	205–208°C (HCl)

8.1.2 Odor and Warning Properties None.
8.2 Production and Use
See section 4.2.
8.3 Exposure Assessment
See section 4.3.
8.4 Toxic Effects
8.4.1 Experimental Studies 8.4.1.1 Acute Toxicity This monofunctional b-chloroethylamine does not have the cytotoxic and leukopenic potency of the nitrogen mustards. Its major actions are local irritation, effects on the autonomic nervous system, and neurotoxicity. The single dose LD_{50} in mice by subcutaneous injection was 200 mg/kg in one study (68) and 250 mg/kg (for the hydrochloride salt) in another study (78). The only other acute information found was an intraperitoneal LD_{50} in mice of 280 mg/kg (79).

8.4.1.2 Subchronic and Chronic Toxicity No specific toxicity studies of repeated exposure in animals were found for dimethyl(b-chloroethyl)amine or its hydrochloride salt.

8.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms No information for absorption, distribution, excretion, or metabolism in mammals was found.

8.4.1.4 Reproductive and Developmental No experimental studies of dimethyl(B-chloroethyl)amine were found to assess its potential to affect the unborn fetus or reproductive performance.

8.4.1.5 Carcinogenesis No studies by common exposure routes have been conducted. In addition, dimethyl(b-chloroethyl)amine (and its hydrochloride salt) has not been evaluated by the IARC for carcinogenic potential.

8.4.1.6 Genetic and Related Cellular Effects Studies Dimethyl(b-chloroethyl)amine was mutagenic in a variety of *in vitro* assays. It was positive in the Ames test, the L5178Y mouse lymphoma cell assay, and the hepatocyte primary culture-DNA repair test, tests designed to detect chemicals that interact with DNA (80). It was also positive in *E. coli* (81), induced sister chromatid exchanges in various rat cells (82), and produced sex chromosome loss and nondisjunction in *Drosophila melanogaster* (83).

8.4.2 Human Experience See section 4.4.
8.5 Standards, Regulations, or Guidelines of Exposure
No workplace limits have been set by OSHA, ACGIH, or AIHA for dimethyl(b-chloroethyl)amine in industrial air.
8.6 Studies on Environmental Impact
None.

Aliphatic and Aromatic Nitrogen Compounds

Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

9.0 Diethyl(b-chloroethyl)amine (Hydrochloride)
9.0.1 CAS Number:
[*100-35-6*]; [*869-24-9*](*HCl)
9.0.2 Synonyms:
Ethanamine, 2-chloro-*N*-*N*-diethyl(hydrochloride); 2-chlorotriethylamine (*HCl); diethylaminoethyl chloride (*HCl)
9.0.3 Trade Name:
None
9.0.4 Molecular Weight:
134.64; 172.10(*HCl)
9.0.5 Molecular Formula:
$C_6H_{14}NCl$
9.0.6 Molecular Structure:
$C_6H_{14}NCl(CH_3CH_2)_2NCH_2CH_2Cl(\cdot HCl)$
9.1 Chemical and Physical Properties
9.1.1 General

Physical State	liquid
Boiling Point	51–52°C at 16 mmHg
Melting Point	208–210°C (HCL)

9.1.2 Odor and Warning Properties None reported.
9.2 Production and Use
See section 4.2.
9.3 Exposure Assessment
See section 4.3.
9.4 Toxic Effects
9.4.1 Experimental Studies 9.4.1.1 Acute Toxicity The acute toxicological effects of diethyl(b-chloroethyl)amine are similar to those of the preceding dimethyl derivative in that it is not as cytotoxic or leukopenic as the other bifunctional nitrogen mustards. Its intravenous LD_{50} in mice and rabbits was 100 and 40 mg/kg, respectively, and its subcutaneous LD_{50} in mice was 100 mg/kg (46). In the rat, the oral LD_{50} is 17 mg/kg, and this material was also a moderate skin and severe eye irritant. Finally, its dermal LD_{50} in rabbits was 300 mg/kg (84).

9.4.1.2 Subchronic and Chronic Toxicity No animal toxicity studies of repeated exposure were found.

9.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms No information for absorption, distribution, excretion or metabolism of diethyl(b-chloroethyl)anime in mammals was found.

9.4.1.4 Reproductive and Developmental No studies to assess the effects of diethyl(b-chloroethyl) amine on the unborn fetus or on reproductive performance were found.

9.4.1.5 Carcinogenesis No studies to assess carcinogenic potential were found. In addition, this chemical has not been evaluated for carcinogenicity potential by the IARC or ACGIH. However, its dimethyl analog produced lung tumors in strain A mice following intraperitoneal injection (85).

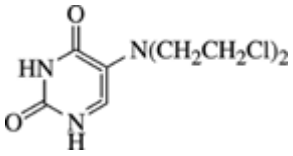
9.4.1.6 Genetic and Related Cellular Effects Studies Like its dimethyl analog, diethyl(b-chlorethyl) amine is mutagenic in a variety of *in vitro* assays. It was positive in the Ames test, the L5178Y mouse lymphoma cell assay, and the hepatocyte primary-culture DNA-repair test (80). It was also

positive in *E. coli* (86) and induced sister chromatid exchanges in various types of rat cells (82).

9.4.2 Human Experience See section 4.4.
9.5 Standards, Regulations, or Guidelines of Exposure
No workplace limits have been set by OSHA, ACGIH, or AIHA for diethyl(b-chloroethyl)amine in industrial air.
9.6 Studies on Environmental Impact
None.

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

10.0 Uracil Mustard
10.0.1 CAS Number:
[*66-75-1*]
10.0.2–10.0.3 Synonyms and Trade Names:
5[Bis(2-chloroethyl)amino]-2, 4-(1H,3H)-pyrimidinedione; Uracil nitrogen mustard; Aminouracil mustard; Chlorethaminacil; CB-4835; Desmethyldopan; Nordopan; sk-19849; U-8344; Uracillost; Uracilmostaza; Uramustine; 2,6-dihydroxy-5-bis[2-chloroethyl]aminopyridimidine; 5-[bis(2-chloroethyl)amino]uracil; 5-[di(beta-chloroethyl)amino]uracil; 5-*N*,*N*-bis(2-chloroethyl)aminouracil
10.0.4 Molecular Weight:
252.10
10.0.5 Molecular Formula:
$C_8H_{11}Cl_2N_3O_2$
10.0.6 Molecular Structure:



10.1 Chemical and Physical Properties
10.1.1 General

Physical State	white, odorless crystals
Melting Point	206°C
Solubility	very slightly soluble in water; slightly soluble in methanol and acetone
Stability	unstable in water and acid solutions

10.1.2 Odor and Warning Properties None reported.
10.2 Production and Use
See section 4.2.
10.3 Exposure Assessment
See section 4.3.
10.4 Toxic Effects
10.4.1 Experimental Studies 10.4.1.1 Acute Toxicity Uracil mustard is highly toxic on an acute basis. Its oral LD_{50} in mice and rats ranges from 2 to 6 mg/kg and its LD_{50} by either intramuscular or intraperitoneal routes ranges from 1 to 3 mg/kg (86). In another study (87), the oral LD_{50} in rats

was 3.5 mg/kg, and rats exhibited sleepiness, muscle weakness, and gastrointestinal distress. Extensive damage to bone marrow and testis was also reported.

10.4.1.2 Subchronic and Chronic Toxicity No standard toxicity studies for repeated exposure were found. However, as part of a limited carcinogenicity study (88), mice injected intraperitoneally (0.18 to 12 mg/kg body weight) three times a week for 4 weeks and observed for several months showed liver damage such as early portal cirrhosis.

10.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Only a few limited studies were found. When ^{14}C-uracil mustard was given to Walker carcinosarcoma-bearing rats at a 4 mg/kg dose, incorporation of the ^{14}C-label into macromolecules in subcellular fractions of various tissues was maximal by 1 h after administration and was more extensive in RNA than in DNA or in protein (89). In one other study, when 0.2 mmol/ml uracil mustard was added to heparinized human blood *in vitro*, about 50% of it was no longer detectable (colorimetrically) after 30 min (90).

10.4.1.4 Reproductive and Developmental In a limited developmental toxicity study, administration of uracil mustard to female rats in doses of 0.3 and 0.6 mg/kg body weight on the 12th day of pregnancy produced retarded and clubbed appendages, exencephaly, and deformed paws and tails in the surviving offspring at 21 days (91). Although no standard studies to assess reproductive performance were found, uracil mustard, like other nitrogen mustards, probably is an antifertility agent. In one older study (87), rats given 3.5 mg/kg uracil mustard orally exhibited extensive damage to the testis.

10.4.1.5 Carcinogenesis Uracil mustard was reportedly carcinogenic in both mice and rats following multiple intraperitoneal injections. It produced a dose-related increase in lung tumor incidence in mice and tumors in a variety of other organs in both mice and rats. The IARC reviewed the preceding data and deemed it “sufficient evidence of carcinogenity in animals.” Based on this information, its mutagenic potential, analogy to other nitrogen mustards, and a lack of carcinogenicity data in humans, the IARC classified uracil mustard in Group 2B (possibly carcinogenic to humans) (2, 3). Uracil mustard compared to nitrogen mustard itself in the same assay (lung tumor assay in strain A mice, intraperitoneal dosing), was more potent a tumorigen than nitrogen mustard (92).

10.4.1.6 Genetic and Related Cellular Effects Studies Uracil mustard is mutagenic in several *in vitro* and *in vivo* assays. It is positive in *Salmonella typhimurium, E. coli*, and *Saccharomyces cerevisiae* and in a host-mediated assay using the mouse and *S. typhimurium* (93). It was also mutagenic in *Drosophila melanogaster* (94) and in a microsomal assay using mouse lymphocytes (95).

10.4.2 Human Experience See section 4.4.

10.5 Standards, Regulations, or Guidelines of Exposure

No workplace limits have been set by OSHA, ACGIH, or NIOSH for uracil mustard in industrial air.

10.6 Studies on Environmental Impact

Uracil mustard's production and use as an antineoplastic agent may result in its release to the environment through various waste streams. If released to soil, uracil mustard should have high mobility. Volatilization of uracil mustard should not be important from moist or dry soil surfaces. Insufficient data are available to determine the rate or importance of biodegradation of uracil mustard in soil or water. If released to water, uracil mustard would not adsorb to suspended solids and sediment. Uracil mustard will be essentially nonvolatile from aqueous surfaces. An estimated BCF value of 1.8 suggests that uracil mustard will not bioconcentrate in aquatic organisms. Uracil mustard will hydrolyze rapidly in water and moist soil. Experimental neutral and base-catalyzed hydrolysis rates in water at 25°C are 0.57/hour and 2.05/hour, respectively, which correspond to a calculated half-life of 1.2 hours at a pH of 7. If released to the atmosphere, uracil mustard will exist almost entirely in the particulate phase. Vapor-phase uracil mustard is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals and the estimated half-life is about 19

hours. Vapor-phase uracil mustard is also degraded in the atmosphere by reaction with atmospheric ozone, and then an estimated half-life is about 6.5 days. Particulate-phase uracil mustard may be physically removed from the air by wet deposition. Direct human exposure may occur by ingestion of the drug when dispensed in capsule form. Workers involved in formulating and dispensing the drug may be exposed through dermal contact or inhalation of dust (20).

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

11.0 Pyrrolidine
11.0.1 CAS Number:
[*123-75-1*]; [*25150-61-2*] (HCl)
11.0.2 Synonyms:
Tetrahydropyrrole; tetramethyleneimine; 1-azacyclopentane
11.0.3 Trade Names:
NA
11.0.4 Molecular Weight:
71.12
11.0.5 Molecular Formula:
C_4H_9N
11.0.6 Molecular Structure:

11.1 Chemical and Physical Properties
11.1.1 General

Physical Form	colorless liquid that fumes in air
Boiling Point	87°C
Freezing Point	–60°C
Specific Gravity	0.852
Vapor Pressure	128 mmHg at 39°C
Vapor Density	2.5
Flammability	
Flash Point	3°C
LEL	2.9% at –2°C
UEL	13.0% at 29.8°C

11.1.2 Odor and Warning Properties Unpleasant ammonia-like odor.
11.2 Production and Use
Pyrrolidine is a flammable alkaline liquid that undergoes reactions typical of secondary amines. It is used to prepare pesticides and rubber accelerators and as a chemical intermediate (usually the hydrochloride form) in the pharmaceutical industry. There is relatively limited industrial exposure to this material.
11.3 Exposure Assessment
Trace amounts (<0.1 ppm) of pyrrolidine are found in baked ham and frankfurters, and 0.06 to 6 ppm

pyrrolidine can be found in beverages such as wine, unpasteurized milk, and coffee (96).

Pyrrolidine can be detected in solids and liquids by using HPLC techniques (97).

No other data to assess human exposure were found.

A recent method for collection, desorption, and analysis of volatile organic compounds, including pyrrolidine, has been reported (107).

11.4 Toxic Effects

11.4.1 Experimental Studies 11.4.1.1 Acute Toxicity Pyrrolidine is moderately toxic on an acute toxicity basis. Its oral LD_{50} is 300 mg/kg in rats (98), 450 mg/kg in mice (99), and 250 mg/kg in rabbits and guinea pigs (8). By the intraperitoneal route, the LD_{50} in mice is 420 mg/kg for pyrrolidine itself (100) and 241 mg/kg for the hydrochloride salt (101). The mouse 2-hr LC_{50} was reported as 1300 mg/m^3 (98).

Lethal oral doses in rats affected gastrointestinal mucosa and caused vascular disorders. Inhalation exposures in mice resulted in irritation, excitement, and convulsions (98). Small intravenous doses (<1 mg/kg) in dogs and cats caused an increase in blood pressure and respiratory rate. This activity was reduced by ganglionic blocking agents or sympathectomy (102).

Finally, primary skin irritation studies on adult albino rabbits indicate pyrrolidine to be a severe skin irritant (103). Based on its alkaline characteristics, it is probably a severe eye irritant, even as a 20% solution (98).

11.4.1.2 Chronic and Subchronic Toxicity During or after 10 oral doses of 135 mg/kg, rats showed no evidence of toxicity (104). A limited chronic inhalation study with rats at 2.6 mg/m^3, 4 hr/day for 6 months resulted in increased excitability of the nervous system, decreased diuresis, and decreased hemoglobin (98). No other repeated exposure studies were found.

11.4.1.3 Pharmacokinetics, Metabolism, and Mechanism No information on absorption, distribution, metabolism and excretion of pyrrolidine in mammals was found.

11.4.1.4 Reproductive and Developmental Toxicity No studies on pyrrolidine were found to assess developmental or reproductive toxicity potential.

11.4.1.5 Carcinogenesis See reference 98 in Section 11.4.1.2.

11.4.1.6 Genetic and Related Cellular Effects Studies Pyrrolidine was negative for mutagenicity potential in a direct bacterial assay, a microsomal mutagenesis asssay, and a host-mediated assay, all using *Salmonella typhimurium* bacteria (105). It was also negative for aneuploidy induction in a *Saccharomyces cerevisiae* assay (106).

11.4.1.7 Other None

11.4.2 Human Experience No human exposure information, case histories, or epidemiological studies on pyrrolidine were found.

11.5 Standards, Regulations, or Guidelines of Exposure

No OSHA permissible exposure limit (PEL) or ACGIH TLV has been established for pyrrolidine.

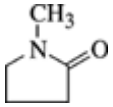
For routine handling, rubber gloves and safety glasses are recommended. Procedures for flammable solvents should be followed. For acute respiratory protections, organic vapor canister-type gas masks should be used (103).

11.6 Studies on Environmental Impact

None.
11.7 Summary
Pyrrolidine is moderately toxic on an acute basis with an oral LD_{50} in rats of 300 mg/kg and a 2-hr LC_{50} in mice of 1300 mg/m^3. It is also mutagenic in several *in vitro* assays. No other information was found relative to dermal and eye toxicity, repeated exposure responses, developmental/reproductive toxicity, carcinogenicity potential, or pharmacokinetics/metabolism.

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

12.0 **N**-Methyl-2-Pyrrolidinone
12.0.1 CAS Number:
[*872-50-4*]
12.0.2 Synonyms:
NMP, 2-Pyrrolidinone, N-Methyl-; and NMP
12.0.3 Trade Names:
NA
12.0.4 Molecular Weight:
99.13
12.0.5 Molecular Formula:
C_5H_9NO
12.0.6 Molecular Structure:



12.1 Chemical and Physical Properties
12.1.1 General

Physical Form	colorless to light yellow liquid
Boiling point	20°C
Density	1.026 at 25°C
Vapor Pressure	0.5 mmHg at 25°C

12.1.2 Odor and Warning Properties Mild, amine-like odor.
12.2 Production and Use
N-Methyl-2-pyrrolidinone (NMP) is a highly polar liquid. It is synthesized by combining acetylene and formaldehyde to form butynediol which is then converted to butanediol, which is further rearranged to butyrolactone and then NMP.

NMP has good chemical stability and is used by the chemical industry as a chemical reaction medium and in the petrochemical industry as a solvent for recovery/purification of aromatics, concentration of acetylene, and removal of sulfur from natural gas. It is also used as a formulating solvent for coating systems such as vinyl coatings, paints, and acrylic-styrene emulsion-type floor finishes. As a solvent, it also serves in stripping and cleaning systems for microelectronic components and various coating systems.
12.3 Exposure Assessment

No information to assess human exposure potential was found.

A method is available for simultaneous analytical determination of 2 NMP metabolites in urine using a GLC technique that has a detection limit of 0.2 mg/ml. This method can also be used to monitor NMP in the workplace (108). Another method to monitor wastewater uses GLC techniques following concentration on XAD-2 resin from NaCl solutions and elution with methanol (109).
12.4 Toxic Effects
12.4.1 Experimental Studies 12.4.1.1 Acute Toxicity NMP has slight acute oral toxicity and an LD_{50} of 4320 mg/kg in rats. NMP also has slight dermal toxicity and no deaths or symptoms of toxicity when 2000 mg/kg is administered onto the skin of rabbits (110), and in guinea pigs, it produced no irritation and was not a skin sensitizer (111). In the rabbit eye, NMP produced moderate irritation (111). By the inhalation route, NMP was moderately toxic to the rat exposed to a 4-h ALC of 1.7 mg/1 as an aerosol-vapor mixture (111).

12.4.1.2 Subchronic and Chronic Toxicity Rats were exposed to an aerosol-vapor mixture of NMP at concentrations of 0, 0.1, 0.5, and 1.0 mg/l for 6 h/day, 5 days/week for 4 weeks. At 0.1- and 0.5-mg/L levels, rats did not show any significant clinical signs or pathological lesions. However, lethargy, respiratory difficulty, and excessive mortality were found in rats exposed to 1.0 mg/L. These rats had focal pneumonia, bone marrow hypoplasia, and atrophy of lymphoid tissue in the spleen and thymus. The lesions were reversible in surviving rats following 2 weeks of recovery. Increases in the relative and absolute numbers of neutrophils were observed during exposure at 1.0 mg/L, but returned to normal limits after 2 weeks of recovery (111). In another subchronic inhalation study, exposure of rats to air saturated with NMP (370 ppm) had no adverse effects (112). Data from subchronic oral studies showed that NMP had a low level of toxicity and NOELs of 80 mg/kg/day in 90-day studies in rats and dogs (110).

Rats and mice were fed either 2,000, 6,000, 18,000, or 30,000 ppm NMP (rats) or 500, 2,500, 7,500, or 10,000 ppm (mice) for 28 days, and complete toxicological workups were conducted. The NOEL was 6,000 ppm for male rats and body weight decreases occurred at higher levels. The NOEL was 18,000 ppm for female rats (same end-point effects). Mild alterations in lipid, protein, and carbohydrate metabolism occurred at 18,000 ppm or higher. In mice, the NOEL in both sexes was 2,500 ppm, and kidney changes were seen at 7,500 ppm and higher (113).

Ninety-day feeding studies were also conducted in rats (3,000, 7,500, or 18,000 ppm NMP) and mice (1,000, 2,500, or 7,500 ppm NMP). A complete toxicity profile was obtained. Decreases in mean body weights were observed in male and female rats fed either 7,500 or 18,000 ppm NMP. Of 36 neurobehavioral parameters investigated, male rats in the 7,500- and 18,000-ppm groups showed an increase in foot splay, and 18,000-ppm males had a higher incidence of low arousal and slight palpebral closure suggestive of a sedative effect. Absolute and relative liver weights were increased in 18,000-ppm females, were associated with an increased incidence of centrilobular hepatocellular hypertrophy, and were considered to be an adaptive/physiological response. In mice, liver weight increases (considered an adaptive response) occurred at 2,500 and 7,500 ppm; no other NMP-related effects were seen (114).

12.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Studies to explore the metabolism of NMP in rats were performed with ^{14}C- and ^{3}H-labeled NMP. Half-lives of about 7 h for the ^{14}C isotope and 10 h for the ^{3}H isotope were measured. Urinary excretion accounted for about 70% of the total dose within 12 h. One major (70 to 75%) and two minor urinary metabolites were seen. The liver was the major organ for tissue distribution (115, 116).

The kinetics of NMP in nonpregnant and in pregnant rats and their fetuses were investigated in a study in which the animals were exposed by inhalation for 6 hours to 150 ppm on day 19 or 20 of pregnancy. Similar concentrations of *N*-methylpyrrolidone in fetal and maternal blood were measured. The half-life was more than 16 hours (117).

In one other limited study (118), the major urinary metabolite of NMP in rats was 5-hydroxy-*N*-methylpyrrolidinone based on thin-layer chromatography and MS comparisons with an authentic sample.

12.4.1.4 Reproductive and Developmental NMP has been tested for its developmental toxicity by the inhalation, oral, dermal, and intraperitoneal routes of administration. In an inhalation study, pregnant rats were exposed 6 h/day on days 6 to 15 of gestation to 0.1 or 0.36 mg/L of an NMP aerosol. Except for sporadic lethargy and irregular respiration in several rats at both exposure levels during the first three days of exposure, no clinical signs of toxicity were observed. NMP was not embryotoxic, and no major external or skeletal malformations were found in the fetuses (111).

In two limited inhalation studies, slight embryo and maternal toxicity was observed in rats exposed to 800 ppm (the maximum saturated concentration in air at 25°C), 6 h/day, on either days 4 to 8 or days 11 to 15 of gestation (119).

Groups of pregnant rats were orally administered either 332 or 997 mg/kg/day on days 6 to 15 of gestation. Embryolethality and marked fetal retardation were noted only at the high dose. A marked reduction in maternal body weight gain was also noted in the dams. At the low dose, a slight retardation of ossification was reported in the fetuses, and no maternal toxicity was noted (119).

Groups of pregnant mice were orally administered 1054 to 2637 mg/kg/day on days 11 to 15 of gestation. No maternal effects were reported. At the high dose, there was an increase in resorptions, decreased litter size, general toxic effects on fetal development, and an increase in cleft palate incidence (19.2 versus 9.5% in controls). No adverse effects were noted in the low-dose group (120).

Pregnant rats were dermally administered 75, 237, or 750 mg/kg/day of NMP on days 6 to 15 of gestation. Maternal toxicity was observed at 750 mg/kg manifested by reduced body weight gain during gestation. Fetal toxicity at 750 mg/kg was indicated by fewer live fetuses per dam, an increase in the percentage of resorption sites, reduced fetal body weights, and apparent retardation in skeletal development. No maternal or fetal toxicity was noted at either 75 or 237 mg/kg (121).

When three different strains of pregnant mice were given NMP by intraperitoneal injection during gestation, increased resorptions and malformations were seen at daily dose levels of 24 to 1568 mg/kg, but sensitivity to these effects varied widely among the different strains (120).

Groups of sexually immature male and female rats were exposed to 10.3, 50.8, or 116 ppm of NMP, 6 h/day, 7 days/week, from day 34 of age until they produced a litter. Clinical signs noted among male and female rats exposed to 116 ppm were lethargy and chromodacryorrhea. No reproductive effects were noted in the parents or in their offspring. Additionally, no effect on reproductive ability was noted in female rats exposed to 116 ppm of NMP and then mated with unexposed male rats or in male rats exposed to 116 ppm of NMP and then mated with unexposed female rats (122).

Prenatal exposure of pregnant rats to NMP at 165 ppm caused preimplantation loss, low fetal weights, and delayed ossification (123). In an earlier study, these authors reported that decreased fetal weight was related to impairments of neurobehavioral function in adults although no dose-response was seen and the end point examined did not necessarily indicate cause and effect (124).

In a two-generation reproduction study, rats were exposed by inhalation to 0, 10, 51 or 116 ppm NMP for 6 h/day, 5 days/week from premating through two generations. No evidence of altered reproductive function was seen. No developmental effects were seen although there was a slight decrease in fetal weight at the 116-ppm dose (125).

12.4.1.5 Carcinogenesis Rats were exposed to NMP vapor at either 0, 0.04 or 0.4 mg/L for 6 h/day, 5

days/week for 2 years. Male rats at 0.4 mg/L showed slightly reduced mean body weight. No life-shortening toxic or carcinogenic effects were observed in rats exposed for 2 years to either 0.04 or 0.4 mg/L of NMP. By the dermal route, a group of 32 mice received an initiation dose of 25 mg of NMP followed 2 weeks later by applications of the tumor promotor phorbol myristate acetate, three times a week, for more than 25 weeks. Dimethylcarbamoyl chloride and dimethylbenzanthracene served as positive controls. Although the NMP group had three skin tumors, this response was not considered significant when compared with that of the positive controls (122).

A group of mice received nine 25 mg subcutaneous injections of NMP during a 17-month period. Tumor incidence for the NMP treatment (21/49) was comparable to that of the untreated control group (28/49) (126).

12.4.1.6 Genetic and Related Cellular Effects Studies NMP was not mutagenic in the Ames test with or without metabolic activation (115, 122) or in the mouse lymphoma assay (122). NMP did induce aneuploidy in the yeast *Saccharomyces cerevisiae* (127). NMP at single oral doses up to 3,800 mg/kg body weight did not lead to an increase either in micronucleated erythrocytes or in structural or numerical chromosomal aberrations when bone marrow was sampled after 16, 24, and 48 hour later in the micronucleus test or after 24 and 48 hours for karyotype analysis (128).

12.4.2 Human Experience In one published industrial hygiene study in the semiconductor industry, headaches and chronic eye irritation were described in some employees exposed to levels as low as 0.7 ppm. Levels of 49 to 83 ppm were found unbearable by the workers (121). Repeat patch testing over 24 h showed no irritation (110).

Six male volunteers were exposed for eight hours on four different days to 0, 10, 25, and 50 mg/m^3. NMP was absorbed through the respiratory tract and readily eliminated from the body, mainly by biotransformation to other compounds. Exposure to 10, 25, or 50 mg/m^3 NMP did not cause nose, eye, or airway irritation (129).

A case report was presented of a pregnant laboratory technician who suffered intrauterine growth retardation and stillbirth following exposure to NMP (130). It is not clear that there is any cause and effect relationship.

Several workers in a small electrotechnical company in Norway experienced irritant reactions of the skin after a few days of working with NMP. The involved workers displayed acute irritant contact dermatitis of the hands (131).

12.5 Standards, Regulations, or Guidelines of Exposure

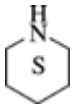
No workplace exposure limit for NMP has been set by OSHA or ACGIH, but a workplace environmental exposure level guide (WEEL) of 10 ppm, 8-h TWA, has been established by the American Industrial Hygiene Association (AIHA) WEEL Committee.

12.6 Studies on Environmental Impact

NMP may be released to the environment as a fugitive emission during production and use. If released to soil, NMP can biodegrade under aerobic conditions. It is expected to display very high mobility in soil. NMP may slowly volatilize from dry soil to the atmosphere, but it is not expected to volatilize significantly from moist soil. If released to water, screening studies indicate that NMP will biodegrade under aerobic conditions after a short lag. A calculated bioconcentration factor of 0.16 indicates that NMP is not expected to bioconcentrate significantly in fish and aquatic organisms, nor is it expected to significantly absorb to sediment or suspended organic matter. An estimated Henry's law constant of 1.56×10^{-8} atm-cu m/mole at 25°C indicates that NMP is not expected to volatilize significantly from water to the atmosphere. The estimated half-life for volatilization of NMP from a model river is 2335 days. If released to the atmosphere, NMP is expected to undergo a gas-phase reaction with photochemically produced hydroxyl radicals, and the estimated half-life is 5.2 hrs. It may undergo atmospheric removal by wet deposition processes (120).

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

13.0 Piperidine
13.0.1 CAS Number:
[*110-89-4*]
13.0.2–13.0.3 Synonyms and Trade Names:
Hexahydropyridine: pentamethylenimine; hexazane; cyclopentimine; Cypentil; azocyclohexane
13.0.4 Molecular Weight:
85.15
13.0.5 Molecular Formula:
$C_5H_{11}N$
13.05 Molecular Structure:



13.1 Chemical and Physical Properties
13.1.1 General

Physical Form	colorless liquid that fumes in air
Boiling Point	106.3°C
Freezing Point	–13°C
Melting Point	–13°C
Specific Gravity	0.861
Vapor Pressure	40 mmHg at 29.2°C
Flash Point	16°C

13.1.2 Odor and Warning Properties Pepper-like odor, threshold <2 ppm (132); strong base; soapy consistency.
13.2 Production and Use
Piperidine is a clear, colorless, flammable liquid that has an amine-like pungent odor. It is strongly basic (pK_b = 2.88) and reacts vigorously with oxidizing agents. Piperidine and its derivatives are usually produced by reducing pyridine and corresponding derivatives. Chemically, piperidine has been closely identified with alkaloids because the piperidine nucleus occurs in a wide variety of these plant derivatives.

Piperidine is used in many active pharmaceuticals (analgesics, germicides, anesthetics), as a wetting agent, as a hardening agent for epoxy resins, as a rubber additive, and as a catalyst in silicone esters. Industrial exposure is limited. The chemical is highly basic making it reactive on contact with all tissues. It has an appreciable vapor pressure, so its reactivity, flammability, and volatility make it a serious potential hazard in the workplace.
13.3 Exposure Assessment
Trace amounts of piperidine (<0.2 ppm) have been found in baked ham, and 0.3 ppm can be found in beverages such as coffee or milk (96).

No other data to assess human exposure potential were found.

13.4 Toxic Effects

13.4.1 Experimental Studies 13.4.1.1 Acute Toxicity Piperidine has reported oral LD_{50}s in the rat of 133 mg/kg (133), 447 mg/kg, (134) or 337 mg/kg (135). Rats treated with 100 mg/kg in water showed weakness, respiratory distress, and convulsions (136). The corresponding oral value in the rabbit is 321 mg/kg (137), and therefore the chemical is considered highly to moderately toxic following acute oral exposure. No changes in liver biochemistry (hepatic DNA, ornithine decarboxylase and alanine aminotransferase activities, cytochrome P450 and glutathione content) were seen in rats following single oral exposures from 5 to 142 mg/kg (138). Injection studies have produced LD_{50} values of <50 mg/kg intraperitoneally in the rat; 330 mg/kg intraperitoneally, 30 mg/kg subcutaneously, and 160 mg/kg intravenously in the mouse; and 5 to 10 mg/kg in both the dog and cat (139). Like many secondary aliphatic amines, piperidine produces a significant hypertensive response (136), stimulates respiration, and increases the heart rate (102, 140, 141). A 4-h inhalation exposure of 4000 ppm killed all four rats tested (134). The 4-h LC_{50} in mice was 1723 ppm and the 1-h LC_{50} in guinea pigs was 3444 ppm (133).

Severe injury that involved nonreversible corneal damage was produced by instillation of piperidine into the rabbit eye (133, 134). The chemical is also severely irritating to the skin of rats, mice, and rabbits (136), and necrosis was seen in all six rabbits when the neat material was applied to the belly (134). The LD_{50} in the rabbit following dermal application ranges from 275 mg/kg (134) to 1000 mg/kg (133), which indicates that the material is moderately to highly toxic by the dermal route.

Other simple alkylpiperidine derivatives have been studied for their acute toxicity. 5-Ethyl-2-methylpiperidine was highly irritating to the rabbit eye and skin and, like piperidine, was readily absorbed through the skin (dermal LD_{50} in rabbits of 630 mg/kg); it also produced an oral LD_{50} in rats of 540 mg/kg. Five out of six rats exposed by inhalation to 250 ppm for 4 h died. This represents a greater degree of toxicity than determined in the same laboratory for 5-ethyl-2-methylpyridine, for which the oral LD_{50} in rats was 1540 mg/kg, the percutaneous LD_{50} in rabbits was 3420 mg/kg, and exposure to 1000 ppm for 4 h produced death in five of six rats (84). The 1-ethyl derivative of piperidine is also a strong skin irritant and highly toxic to rats when administered undiluted.

13.4.1.2 Chronic and Subchronic Toxicity Rats and rabbits were exposed by inhalation to either 0.57 to 2.87 ppm piperidine 4 h/day for 4 months. The authors reported that 0.57 was the “threshold” of chronic toxicity, and decreased arterial pressure, increased permeability of skin capillaries, and increased neuromuscular irritability were reported. At 2.87 ppm a number of additional observations were reported including altered brain electrical activity, cardiovascular system alterations and spermatogenesis, decreased body weight gain, and dystrophic changes in the liver and kidney (details not reported) (142). Ten doses of piperidine at 90 mg/kg during a 2-week period produced marked weight loss, necrosis of the liver, and possible kidney damage in rats (143).

13.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Piperidine has been identified in the urine of animals and humans (140). The presence of piperidine in the urine can be easily measured with HPLC and chemiluminescence (144) or gas–liquid chromatography (145). Derived from cadaverine and lysine, piperidine is excreted from humans at 3 to 20 mg/day. Oral administration of cadaverine to rabbits causes a severalfold increase in piperidine excretion. Injected into chickens or rabbits, the major portion is excreted unchanged (146). Piperidine is well absorbed from the gastrointestinal tracts, and the amount absorbed through skin is sufficient to produce death in laboratory animals.

13.4.1.4 Reproductive and Developmental Inhalation of 0.9, 4.3, or 28.7 ppm by pregnant rats produced no teratogenic effects, but embryo length and weight were reduced at the two higher levels tested (147).

13.4.1.5 Carcinogenesis No tumors were produced in rats given piperidine (0.09%) in drinking water for 1 year. Piperidine and sodium nitrite given together also failed to produce tumors. The failure of this treatment was surprising because nitrosopiperidine induced a high incidence of lung and esophageal tumors. The authors suggest that the relative strong basicity of piperidine reduced the rate of reaction with nitrite to such an extent that an ineffective amount of nitrosopiperidine was formed (148). In mice that had cholesterol pellets containing piperidine implanted in their bladders and were given sodium nitrite in their drinking water, an increase in bladder cancers was produced (149). Piperidine given as a series of 24 injections in groups of mice failed to produce lung tumors in the strain A mouse cancer screen (92). When piperidine and sodium nitrite were incubated in the isolated rat urinary bladder, nitrosopiperidine was detected in the bladder contents. No studies designed to evaluate the carcinogenic potential of piperidine alone following lifetime exposures have been reported.

13.4.1.6 Genetic and Related Cellular Effects Studies Piperidine did not produce an increase in mutational frequency in the host-mediated assay using the mouse following a series of intraperitoneal injections (105). No increase in mutational rate was seen in two *E. coli* strains incubated with 40 mM piperidine (150). In the mouse lymphoma assay, DNA strand breaks were seen following incubation with an S9 microsomal fraction. No response was seen without the microsomal fraction (151). Only high concentrations (5 to 7 $\times 10^{-3}$ mM) produced increased DNA breaks without the microsomal fraction, and no changes were reported with the S9 enzyme (152). Piperidine produced single-strand DNA breaks in rat liver DNA followed by repair (153). Chromosomal and mitotic abnormalities were produced by piperidine in onion plants at dose-related concentrations ranging from 50–1000 ppm (154).

13.4.2 Human Experience Skin exposure to liquid piperidine for less than 3 min produced severe epithelial damage and a chemical burn (155). In a workplace in which piperidine was being transferred from drums in a semi-closed system, airborne levels of 2 to 5 ppm were measured (132). The pungent odor could be tolerated by an unacclimated individual for only a brief time, although no actual irritation was perceived. Volunteers reported an irritation threshold of 26 ppm (156).

No other human exposure data, clinical case histories, or epidemiology studies of piperidine were located.

13.5 Standards, Regulations, or Guidelines of Exposure

A WEEL of 1 ppm as an 8-h TWA for a 40-h week has been recommended by AIHA (157). A skin notation is included and the value is based on piperidine vapor irritating the respiratory tract and the eyes. The liquid is corrosive to skin and may cause permanent eye injury; the odor is considered to be objectionable above 2 ppm. Good ventilation is essential to minimize inhalation exposure, and the use of personal protection to prevent accidental eye and skin contact is clearly indicated. Safety procedures to handle flammable materials should be followed.

13.6 Studies on Environmental Impact

Piperidine is found naturally in foods and fish. In soil and water, it is likely to biodegrade, and in soil, it is likely to leach. In water at neutral conditions, piperidine will be dissociated and therefore, evaporation will be pH dependent. In dry soil, its high vapor pressure would suggest significant evaporation. Because of its low octanol/water partition coefficient, bioconcentration of piperidine in fish is unlikely. Estimations of its fate in the atmosphere suggest a half-life of 3.4 days. Primary human exposure is due to food consumption (20).

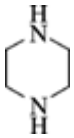
Aliphatic and Aromatic Nitrogen Compounds

Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

14.0 Piperazine

14.0.1 CAS Number:
[*110-85-0*] (anhydrous); [*142-63-2*] (hexahydrate)
14.0.2 Synonyms:
Hexahydropyrazine; diethylenediamine; piperazidine
14.0.3 Trade Name:
Lumbrical; Wurmirazin
14.0.4 Molecular Weight:
86.14 (anhydrous)

194.23 (hexahydrate)
14.0.5 Molecular Formula:
$C_4H_{10}N_2$, $C_4H_{22}N_2O_6$(hexahydrate)
14.0.6 Molecular Structure:



14.1 Chemical and Physical Properties
14.1.1 General

Physical Form	deliquescent solid (anhydrous); minute crystals (hexahydrate)
Boiling Point	146°C (anhydrous), 145–156°C (hexahydrate)
Melting Point	106°C (anhydrous), 44–45°C (hexahydrate)
Specific Gravity	1.1 (anhydrous)
Vapor Pressure	<1.0 mmHg at 20°C
Vapor Density	3.0 (anhydrous)
Flash Point	82°C (anhydrous); 87°C (hexahydrate)

14.1.2 Odor and Warning Properties Salty taste; no definable odor.
14.2 Production and Use
Piperazine is a transparent, deliquescent solid. Aqueous solutions of the base are strongly alkaline (pK_b = 4.19); the pH of a 10% aqueous solution is 11. It is used in medicinals, insecticides, and corrosion inhibitors, and as an accelerator for curing polychloroprene. Piperazine and several piperazine salts are used in humans and animals to treat parasitic infestations.

Industrial exposure is not extensive. The major producers make piperazine from higher amines (e.g., ethylenediamine or diethylenetriamine) and forms of triethanolamine. Formulations of 30 to 40% piperazine are sold to reprocessors, who make products of various salts or anhydrous and hexahydrate piperazine (158).

Primary routes of exposure are skin or eye contact or inhalation of vapors (or the dusts of salts). The salts are less hazardous than anhydrous or hexahydrate forms of piperazine.
14.3 Exposure Assessment
No information to assess human exposure potential to piperazine was found.

Piperazine can be detected in food crops at a concentration as low as 0.03 ppm (159). A method is applicable for aqueous solutions from the Association of Official Analytical Chemists (160).

Methods for detecting piperazine in human tissue have also been developed (161).

14.4 Toxic Effects

14.4.1 Experimental Studies 14.4.1.1 Acute Toxicity The oral LD_{50} of piperazine in the rat ranges from 2050 to 3000 mg/kg (147, 162, 163) and in the mouse from 600 (99) to 1900 mg/kg (147). In another study, the lowest concentration that produced mortality in the rat was 5000 mg/kg, and gastrointestinal irritation was noted at doses of 450 mg/kg or greater (164). No deaths occurred in groups of six rats exposed for 2 h to an aerosol that had a nominal concentration of approximately 40 mg/L. Clinical signs indicative of respiratory irritation were seen but no pathological changes were seen 14 days postexposure (165). Changes in motor activities and muscle contractions were seen in mice that inhaled 5400 mg/m^3 for 2 h. The animals apparently survived this exposure (147). Subcutaneous injection to mice produced LD_{50}s of 1100 mg/kg (166) and 2030 mg/kg (167). Intraperitoneal injection in the mouse produced an LD_{50} of approximately 1900 mg/kg (139, 168). Piperazine produced a biphasic effect on the rat cardiovascular system. This effect included an initial fall in blood pressure and heart rate followed by a transient rise in both. Atropine antagonized the initial reaction. Piperazine did not produce any electrocardiographic changes when injected (route unspecified) alone (169).

The dermal LD_{50} of piperazine is 4000 mg/kg in rabbits (163). Contact of rabbit skin with undiluted piperazine for 30 min produced slight irritation that became a chemical burn in 70 min (162). The reaction of the belly skin of rabbits was less marked, and only transient erythema was observed following application of approximately 500 mg piperazine (163). Only transient redness was seen in guinea pigs from a 50% aqueous solution, but necrosis was produced following immersion of the mouse tail in neat material (147). Mild irritation was produced in guinea pigs with 5 to 35% concentrations in water (170), but no evidence of dermal sensitization was seen (171, 172). Severe eye damage, presumed to be permanent, was produced in the rabbit eye following instillation of a single drop of the undiluted chemical (49, 162), and a 5% aqueous solution produced a score of 9 (out of 10). A dose of 250 mg placed in the conjunctival sac produced severe irritation in the rabbit eye (173).

14.4.1.2 Chronic and Subchronic Toxicity Inhalation of 100 ppm by guinea pigs (3 h exposure, seven exposures in 11 days) produced no effects (162). Rats were fed diets that contained 1000 ppm for 90 days without adverse effects. Liver and kidney damage was seen at both 3000 and 10,000 ppm (162). In another feeding study, rats fed 150 mg/kg/day for 30 days showed decreased serum and tissue lipid levels but little change in glucose tolerance, tissue glycogen levels, and liver DNA, RNA, and protein contents (174). No interference with the immune response was seen in mice treated with 5000 ppm piperazine for 2 weeks (175).

14.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Piperazine is partly metabolized in humans; only 15% of a 2-g dose was excreted unchanged. Piperazine itself is a metabolite of the antihistaminic agent chlorocyclizine (176).

Volunteers who inhaled 0.3 mg piperazine/m^3 for 4 to 16 h were given diets that contained nitrate and/or ascorbate. *N*-Mononitrosopiperazine, but not *N*, *N*-dinitrosopiperazine, was detected in the urine (177). This was also seen in workers exposed to concentrations of 0.06 to 1.7 mg/m^3 during a 12-h work shift (178). The mononitrosopiperazine metabolite was detected in gastric juice and urine following oral administration of 480 mg piperazine to four male volunteers (179).

14.4.1.4 Reproductive and Developmental No complete studies to evaluate the developmental toxicity potential of piperazine have been reported. No effects were produced in 13-day-old rat fetuses following intrauterine application of 50 mg piperazine (180). No effects in piglets were reported following oral administration (dose and duration unspecified) (181).

14.4.1.5 Carcinogenesis No increase in lung adenomas was produced in mice administered 0.69 to 18.75 mg of piperazine/kg in drinking water for 20 to 25 weeks and sacrificed 10 to 13 weeks later

(182, 183). An increase in lung adenomas was produced in this bioassay by administration of piperazine together with sodium nitrate, suggesting the formation of the active nitroso derivative (184). Sodium ascorbate inhibited tumor formation, in theory, by preventing piperazine nitrosation (185). Co-administration of 250 ppm piperazine and 500 ppm sodium nitrate in drinking water did not produce tumors in rats (172). None of these studies were conducted using currently accepted methods for evaluating carcinogenic potential but piperazine alone, in these assays, was noncarcinogenic.

14.4.1.6 Genetic and Related Cellular Effects Studies Piperazine dihydrochloride was not mutagenic in the mouse host-mediated assay. However, when tested in combination with sodium nitrate (to produce the N-nitroso derivative), a mutagenic response was seen (186). Piperazine was inactive when tested in four *Salmonella* strains in amounts ranging from 33 to 2167 mg (187). No evidence of genetic damage was reported in the LS1784 mouse lymphoma assay and the BALB/3T3 transformation assay (188). Administration of 50 mg/kg intraperitoneally to rats did not cause DNA strand breaks, although similar administration of the dinitroso derivative caused single-strand breakage that required 6 days or longer to repair (153). Urinary metabolites isolated from mice given oral doses of both piperazine and sodium nitrate were also mutagenic (189).

14.4.2 Human Experience Piperazine (as the hydrochloride salt) is used as a vermifuge in humans, and doses range from 75 to 3500 mg/kg. Side reactions have included hives, headaches, nausea and vomiting, diarrhea, lethargy, tremor, incoordination, and muscular weakness. These findings have been transient and disappear when medication is stopped (190). Severe thrombocytopenia was described in a male patient who took 2.25 g/day for 14 days followed by a single dose 14 days later. This reaction resolved and was attributed to hypersensitivity following a course of therapy 15 years earlier (191).

Severe, but reversible, neurological disorders accompanied by electroencephalographic changes, also reversible, have been seen following the medicinal use of piperazine (192). Three cases of occupational dermatitis attributed to piperazine, confirmed by patch testing, have been reported (193–195). Respiratory sensitization has also been reported (193, 196). Piperazine was the inducing agent in 29 cases of occupational asthma reported in 130 workers who handled amines and other chemicals. The TWA concentration of piperazine associated with induction of an asthmatic state was estimated at 1.2 mg/m^3 (197). A strong exposure–response relationship as to the frequency of work-related airway symptoms (including chronic bronchitis) that indicated asthma was detected in a cohort of 602 studied by a mailed questionnaire (198). In the highest exposed group (no quantitative exposure levels presented), one of four workers had chronic bronchitis. However, no association between specific IgE antibodies, occupational asthma, and piperazine exposure was determined in a cross-sectional study that involved 140 workers at a chemical plant, some of whom were exposed to this substance during the course of their work (199). Miosis is occasionally induced by interference with the sympathetic supply to the eye, and slight disturbances of accommodation may have the same basis (200, 201). Descriptions of the visual effects are vague, variously characterized as difficulty in vision, difficulty in focusing, disturbance in color vision, or occurrence of flashes on closing the eyes at night, usually associated with giddiness, lack of coordination, and a sense of detachment. In any case, the visual disturbances are rare and inconsequential (202). In contrast to the association of piperazine and asthma, workers who manufactured piperazine products showed no signs of any small airway disease (volume of trapped gas, forced expiratory volume, vital capacity, and total lung capacity measurements were all normal) (203).

No differences in chromosomal aberrations or micronuclei in lymphocytes were seen in peripheral blood in chemical factory workers. Piperazine was one of the many agents to which these workers were exposed (204). No association between exposure and other biochemical activities or mononuclear leukocytes was detected in these workers (205, 206). Although there was an increased frequency of b-lymphocyte tumors and lung cancer in 85 workers at this plant, no association with any specific chemical exposure in the plant could be established (179). In 30 workers employed in a

chemical plant where piperazine was used (not quantified), the micronucleus frequency in red blood cells was elevated (206).

14.5 Standards, Regulations, or Guidelines of Exposure

A TLV® of 5 mg/m^3 has been established for the dihydrochloride salt of piperazine. This limit is based on acute human exposures that produced mild to moderate skin burns and sensitization and mild to moderate asthma associated with inhalation of the dust. It was felt this exposure should prevent systemic toxicity (5). Anhydrous and hexahydrate piperazine must be handled with great care in view of the strongly basic nature of the material. Skin and eye contact should be minimized and immediate flushing with water is necessary to reduce damage. Minimizing inhalation exposure is essential, and piperazine should be used only in well-ventilated areas.

Methods are available to analyze piperazine in pharmaceuticals and animal feeds. Polarographic, titrimetric, colorimetric, and gas–liquid chromatographic methods have been published (207–210). Capillary gas chromatography may be used to determine piperazine in the air and in human urine (211). High-performance thin-layer chromatographic methods may also be helpful in separating piperazine from other polyethyleneamines (212).

14.6 Studies on Environmental Impact

None.

Aliphatic and Aromatic Nitrogen Compounds

Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

15.0 Morpholine

15.0.1 CAS Number:

[*110-91-8*]

15.0.2 Synonyms:

Diethyleneimide oxide; tetrahydro-1,4-oxazine; tetrahydro-*p*-oxazine

15.0.3 Trade Name:

None

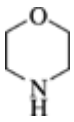
15.0.4 Molecular Weight:

87.12

15.0.5 Molecular Formula:

C_4H_9NO

15.0.6 Molecular Structure:



5.1 Chemical and Physical Properties

15.1.1 General

Physical Form	colorless, flammable, hygroscopic liquid
Boiling Point	128.9°C
Melting Point	–4.9°C
Specific Gravity	1.007
Vapor Pressure	6.6 mmHg at 20°C
Flash Point	35°C closed cup; 38°C open cup
Explosive Limits	LEL: 1.8%

UEL 11%

15.1.2 Odor and Warning Properties Weak ammonia-like odor.
15.2 Production and Use
Morpholine is made by dehydrating ethanolamines. Its main use is as a rubber accelerator in manufacturing tires. This process requires high temperature (300°F) and pressure, which increase the hazards. Morpholine is also used as a boiler water additive, brightener for detergents, and corrosion inhibitor, in the preservation of book paper, in waxes and polishes, and in organic synthesis.
15.3 Exposure Assessment
Morpholine is a natural constituent of tobacco smoke (213). It is also found in fish at concentrations ranging from <1 ppm to 9 ppm, in canned meats at 0.4 to 0.5 ppm, and in herrings at levels of 0.2 to 1 ppm (96).

Analytic methods for separating and/or determining morpholine include ion-exchange chromatography (214), mass spectrometry (96), thermogravimetric analysis (215), spectrophotometry (216), colorimetric analysis (217), and gas chromatography (213, 218, 219). Gas chromatography coupled with a thermal energy analyzer may also be used to determine traces of nitrosomorpholine resulting from the N-nitrosation of morpholine. The detection limit of this method is 2 ng/g (220).

High-performance liquid chromatography has been used to separate morpholine and its metabolites (*N*-hydroxymorpholine, *N*-methylmorpholine,*N*-methylmorpholine *N*-oxide) from biological fluids and tissue preparations (221). Morpholine also may be detected in such biological samples as urine, feces, blood, plasma, bile, and tissue by gas and gas–liquid chromatography (222, 223).

NIOSH Analytical Method 5150 is recommended for determining workplace exposure (1223a).

No other human exposure information relative to workplace levels or other background concentrations of morpholine was found.
15.4 Toxic Effects
15.4.1 Experimental Studies 15.4.1.1 Acute Toxicity Morpholine is moderately to slightly toxic in animals following single acute exposures by various routes (Table 59.4) (224–233). Single doses from 100 to 10,000 mg/kg fed to rats and guinea pigs produced hemorrhage in the small intestine and, in some animals, the nasal area. These doses were not tolerated and produced some mortality (226). Rabbits given dermal doses showed necrotic epithelium and inflamed edematous dermis. Morpholine is corrosive to the skin (226).

Table 59.4. Acute Toxicity of Morpholine

Route	Species	LD_{50} (mg/kg)	Ref.
Oral	Rat	1050	224
		1420	225
		1610	179
		1600	226
	Mouse	525	227
	Guinea pig	900	228
Dermal	Rabbit	310–810	229
		500	230
Inhalation	Rat		231

	Male	2250[a]	231
	Female	2151[a]	231
Mouse			
	Male	1450[a]	231
	Female	1900[a]	231
	Unspecified	1390	232
	Unspecified	365[b]	233
Intraperitoneal			
	Mouse	413	79
	Mouse	1350	139

[a] ppm, 4-h exposure.
[b] ppm, 2-h exposure.

Rats exposed by inhalation to 73 ppm for 4 h showed an increase in respiratory rate and lung irritation; this irritation was minimal at 11 ppm and not seen at 1 ppm (224). A 1-h exposure of rats to 6283 ppm produced lacrimation, rhinitis, and inactivity, but all rats survived (234).

Undiluted morpholine is necrotic to rabbit skin (235). Using standardized methodologies, skin irritation scores from 6.6 to 8.0 (maximum possible) have been reported (229).

No dermal sensitization or irritation was seen in guinea pigs tested with a 10% solution of morpholine in a system where two morpholine derivatives were sensitizers (228). No dermal irritation was seen in rabbits treated with a formulation containing 1% morpholine (236). Severe corneal necrosis is produced by treatment with 0.009 mL of 40% solution of morpholine (173). The irritation seen with 10 or 20% solutions was considerably less (49). Only slight conjunctival redness was seen in rabbits following instillation of a 1% morpholine-containing formulation into the eye (236).

15.4.1.2 Subchronic and Chronic Toxicity Rats fed 323 mg morpholine/kg for 4 weeks showed lowered weight gains but no gross pathological changes. No effects were seen at either 27.6 or 93 mg/kg, but clinical laboratory tests and microscopic pathology were not conducted (234). Rats given large doses of 120 to 800 mg/kg for 30 days showed lethargy, weight loss, irritation of the intestinal tract, and congestion of the gastric mucosa. Microscopic changes were seen in the liver, kidneys, spleen, stomach, and lungs, and considerable mortality occurred (226). Guinea pigs did not tolerate feeding of 450 mg/kg for 30 days. Liver, kidney, stomach, and lung lesions were seen at these doses, but only kidney and liver changes were seen at 90 mg/kg (226). Guinea pigs were also given daily dermal applications of morpholine, and survival was reduced at doses from 90 to 2780 mg/kg. Skin lesions were pronounced, as were the changes in the kidney and liver (226).

Rats have been used to study the effects of morpholine following inhalation for varying periods of time. Rats that inhaled 25 ppm, 6 h/day, 5 days/week for 13 weeks showed no compound-related changes. At 100 ppm, focal necrosis and necrotic cell debris were seen in the nasal cavity in 2 of 20 rats. Exposure at 250 ppm produced more severe irritation to the upper respiratory tract, and the damage (including increased Harderian gland secretion) at 13 weeks was more severe than that seen at 7 weeks (237).

Exposures to either 950 or 2000 ppm, 4 h/day, 5 days/week for 30 days produced lung and body weight changes (238). Feed consumption decreases, increased lung and kidney weights, and irritation of the eyes and nose were reported in rats that inhaled 450 ppm, 6 h/day, 5 days/week for 8 weeks (231). Irritation of the eyes, nose, and respiratory tract were seen following inhalation of

18,000 ppm (226).

Male and female rats exposed at 10, 50, or 150 ppm, 6 h/day, 5 days/week for 104 weeks showed normal growth, survival, hematology, and clinical chemistries. Rats exposed at 150 ppm had focal erosion and squamous metaplasia of the epithelium of the anterior of the nasal cavity. Signs of eye changes including corneal irritation, uveitis, and corneal damage were seen only in rats exposed at 150 ppm. The distribution of ocular changes in the lower exposure groups was similar to that in the controls (239).

15.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Morpholine given to animals is excreted primarily in the urine. Morpholine is not readily metabolized in the rat (221, 222, 240, 241) or rabbit (242). N-methylation and N-oxidation have been reported in the guinea pig; this occurs to a much smaller extent in the rat and hamster (221). A distribution study suggests that morpholine goes preferentially to the kidney in rabbits (243) and rats (222).

Approximately 92% of an orally administered morpholine dose to rats appeared unchanged in the urine within 48 h. Only 1.4% was excreted in the feces. At 24 h, 1.1, 0.5, 0.05, 0.05, and 0.6% remained in the stomach, intestine, liver, kidney, and blood, respectively (241). The urinary metabolite identified in the hamster, and to a much lesser extent the rat, was *N*-methylmorpholine *N*-oxide (221).

In humans, morpholine reportedly appears predominantly unchanged in the urine (244).

15.4.1.4 Reproductive and Developmental No studies to evaluate the reproductive or developmental toxicity of morpholine have been found, but no evidence of reproductive system damage has been reported in repeated-exposure toxicity studies in animals.

15.4.1.5 Carcinogenesis Morpholine did not produce an increase in tumors in rats that inhaled from 10 to 150 ppm for 2 years (239). No tumors were seen in rats fed 5000 ppm morpholine for 8 weeks and observed for their lifetime (245). Morpholine fed concurrently with sodium nitrate increased the numbers of hepatocellular carcinomas and sarcomas of the liver and lungs of rats and mice, probably mediated through the formation of N-nitrosomorpholine (246–248). The authors concluded that morpholine itself was either weakly carcinogenic or that a nitrate from an unknown source was present.

No cancers were produced when 6330 ppm morpholine was added to the drinking water of mice for their lifetimes (182). Concurrent exposure of morpholine plus nitrite or nitrogen dioxide increased the tumor incidence in a variety of species (182, 249–252). In a recent feeding study (253) where morpholine (0.5% in diet) and sodium nitrate were given concurrently for 23 weeks, rats showed no evidence of cancer.

15.4.1.6 Genetic and Related Cellular Effects Studies Genetic testing has produced both positive and negative findings (Table 59.5) (254–261). In general, *in vivo* assays such as the dominant lethal and host-mediated assays have been either negative or weakly positive. However, chromosomal aberrations were reported in mice (260). In microbial test systems, incubation of morpholine with sodium nitrite produces a strongly positive response, presumably by generating nitrosomorpholine (258).

Table 59.5. Genetic Toxicology of Morpholine

Assay/End Point	Result	Ref.
Salmonella	Negative	254, 255

Mouse lymphoma	Positive	188
Sister chromatid exchange	Positive	188
DNA repair/rat hepatocyte	Negative	256
Mouse host-mediated assay		
Oral	Negative	257
Intravenous	Weakly positive	258
Intramuscular	Weakly positive	186, 259
Chromosomal aberrations		
Mouse	Positive	260
Rat	Negative	261
Dominant lethal—rat	Negative	261

15.4.2 Human Experience Shea (49) reported nose irritation to himself after a 1-min exposure at 12,000 ppm and coughing after 1.5 min. The transfer of morpholine by pipette caused a severe sore throat and reddened mucous membranes. These symptoms cleared when exposure ceased.

The maximum allowable concentration for morpholine is 1400 ppm (v/v) based on 10% of a lower exposure limit. However, relevant toxicological data indicates that irreversible health effects and impairment of escape occur only at concentrations higher than 1400 ppm.

Concentrated morpholine readily permeates the skin. The undiluted compound is very irritating to the eyes and is moderately irritating to the skin (173). The irritation diminishes as the product is diluted to less than 25% with water. No serious chronic effects from morpholine have been observed in humans, although irritation to the skin or respiratory tract has been noted in a few instances of exposures to fumes from the material when heated or in contact with high concentrations (262).

Cosmetic products containing morpholine (1% generally) have been widely tested and are neither irritants (eye or skin) nor sensitizers (263).

No other human exposure data, case histories, or epidemiology studies on morpholine were found.

15.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH (5) has a TLV® of 20 ppm (8 hour TWA) to protect against both the irritating and systemic effects of morpholine. The OSHA PEL and NIOSH REL are also 20 ppm.

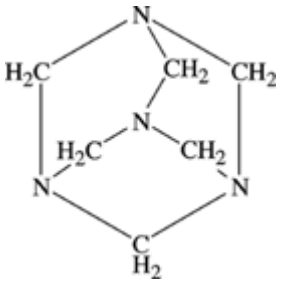
15.6 Studies on Environmental Impact

Morpholine may be released to the environment in effluents and emissions as a result of its manufacture, transport, storage, disposal, and use as a chemical intermediate (catalysts, antioxidants, pharmaceuticals, bactericides), in textile chemicals, photographic developers, hair conditioners, waxes and polishes, and in preservation of book paper. Total demand of morpholine was 11,000 metric tons (1975) and the U.S. estimated morpholine emissions into the atmosphere (as of 1978) were about 10 million pounds/year. If released to soil, morpholine may volatilize from dry soil surfaces but not from moist soil. Morpholine in soil will move with soil moisture and is expected to leach extensively. Based on screening test results, biodegradation may be significant but only after a long adaptation period. Morpholine released to natural waters will not tend to bioconcentrate, volatilize, or adsorb to sediment or organic particulate matter in the water column. Morpholine is biodegradable in screening tests, but it is unlikely that significant morpholine degradation will occur because of the long lag required (264). Morpholine reacts with photochemically produced hydroxyl radicals in the atmosphere and that results in an estimated half-life of 2.6 hours. The general population may be exposed to morpholine by eating foods such as baked ham and fish and breathing

cigarette smoke. Occupational exposure would occur via inhalation and dermal contact (20).

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

16.0 Hexamethylenetetramine
16.0.1 CAS Number:
[*100-97-0*]
16.0.2 Synonyms:
HMTA; HEXA; hexamine; methenamine; formamine
16.0.3 Trade Name:
Urotropin
16.0.4 Molecular Weight:
140.19
16.0.5 Molecular Formula:
$C_6H_{12}N_4$
16.0.6 Molecular Structure:



16.1 Chemical and Physical Properties
16.1.1 General

Physical Form	hygroscopic, white crystalline solid
Melting Point	280°C
Density	1.33
Flammability	Flammable
Vapor Pressure	4.0×10^{-3} mmHg at 20°C
Flash Point	250°C
Water Solubility	≥10 g/100 mL at 20°C

16.1.2 Odor and Warning Properties Slight ammonia-like odor.
16.2 Production and Use
HMTA is a tertiary aliphatic amine made by reacting aqueous formaldehyde with liquid or gaseous ammonia. HMTA is used in the rubber industry to prevent vulcanized rubber from blocking and as an accelerator, as a curing agent for thermosetting resins (particularly phenyl-formaldehyde and urea-formaldehyde resins); in foundry mold castings as part of binder resins, in the production of nitrilotriacetic acid; in the manufacture of adhesives and coatings; in firelogs and briquettes for camping; and in flame-retardant materials. Because of its unique ability to hydrolyze to formaldehyde and ammonia under acidic conditions, it is also used in pharmaceuticals, for intestinal infection, and as a preservative in the food industry.

Industrial exposure potential to HMTA is quite large. Primary routes of exposure would be skin or eye contact with powder and inhalation of the dust. Ingestion of HMTA should be a minor route of exposure.

16.3 Exposure Assessment

No information to assess the human exposure potential of hexamethylenetetramine was found.

A method using GC combined with quadruple MS has been used to analyze air samples (265).

HMTA in air can also be analyzed by HPLC (266). Detection of 0.1 mg/sample is reported using thin-layer chromatography and spectrophotometry (267). Urinary concentration following separation can be accomplished using ion-pair extraction and spectrophotometric techniques (268).

16.4 Toxic Effects

16.4.1 Experimental Studies 16.4.1.1 Acute Toxicity The dose at which mice begin to die following acute oral exposure is reportedly 512 mg/kg (269). Injection (intravenous, intraperitoneal, subcutaneous) LD_{50}s in rats, mice, cats, and guinea pigs range from 200 to 512 mg/kg (270–272). This limited information suggests that HMTA is moderately toxic following acute exposure.

No skin irritation was seen from a neoprene sponge containing an unspecified concentration of HMTA (273), and mild irritation occurred when a 5% solution of a mixture that contained 40% HMTA was placed on the skin of guinea pigs. No sensitization was observed (274). No specific data relating to the effects in or on the eyes have been found.

16.4.1.2 Chronic and Subchronic Toxicity Rats fed diets that contained 1600 ppm HMTA for their lifetimes showed no effects in body weight, life span, cause of death, organ weights, or fertility (275). No adverse effects were seen in rats given 400 mg HMTA by gavage for 90 to 333 days (276). Mice fed 5 g/kg/day for 10 days showed no toxic effects (277). No major adverse effects were seen in mice given 5000 or 10,000 ppm in drinking water for 60 weeks or 50,000 ppm for 30 weeks; rats were unaffected following exposure to 10,000 ppm for 2 years or 50,000 ppm for 2 weeks (278, 279). Rats given daily intramuscular injections of 200 mg HMTA for 90 days showed no signs of systemic toxicity (276).

16.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The absorption, metabolism, and excretion of HMTA have not been adequately characterized. In human acid media (such as stomach contents and urine), HMTA slowly decomposes to form formaldehyde (280). However, the quantity found in the urine is minimal (281). Both HMTA and formaldehyde were seen in the urine of human volunteers (136). Most of ingested HMTA was reportedly excreted unchanged within 3 h (species unspecified) (282).

HMTA reportedly produces formic acid when it reacts with acidic sweat, water, and air on the skin (283, 284).

The bioavailability of HMTA was studied in 10 healthy human volunteers. HMTA taken orally was recovered in the urine (82%) within 24 h, and the serum elimination half-time was 4.3 h (285). A similar response was seen over a dosage range of 100 to 500 mg (286). More recent oral data (287) are confirmatory.

16.4.1.4 Reproductive and Developmental No differences in fertility were seen in rats given 10,000 ppm HMTA before and during mating (288). In a second study, no effects on fertility were seen in rats fed 6600 ppm (275). In addition, five generations of rats given up to 50 mg/kg daily in drinking water were unaffected (289). Similarly, no reproductive effects were seen in dogs fed either 600 or 1250 ppm after mating although the percentage of stillborn pups increased slightly, and the survival and weight gain were reduced (290).

No effects were seen in a developmental toxicity screening study in which small groups of mice were given oral doses of 1 g/kg from gestation days 7 through 16 inclusive (291).

16.4.1.5 Carcinogenesis No significantly increased incidence of tumors was observed in rats or mice given HMTA for their lifetimes. Exposures in rats included 400 mg/day for 1 year (276), 10,000 ppm in drinking water for 2 years in each of three generations (288), 10,000 ppm in water for a lifetime (148), and up to 1000 ppm in the diet for 2 years (292). In mice, testing conditions included up to 10,000 ppm in drinking water for 60 weeks or 50,000 ppm for 30 weeks and a lifetime holding period (277, 278), and up to 10,000 ppm in the diet for 2 years (293).

Injection of 25 to 30 g subcutaneously per mouse led to an increase in subcutaneous sarcomas in two experiments (293, 294) but not in two other studies (295). The relevance of this methodology to the workplace condition is questionable.

16.4.1.6 Genetic and Related Cellular Effects Studies HMTA is generally positive in microbial assays that examined the mutagenic potential of the chemical. HMTA was positive in the *Salmonella typhimurium assay* (296, 297), in *E. coli* (298), in *Drosophila* (299), and in onion cells (300). Sublethal doses (not specified) slightly increased the number of meiotic abnormalities in male mice (31).

Conversely, HMTA was reportedly negative in *Salmonella typhimurium* and in *E. coli* (302, 303). No mutagenic activity was detected *in vivo* in the bone marrow of mice exposed to HMTA (304).

HMTA was not mutagenic *in vivo* in the mouse dominant lethal test following both oral (305) and intraperitoneal doses (31) of 25 g/kg.

16.4.2 Human Experience HMTA is a skin sensitizer, and vapors or solutions have produced skin irritation (306, 307). Inhalation may cause asthma-like reactions in previously sensitized individuals (308). Rash and inflammation have been seen in workers, and in severe cases blisters with watery flow result (309–311). Some workers develop a tolerance to further irritation (310, 311). Hypersensitivity of the airways has been related to exposure to HMTA in foundry workers, although exposure to other potential irritants was certainly possible (312). One death in a 10-day-old infant was reported following administration of an aqueous solution (concentration, amount unspecified) in which ammonia and formaldehyde were detected in the major organs (313).

HMTA has been suggested as a potential cause of the higher incidences of gastrointestinal and skin cancer, because it is used as one of several accelerators in the rubber industry (314). This link was made because of HMTA's ability to cause dermatitis and skin sensitization but there are no definitive studies.

No other human exposure data or epidemiological studies of HMTA were found.

16.5 Standards, Regulations, or Guidelines of Exposure

Because HMTA has been consumed in small amounts as a food preservative and has been used medically as a urinary antibacterial-antiseptic, the World Health Organization suggested a temporary acceptance level of 5 mg/kg as an estimate of the acceptable daily intake of HMTA in humans (315). No workplace airborne control-level guidance value has been proposed.

16.6 Studies on Environmental Impact

HMTA's production and use as an ammonia or formaldehyde donor may result in its release to the environment through various waste streams. If released to air, HMTA's vapor pressure of 4.0×10^{-3} mmHg at 25°C indicates that it will exist solely as a vapor in the ambient atmosphere. Vapor-phase HMTA will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated at 15 minutes. If released to soil, HMTA is expected to have high mobility based upon an estimated K_{oc} of 55. Volatilization from moist soil and dry soil surfaces is not expected to be an important fate process based upon an estimated Henry's law

constant of 1.6×10^{-9} atm-cu m/mole and this compound's vapor pressure, respectively. Hydrolysis may be important in some soils. HMTA hydrolyzes in water at pH 3 to 7; the half-life in each case is slightly more than 1 day. If released into water, it is not expected to adsorb to suspended solids and sediment in water based upon the estimated K_{oc}. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated Henry's law constant. An estimated BCF of 0.40 suggests that the potential for bioconcentration in aquatic organisms is low. In a semicontinuous activated sludge system, HMTA removal ranged from 1.1% after 5 days to 52.5% after 50 days; removal was attributed to acid hydrolysis to formaldehyde and ammonia followed by biodegradation of these two compounds. Removal of 70 to 87% was observed after 28 days using an activated sludge inoculum. In a 5-day BOD test using a sewage seed, HMTA reached 2.02% of its theoretical BOD. Occupational exposure to HMTA may occur through inhalation of dust particles and dermal contact with this compound at workplaces where it is produced or used (20).

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

17.0 Pyrrole
17.0.1 CAS Number:
[*109-97-7*]
17.0.2 Synonyms:
Azile; Divinylenimine; imidole
17.0.3 Trade Name:
None
17.0.4 Molecular Weight:
67.09
17.0.5 Molecular Formula:
C_4H_5N
17.0.6 Molecular Structure:

17.1 Chemical and Physical Properties
17.1.1 General

Physical Form	colorless liquid
Boiling Point	129–131°C
Freezing Point	–24°C
Melting Point	–23°C
Specific Gravity	0.967
Vapor Density	2.31 (air = 1)
Flash Point	33°C

17.1.2 Odor and Warning Properties Chloroform-like odor.
17.2 Production and Use
Pyrrole is a constituent of coal tar and bone oil. It is a weakly basic (pK = 13.6), colorless liquid that

darkens with exposure to air. It is used in drug manufacture. Industrial exposure is limited.
17.3 Exposure Assessment
17.4 Toxic Effects
17.4.1 Experimental Studies 17.4.1.1 Acute Toxicity Acute toxicity data are scarce. The subcutaneous LD_{50} in mice is 61 mg/kg. LD_{LO}s in rabbits are reported for the oral (147 mg/kg), subcutaneous (250 mg/kg), and intraperitoneal (150 mg/kg) routes (316). Intraperitoneal injections of large doses into dogs caused convulsions and liver injury. Pyrrole generally causes discoloration of urine and lung and liver injury in mammals. Death that follows large doses is accompanied by acute emphysema and pulmonary stasis (11). Pyrrole did not produce an increase in mutational frequency in several strains of *S. typhimurium* (Ames test) (317) and was negative in the rat hepatocyte DNA-repair test (318).

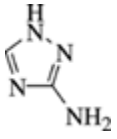
Somewhat more data are available for *N*-methylpyrrole. The minimum oral lethal dose in rats is about 2.5 mL/kg. Repeated oral doses to rats (five per week for 6 weeks) of 0.1 mL caused practically no effects. Fatal oral doses (>2.5 mL/kg) to rats produced interstitial hemorrhages in the lungs and hemorrhagic necrosis in the liver. *N*-Methylpyrrole did not produce skin irritation or sensitization in guinea pigs (319).

17.4.1.2 Chronic and Subchronic Toxicity No other toxicity information was found for pyrrole relative to repeated exposure toxicity, pharmacokinetics/metabolism, reproductive and developmental toxicity, carcinogenicity, or mutagenicity.

17.4.2 Human Experience No human experience data, case histories, or epidemiology studies of pyrrole were found.
17.5 Standards, Regulations, or Guidelines of Exposure
No occupational exposure standards have been established.
17.6 Studies on Environmental Impact
No information was found.

Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

18.0 Aminotriazole
18.0.1 CAS Number:
[*61-82-5*]
18.0.2 Synonyms:
3-AT; Amitrole; ATA; 3-Aminotriazole; 2-Amino-1,3,4 triazole; 3-Amino-1,2,4-triazole
18.0.3 Trade Name:
Amitrole
18.0.4 Molecular Weight:
84.08
18.0.5 Molecular Formula:
$C_2H_4N_4$
18.0.6 Molecular Structure:



18.1 Chemical and Physical Properties
18.1.1 General

Physical Form	white to colorless crystals
Melting Point	159°C
Boiling Point	200°C
Specific Gravity	1.138
Vapor Pressure	0.055 mmHg at 20°C
Solubility	soluble in water, alcohol; insoluble in acetone, benzene

18.1.2 Odor and Warning Properties None.
18.2 Production and Use
Amitrole is synthesized by condensing formic acid with aminoguanidine and can be purified by recrystallization from methanol. The chemical is effective in killing mostly woody plants, including hardwood and coniferous species. Amitrole is an effective contact spray for controlling herbaceous perennials, as well as most annual broadleaf weeds and grasses. It is applied as a foliar spray or as crystals or concentrated solution to cut surfaces. Human exposures are primarily by dermal contact or by inhalation following spray applications. This is the chemical responsible for the cranberry crisis in the United States in 1959 (320) in which the crop of that year was reportedly contaminated by amitrole, a chemical that could produce cancer of the thyroid when fed to rats.
18.3 Exposure Assessment
Amitrole residues can be measured to 0.1 mg (321, 322), and these techniques can be used to determine airborne concentrations.

Aminotriazole may be measured in the workplace using NIOSH Analytical Method 0500(4a).
18.4 Toxic Effects
18.4.1 Experimental Studies 18.4.1.1 Acute Toxicity Amitrole is very low in acute toxicity. The oral LD_{50} in mice is 11,000 mg/kg and in sheep is 4000 mg/kg (323). Other reported LD_{50} values in rodents include 24,600 mg/kg in the rat, 15,000 mg/kg in the mouse (324), and >4080 mg/kg in both young and old rats (325). Depending on the dose, the symptoms of overexposure include extreme depression, difficulty in breathing, clonic spasms, and coma (323). One dog tolerated a single oral dose of 2150 mg/kg, but vomiting was seen at 4640 mg/kg (326). Dermal exposures of 10,000 mg/kg to rabbits and 2500 mg/kg to rats were nonlethal (327). When amitrole was injected, the LD_{50} in mice was >5000 mg/kg both intraperitoneally (25) and intravenously (328). No adverse signs were seen after intravenous injection of 1750 mg/kg in cats and 1200 mg/kg in dogs (329). Doses of 1000 mg/kg in narcotized cats and dogs produced death due to cardiac or circulatory failure (323). Amitrole in the acid form produced mild irritation, reversible in 48 h, in the rabbit eye (324).

18.4.1.2 Subchronic and Chronic Toxicity Rats given 29 mg/kg in the diet for 2 weeks showed decreases in thyroid hormone levels (330). Kidney weight decreases were detected in rats given 500 mg/kg in the diet for 4 weeks, an effect that could be blocked by injection of thyroid hormone (331). Thyroid growth was modified by treatment of rats for 80 days with amitrole (332). No thyroid hyperplasia was seen in rats fed 2000 ppm for 12 weeks (333), although thyroid changes were seen in rats fed 50 ppm for 90 days (334). Serum T3/T4 ratios and thyroid weights were altered in rats fed amitrole (concentration not specified) for 5 months (332). Body weights were reduced in rats given 1000 ppm in drinking water for 1 year but nonneoplastic lesions were not discussed in the report (332).

Hyperplasia of the thyroid occurred in rats fed 100 ppm but not in rats fed 25 ppm for extended periods. Atrophy of the thymus and spleen was also reported at feeding levels of 500 and 1000 ppm (325). Similar changes have been confirmed in rats (335) and mice (336). Goiter was seen in dogs treated for 50 weeks but no other specific organ toxicity was seen (337). No toxicological changes

were seen in a 2-year inhalation study in which rats were exposed to 2000 mg/m^3 for 1 hour each week (338).

Liver enzymes, including cytochrome P450, d-aminolevulenic acid dehydrase, and peroxidase, have been affected following repeated exposures to amitrole (339–343). The short-term effects on the thyroid gland are striking and have been extensively studied and reported (335, 344–346).

18.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 18.4.1.3.1 Absorption Amitrole is rapidly absorbed from the stomach. The highest tissue levels were reached in 1 h and declined after 2 to 6 h (347).

18.4.1.3.2 Distribution After intravenous injection to mice, amitrole was distributed to many soft tissues and reached higher concentrations in actively growing parts of transplanted tumors than in normal tissue.

18.4.1.3.3 Excretion Following oral administration of ^{14}C-amitrole to rats, most of the radioactivity that appeared in the urine during the first 24 h was unmetabolized amitrole, but 3-amino-5-mercapto-1,2,4-triazole and 3-amino-1,2,4-triazolyl-*S*-mercapturic acid were also present (348).

Only insignificant traces of ^{14}C were seen in the expired air of rats 3 days after an oral exposure. In the first 24 h, 70 to 95% of the radioactivity was in the urine. Radioactivity in the body after 6 days ranged from 0.28 to 1.47% of the dose, and most activity was in the liver (349).

18.4.1.4 Reproductive and Developmental Reproductive organs were not the target tissue in the repeated-exposure toxicity studies reported earlier, although it is not certain that appropriate evaluation was always conducted. In a two-generation study in rats, the number of pups per litter and the pup weight were reduced at 500 or 1000 ppm. Most of these pups died from a condition resembling runt disease and, upon autopsy, had atrophic thymuses and spleens. These effects were not seen at either 25 or 100 ppm. No developmental effects were seen in pups following administration to pregnant rats of up to 100 mg/kg via gavage from gestation days 7 through 15 (325). Marked retardation of development without structural defects has been seen in mice (350).

Amitrole did not induce abnormal sperm morphology in mice given five daily intraperitoneal injections at doses ranging from 50 to 500 mg/kg (351).

18.4.1.5 Carcinogenesis A dose-related increase in thyroid adenomas was seen in rats fed 10, 50, and 100 ppm for 2 years (352). A high incidence of thyroid and liver tumors was seen in rats given amitrole either in drinking water (20 to 25 mg/day) or in food (250 or 500 mg/day) for 10 to 32 months (353). Mice given 1000 mg/kg by gavage early in life, followed by 53 to 60 weeks feeding of 2192 ppm, showed carcinomas of the thyroid and liver hepatomas (14). However, mice fed 1, 10, or 110 ppm for 21 to 23 months showed no carcinogenic response (354). No changes in tumor incidence or types were seen in hamsters following lifetime (900 days) feeding of either 1, 10, or 100 ppm (354). No tumors were reported in dogs fed 10, 50, 100, or 200 ppm for 1 year (348). No tumors were seen in rats that inhaled 2000 mg/m^3 amitrole for 1 h/week for 2 years (338). No skin tumors were seen in mice that received weekly applications of either 0.1 or 10 mg for their lifetimes (355).

18.4.1.6 Genetic and Related Cellular Effects Studies Amitrole was negative in short-term bioassays, including the Ames *Salmonella* test (329), in *in vitro* human lymphocyte clastogenicity (330), and a mouse lymphomas cell forward-mutation assay (331) (Table 59.6) (356–397). Additionally, amitrole did not induce any gene expression in *Salmonella typhimurium* (322). Amitrole did not cause a dominant lethal effect and did not cause chromosomal aberrations in mice (2, 3, 324). Amitrole was positive in three *in vitro* mammalian cell assays: unscheduled DNA synthesis, sister chromatid exchange, and cell transformation (334). A positive response was also seen in Syrian hamster

embryo cells; a dose-dependent increase in morphological transformation, as well as a dose-dependent increase in gene mutations, was observed (398). Amitrole was also positive for intrachromosomal recombination that results in genome rearrangement in the yeast *S. cerevisiae* (337).

Table 59.6. Mutagenicity Tests with Aminotriazole

Assay/end point	Result	Ref.
Salmonella	Negative	24, 331, 337, 356–366, 339
	Positive	366
E. coli	Negative	362, 363, 367–372
	Positive	362
Saccharomyces	Negative	373–377
	Positive	378–380
Bacillus	Negative—5 strains	381
	Positive—1 strain	381
Drosophila	Negative	382
Unscheduled DNA synthesis	Negative	383, 384
Sister chromatid exchange	Negative	383, 385
	Positive	386
Bone marrow—mouse	Negative	387
Cytogenetics—rat	Negative	388
Mouse micronucleus	Negative	389
Dominant lethal—mouse	Negative	390, 391
Mouse lymphoma	Negative	392–394
Cell transformation	Negative	395–397

Amitrole was studied in the International Collaborative Program for evaluating short-term tests for carcinogenicity (356). These data were reviewed and evaluated by the IARC (320), who concluded that amitrole had a limited degree of evidence for genetic activity in short-term tests.

18.4.2 Human Experience A single oral dose of 100 mg inhibited the uptake of ^{131}I by the thyroid gland for 24 h in healthy subjects and in patients with hyperthyroidism. A dose of 10 mg had only a very weak effect (399). In an attempted suicide, a 39-year-old woman ingested a mixture that included amitrole; the amount ingested was 20 mg/kg. She did not become ill, although unchanged amitrole at a concentration of 1000 ppm was isolated from the urine (400).

A study was made of railroad workers who had been exposed to one or more herbicides for a total of 46 days or more within the period from 1957 to 1971. Of a total of 324 workers, 143 had been exposed mainly to amitrole. The incidence of cancer among these 143 persons was 7 (each in a different organ), compared to the 1.9 expected on the basis of national statistics adjusted for age and sex. In addition, there were two cancers of the lung, whereas 0.24 cancers were expected. However, both patients with lung cancer had smoked, and the tumors were of different cell types (41, 402). The lack of a similar report regarding persons heavily exposed to amitrole in its manufacture is noteworthy.

18.5 Standards, Regulations, or Guidelines of Exposure

An 8-hour Time Weighted Average of 0.2 mg/m^3 has been established by the ACGIH TLV® Committee. It has been placed in Group A3 (confirmed animal carcinogen with unknown relevance to humans) by that committee (5). The NIOSH REL is 0.2 mg/m^3.

18.6 Studies on Environmental Impact

Amitrole is released into the environment primarily from its applications as a herbicide. If released to soil, amitrole will degrade microbially and possibly chemically with a resultant average persistence of 2 to 4 weeks at recommended herbicidal concentrations. The degree of leaching in soil may depend upon the chemical and organic content of an individual soil. Loss of amitrole from soil by volatilization or photodegradation is minor. If released to the aquatic environment, amitrole is not expected to hydrolyze, directly photolyze, volatilize, or bioconcentrate significantly in aquatic organisms. Amitrole degradation in natural waters may be possible by oxidation with photochemically produced peroxy radicals or by photosensitized photolysis; biodegradation is not a rapid removal process from water. Adorption of amitrole to hydrosoil may be an important transport mechanism. An initial maximum half-life of 68 days was observed for amitrole applied to an outdoor pond, and persistence exceeded 200 days. If released to the atmosphere, vapor-phase amitrole reacts rapidly with photochemically produced hydroxyl radicals (estimated half-life of 3.8 days at 25°C), but does not react with ozone or directly photolyze (20).

Aliphatic and Aromatic Nitrogen Compounds

Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

19.0 Captan

19.0.1 CAS Number:

[*133-06-2*]

19.0.2 Synonyms:

1*H*-Isoindole-1,2-(2*H*)-dione; 3a,4,7,7d-tetra-hydro-2-[(trichloromethyl)thio]-

19.0.3 Trade Names:

Agrox; Captal; Captec; Captol; Captonex; Clomitrane; Merpan; Meteoro; Othocide; Phytocape; Sepicap; Sorene; Vancide 89

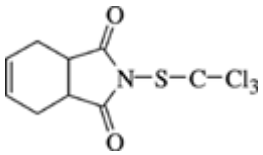
19.0.4 Molecular Weight:

300.6

19.0.5 Molecular Formula:

$C_9H_8Cl_3NO_2S$

19.0.6 Molecular Structure:

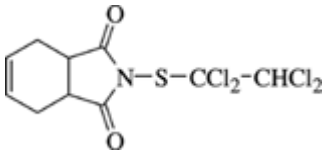


Aliphatic and Aromatic Nitrogen Compounds

Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

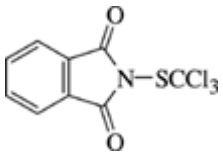
20.0 Captafol

20.0.1 CAS Number:
[*2425-06-1*]
20.0.2 Synonyms:
1H-Isoindole-1,3-(2H)-dione; 3a,4-7,7a-tetrahydro-2-[(1,1,2,2-tetrachloroethyl)thio]-
20.0.3 Trade Names:
Difolaton®, Folcid®
20.0.4 Molecular Weight:
349.06
20.0.5 Molecular Formula:
$C_{10}H_9Cl_4NO_2S$
20.0.6 Molecular Structure:



Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

21.0 Folpet
21.0.1 CAS Number:
[*133-07-3*]
21.0.2 Synonyms:
1H-Isoindole-1, 3(2H)-dione, 2-[(trichloromethyl)thio]-
21.0.3 Trade Names:
Phaltan®
21.0.4 Molecular Weight:
296.5
21.0.5 Molecular Formula:
$C_9H_4Cl_3NO_2S$
21.0.6 Molecular Structure:



19/20/21.1 Chemical and Physical Properties
19/20/21.1.1 General

	Captan	Captafol	Folpet
Physical Form	Yellow amorphous powder	White crystals	White crystals
Melting Point (°C)	178°C(pure)	159–161°C	177–180°C
Vapor Pressure (mmHg)	1.3 mPa (25°C)	—	—
Water Solubility	Insoluble	Insoluble	Practically

19/20/21.1.2 Odor and Warning Properties Captan: none (pure); pungent (tech). Captafol: pungent. Folpet: None

19/20/21.2 Production and Use

These *N*-sulfenyl phthalimide fungicides are used in large quantities worldwide. They became commercially available in 1950. Two producers make these fungicides in the United States (403). All three are primarily agricultural fungicides, but they do find some use in preventing fungal growth in industrial applications (e.g., paints and plastics). Captan is registered for use on more than 80 different crops including many foods, field crops, and ornamentals. Captafol and Folpet have similar uses on crops and are used for seed and plant bed treatment as well. Captan and Folpet are available in wettable powder formulations. All three are available as dusts, and captan and captafol are available in flowable formulations (404). These are broad-spectrum fungicides that inhibit mycelial growth from germinating fungus spores. They have effective protective action but will not eradicate a preexisting infection and are not systemically active.

Industrial exposure in manufacturing is limited. Agricultural workers are exposed to the wettable powders, dusts, and flowable formulations, as well as to aqueous emulsions, by inhalation and by skin contact with dusts, emulsions, and sprays.

19/20/21.3 Exposure Assessment

Several methods are available to measure these compounds in air (405–407). The recommended workplace method for determining these comparative NIOSH method 0500 (4a).

19/20/21.4 Toxic Effects

19/20/21.4.1 Experimental Studies 19/20/21.4.1.1 Acute Toxicity Acute toxicity data on Captan, Captafol and Folpet are summarized in Table 59.7 (408–410).

Table 59.7. Acute Toxicity (408–410)

Study	Captan	Captafol	Folpet
Rat, oral LD_{50}	12,500 mg/kg	6200 mg/kg 2500 mg/kg (80% WP)	>10,000 mg/kg
Rabbit, skin LD_{50}	>9000 mg/kg	>15,400 mg/kg (80% WP)	22,600 mg/kg
Rat, inhalation LC_{50} (2-h)	>5.7 mg/L	—	>5.0 mg/L
Mouse, inhalation LC_{50} (2-h)	4.5 mg/L	5.0 mg/L	>6.0 mg/L
Mouse, i.p. LD_{50}	518 mg/kg	462 mg/L	200 mg/kg

Mouse, oral LD_{50}	7840 mg/kg	7000 mg/kg	—

19/20/21.4.1.2 Chronic and Subchronic Toxicity Captan is a moderate skin sensitizer in guinea pigs (411). Captan was tested in subchronic studies in rats and mice to determine dose levels for chronic studies in the NCI Bioassay Program. Both male and female rats and male and female mice showed transient weight depression at both 2100 and 16,000 ppm (412).

A 54-week feeding study of both technical and recrystallized captan at 10,000 ppm was conducted using both male and female rats. Both sexes exhibited growth depression but no signs of systemic toxicity. At autopsy, testicular atrophy was found in three animals (411).

In two 17-month feeding studies in rats and dogs with folpet, the animals showed high tolerance to this compound (413) (See section 19/20/21.4.1.5).

Captafol apparently is not as well tolerated as captan and folpet after chronic administration, although no effects of tumor incidence were observed (413) (See section 19/20/21.4.1.5).

19/20/21.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Captan and folpet are quite similar. Extensive studies of captan have shown that it is readily absorbed from the gastrointestinal tract, rapidly metabolized, and eliminated from the body. The probable metabolic pathways of both the tetrahydrophthalimide and trichloromethylthio moieties have been elucidated. In rats, the tetrahydrophthalamide moiety is excreted, 92% in 48 h and 97% in 96 h (85% in the urine and 12% in the feces) (414). The trichloromethylthio moiety is converted to thiophosgene, which is further metabolized to thiazolidine-2-thione-4-carboxylic acid, which is excreted in the urine of orally dosed rats; carbon dioxide is also a product of the metabolism of thiophosgene through the intermediate formation of carbonyl sulfide. Thiophosgene is also detoxified by sulfites present in the gut and is excreted in the urine of orally dosed rats to yield dithiobis(methanesulfonic acid) and its disulfide monooxide derivative (415).

Captan is metabolized *in vitro* by liver mixed-function oxidases to carbonyl sulfide, suggesting a pathway similar to that which occurs *in vivo* (416). The metabolic fate of folpet is the same for the trichloromethylthio moiety, and the phthalamide product is hydrolyzed to phthalic acid and ammonia. Folpet is degraded extremely rapidly in the presence of sulfhydryl compounds, giving the same products as from hydrolysis (413).

When hydrolyzed, captafol yields tetrahydrophthalimide, chloride ion, dichloroacetic acid, and inorganic sulfur. No organochlorine is formed in the presence of sulhydryl groups (other products are the same). This reaction with sulfhydryl compounds is much faster than the hydrolytic reaction (413). The fate of the tetrahydrophthalimide moiety is the same as for captan (414).

19/20/21.4.1.4 Reproductive and Developmental The phthalimide moiety of captan, folpet, and captafol is structurally similar to thalidomide, which has produced birth defects. Consequently, many studies have been done on these chemicals to address this toxic end point.

Developmental studies have been conducted with captan, folpet, and captafol in several mammalian species, including nonhuman primates (417–419). In most studies, where these compounds were administered throughout organogenesis, lack of developmental effects was demonstrated. However, results of studies with rabbits were contradictory. There have been two studies with no malformed fetuses and one in which 9 of 75 fetuses were malformed (420). Further investigation did not produce a significant increase in the number of abnormalities (411).

In a study of golden hamsters, effects from a single administration of these compounds were compared with effects from repeated administration throughout organogenesis. At the highest doses (single and multiple with folpet and single with captafol), maternal mortality increased, and some abnormal fetuses were produced. There were no indications of teratogenic activity at the lowest single doses (captafol and folpet) and at all multiple doses (captafol) (419).

19/20/21.4.1.5 Carcinogenesis An NCI bioassay of technical-grade captan was conducted to determine carcinogenicity by administering captan in the feed to Osborne–Mendel rats and $B6C3F_1$ mice. The major outcome was that tumors of the duodenum of $B6C3F_1$ mice were associated with the captan treatment. There was no evidence that the tumors observed in Osborne–Mendel rats were treatment-related (412).

In the NCI study, groups of 50 rats of each sex were fed average doses of 2520 or 6050 ppm captan in the diet for 80 weeks. Groups of 50 mice of each sex were fed 8000 or 16,000 ppm captan in the diet for 80 weeks. These doses are approximately 250 (male) and 450 (female) mg/kg/day (high dose) and 50 (male) to 100 (female) mg/kg/day (low dose) in rats. In mice, these doses are approximately 2100 mg/kg/day (high dose) and 1000 mg/kg/day (low dose).

Other studies to determine the carcinogenic potential of captan reported negative findings. In one study (14), mice were administered 215 mg/kg/day for 3 weeks and then fed a diet containing 560 ppm for the remainder of 18 months. Two feeding studies were conducted, 18 months in mice and 2 years in rats. Doses in mice were 3750 and 7500 ppm technical-grade captan in the diet (414).

Folpet was also tested for carcinogenic potential (14). Mice were administered 215 mg/kg/day for 3 weeks and then fed a diet that contained 603 ppm for the remainder of 18 months. Folpet did not cause a significant increase in tumors in this study. In other chronic studies of folpet, rats were fed 1000, 3200, and 10,000 ppm for 17 months, and dogs were fed 10,000, 40,000, and 60,000 ppm for 17 months. In the rats, neither the incidence nor the character of tumors in test animals differed from those observed in the controls, and the mortality rate of test groups did not differ from those in the controls. There was slight growth retardation at 10,000 ppm. Clinical laboratory tests were normal, and no histological alterations were noted that could be attributed to the feeding of folpet. The dogs all survived. Body weights were normal, as were clinical laboratory tests and histopathological examination of tissues (413).

In a 2-year rat study of captafol added to the diet at 0 (70 males and 70 females), 250, 500, 1500, and 5000 ppm (35 females and 35 males at each test level), there was growth depression at the 1500- and 5000-ppm levels. Mortality was increased in the 5000-ppm group, and no males were alive after 23 months. A lymphocyte-to-neutrophil shift was observed in the surviving males of this group after 21 months. There was an increase in the liver-to-body weight ratio at the 500, 1500, and 5000-ppm levels at 12 months. An increase in this ratio was also seen in males at 250 ppm. At the end of the experiment, there was no longer a significant difference at the two lower test levels. Significant increases were also observed in organ weight and organ to body weight ratios for kidney and adrenal glands of rats fed at 1500 and 5000 ppm. Histopathology revealed liver changes characterized by degeneration of hepatic cells, vacuolization, incipient fat alteration, and infiltration by mononuclear cells. Kidney changes were characterized by alterations in proximal and distal tubular cells, and many giant forms with large irregular nuclei were present.

These changes in liver and kidney were seen only in rats fed the two highest dose levels. No other histopathogical changes were associated with the administration of captafol. No effects on tumor incidence were observed (413).

19/20/21.4.1.6 Genetic and Related Cellular Effects Studies Captan, captafol, and folpet have been tested extensively for mutagenic potential as shown in Table 59.8 (421–426). All have demonstrated

the ability to induce gene mutations in some of the test systems, usually without metabolic activation. In studies with and without activation or added sulfhydryl groups (L-cysteine), it has been shown that these compounds lost mutagenic activity rapidly in the presence of the S-9 activation system or the sulfhydryl groups (414, 427–429).

Table 59.8. Studies to Determine Genotoxicity of Captan, Captafol, and Folpet[ab]

Test-Gene Mutations	Captan	Captafol	Folpet
Aspergillus nidulans	421	421	
Neurospora crassa	422		
E. coli.			
Without activation	423	423	423
With activation	423	423	423
S. typhimurium.			
Without activation	254, 258	424	
S. typhimurium.			
With activation	423, 425	127, 424, 425	425
Drosophila melanogaster	145, 146, 426	145, 426	

[a] + = positive result; – = negative result.
[b] Reference numbers in parentheses.

Captan, folpet, and captafol produced mutations in bacteria and yeast and other cellular systems, but were inactive in *in vivo* mutagenicity tests (430, 431).

19/20/21.4.2 Human Experience Captafol has caused occupational dermatitis in both agricultural workers and nonagricultural workers (408, 432, 433). Sensitization to captafol, it is estimated, occurs in 10 to 40% of those who use this chemical.

In a nonagricultural exposure (432), a welder frequently brushed against large bags of captafol while working at a distributing plant. After 1½ years with no problems, he suddenly developed marked vesiculation and edema of his face and hands and associated wheezing.

In California in 1974 through 1976, 22 cases of skin exposure incidents, three cases of eye exposure incidents, and five eye and skin exposure incidents were reported. The skin exposure incidents were mainly allergic dermatitis. The eye and skin exposure incidents resulted primarily in chemical conjunctivitis, allergic conjunctivitis, and dermatitis. In most of these cases, safety equipment was not required or used (433).

No other human experience data or epidemiology studies were found for these fungicides.

19/20/21.5 Standards, Regulations, or Guidelines of Exposure

A TLV® for captan is 5 mg/m^3 for an 8-hour exposure. The TLV® Committee lists captan in Group A3 (confirmed animal carcinogen with unknown relevance to humans). The TLV for captafol is 0.1 mg/m^3 for an 8-hour exposure. It also has a skin notation and is in Group A4 (not classifiable as a human carcinogen) (5). An exposure limit for folpet has not been established by the TLV Committee. The NIOSH REL for captan is 5 mg/m^3 and for captafol is 0.1 mg/m^3.

19/20/21.6 Studies on Environmental Impact

Captan released to soil is not expected to leach extensively, but evaporation from near the surface of soils may be significant. Captan readily hydrolyzes in water, and it will probably also hydrolyze in

soil, depending upon the pH. Captan half-lives in moist soil range from 1 to 12 days. Captan released to water will have a moderate tendency to adsorb to suspended sediments, biota, and sediments and a low-to-medium tendency to bioconcentrate (BCF = 36 – 900). Volatilization may be significant from shallow rivers and streams but will be slower from lakes and ponds. The primary degradative process for captan in water is hydrolysis. Hydrolysis half-lives will be on the order of hours. Direct photolysis of captan is not important in relatively clear water; indirect photooxidation appears to be important in water with high humic content. A computer estimated half-life for captan in the vapor phase of the atmosphere based upon reaction with hydroxyl radicals is about one hour. Captan may also be present in the atmosphere adsorbed to particulate matter. Captan has been found in food composites at concentrations up to 0.178 ppm. The average daily intake of captan in the U.S. diet in 1979 was 0.005 mg/kg/body weight/day.

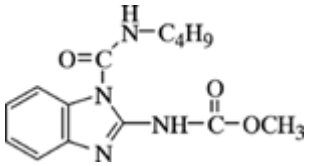
Folpet is released to the environment through its use as a fungicide. If released to soil, folpet is not expected to be mobile and, therefore, very little leaching in soil is expected. Folpet is expected to degrade in the ambient atmosphere by reaction with photochemically produced hydroxyl radicals, and the half-life is 0.37 days. If released to water, neither volatilization nor bioconcentration are expected to be important fate processes. In alkaline aqueous media, folpet undergoes rapid hydrolysis. Absorption of folpet to sediments will be important. Exposure of folpet to the general population is possible by inhalation of air or ingestion of food contaminated by release during its use as a fungicide.

Captafol strongly adsorbs to soil and should therefore remain in the upper layers of soil. In soil, biodegradation and hydrolysis transform captafol. The half-life of captafol in soil is about 11 days. Both biodegradation and hydrolysis are expected to be the major pathways for the loss of captafol in water. The half-life of captafol in river water was estimated at 0.3 day. Volatilization from water or soil should be negligible. The bioconcentration of captafol in aquatic organisms should not be important. Reaction of captafol with photochemically produced hydroxyl radicals and ozone will be the important loss process in the atmosphere. The half-life of captafol in air can be estimated at less than 1.4 h. Partial removal of captafol will also occur as a result of dry and wet deposition. Captafol has rarely been detected in surface water and groundwater in the United States. It has been detected at very low levels in some foods. The applicators of the fungicide and farm workers are the most likely people to be exposed to captafol by inhalation and dermal routes (20).

Aliphatic and Aromatic Nitrogen Compounds

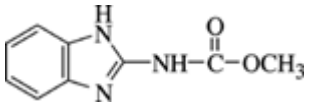
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

22.0 Benomyl
22.0.1 CAS Number:
[*17804-35-2*]
22.0.2 Synonyms:
Carbamic acid, (1-[(butylamino)carbonyl]-1*H*-benzimidazol-2yl)-, methyl ester
22.0.3 Trade Names:
Benlate® Fungicide; Tersan®, 1991
22.0.4 Molecular Weight:
290.32
22.0.5 Molecular Formula:
$C_{14}H_{18}N_4O_3$
22.0.6 Molecular Structure:



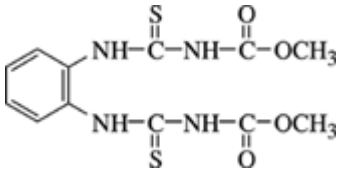
Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

23.0 Carbendazim
23.0.1 CAS Number:
[*10605-21-7*]
23.0.2 Synonyms:
Carbamic acid, 1H-benzimidazol-2-yl-, methyl ester
23.0.3 Trade Names:
MCAB; BCM; Hoe; 17411; Drosal; Bavisitin®; MBC; carbendazim; Delsene® fungicide
23.0.4 Molecular Weight:
191.2
23.0.5 Molecular Formula:
$C_9H_9N_3O_2$
23.0.6 Molecular Structure:



Aliphatic and Aromatic Nitrogen Compounds
Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

24.0 Thiophanate-methyl
24.0.1 CAS Number:
[*23564-05-8*]
24.0.2 Synonyms:
Carbamic acid; [1,2-phenylenebis(imino carbonothioyl)]bis-, dimethyl ester
24.0.3 Trade Name:
Topsin M® thiophanate-methyl
24.0.4 Molecular Weight:
342.39
24.0.5 Molecular Formula:
$C_{12}H_{14}N_4O_4S_2$
24.0.6 Molecular Structure:



22/23/24.1 Chemical and Physical Properties
22/23/24.1.1 General

	Benomyl	Carbendazim	Thiophanate-methyl
Physical Form	white, crystalline solid	light gray powder,	Colorless, crystalline solid
Melting Point (°C)	140	302–307°C	172°C
Boiling Point (°C)	(dec) >300°C	—	—
Water Solubility		<0.1 g/100 mL at 20°C	<0.1 g/100 mL at 21° C
Vapor Pressure	Negligible	Negligible ($<10^{-3}$ mmHg at 125°C)	—
Other	Converts to MBC with moisture	Stable	Converts to MBC with moisture

22/23/24.1.2 Odor and Warning Properties Negligible.
22/23/24.2 Production and Use
There are three major benzimidazole fungicides used worldwide. All are primarily agricultural and turf-ornamental rather than industrial fungicides. They produce their fungicidal effect by systemic action. Benomyl has the largest share of U.S. use and is applied on many food and ornamental plant crops (427). MBC is registered in more than 15 countries for use on at least 25 food crops as well as turf-ornamentals, but is not registered in the United States (414). Thiophanate-methyl, whose major metabolite is a benzimidazole, is a Japanese product that is also used widely. Residue tolerances have been established for nine food crops in the United States.

All three fungicides are available in wettable powder formulations or dispersions that contain from 6 to 70% active ingredient, the balance is either inert ingredients or other fungicides. Industrial exposure at the manufacturing level is limited. However, agricultural workers are exposed to the wettable powders and dispersions, as well as to dilute aqueous emulsions. There are two primary routes of exposure: inhalation of the dusts and skin contact with dusts, emulsions, and sprays. All have similar uses, mechanisms of action, and toxicity. Because MBC is considered the major metabolite of benomyl and thiophanate-methyl is found in and on plant material after use of both products, these three chemicals are discussed together.
22/23/24.3 Exposure Assessment
Analytical methods for determining residues of benomyl are based on conversion to MBC or to 2-aminobenzimidazole. These methods can be easily adapted for determining MBC and thiophanate-methyl and for analyzing air samples (434, 435).

Benomyl-derived residues can be determined by HPL chromatography.

NIOSH Analytical Method 0500 or 6000 is recommended for determining workplace exposure (4a).
22/23/24.4 Toxic Effects
22/23/24.4.1 Experimental Studies 22/23/24.4.1.1 Acute Toxicity Table 59.9 is a compilation of the acute toxicity of benomyl, MBC, and thiophanate-methyl (414). These compounds have very low mammalian toxicity. By most routes of exposure, the maximum feasible dose killed no animals. Clinical signs of acute toxicity from high doses of thiophanate-methyl were tremors leading to tonic or clinic convulsions, nose bleeding and lacrimation in rats; and decreased respiratory rate, lethargy, disappearance of tonus of abdominal muscle, discharge from eyes, and mydriasis in rabbits and dogs (414).

Table 59.9. Acute Toxicity of Benzimidazole Fungicides (435–437)

Species	Sex	Route	Study	Benomyl	MBC	Thiophanate-methyl
Rat	M	Oral	LD_{50}	>10,000 mg/kg	>10,000 mg/kg	7500 mg/kg
	F	Oral	LD_{50}		>10,000 mg/kg	6640 mg/kg
	M	i.p.	LD_{50}	>10,000 mg/kg	>7230 mg/kg	6640 mg/kg
	F	i.p.	LD_{50}		>15,000 mg/kg	1140 mg/kg
	M	Inhalation	LC_{50}		5.6 mg/L	
	M,F	4 h	LD_{50}			>10,000 mg/kg
		Skin		>2 mg/L		
Mouse	M	i.p.	LD_{50}		>15,000 mg/kg	790 mg/kg
	F	i.p.	LD_{50}		>15,000 mg/kg	1110 mg/kg
	M	Oral	LD_{50}			3510 mg/kg
	F	Oral	LD_{50}			3400 mg/kg
	M	Inhalation, 2 h	LC_{50}			>100 mg/L
Rabbit	M	Skin	LD_{50}	>10,000 mg/kg	>10,000 mg/kg	
	M	Skin	Irritation		None	Mild
	M	Eye		Mild	None	None (10%)
	M,F	Oral	Irritation	Mild	>8000 mg/kg	
	M	Unknown				2270 mg/kg
	F	Unknown	LD_{50}			
			LD_{50}			
			LD_{50}			
Dog	M,F	Oral	LD_{50}		>8000 mg/kg	
	M,F	Inhalation, 4 h	LC_{50}	>0.825 mg/L		
	M,F		LD_{50}			4000 mg/kg
			Unknown			

Guinea pig	M	Oral	LD_{50}			3640 mg/kg
	F	Oral	LD_{50}			6700 mg/kg
Mallard duck		Oral, 8 day	LC_{50}	>5000 ppm	>10,000 ppm	
Bobwhite quail		Oral, 8 day	LC_{50}	>5000 ppm	>10,000 ppm	
Japanese quail	M	Oral	LC_{50}		10,996 mg/kg	>5000 mg/kg
	F	Oral	LD_{50}		5826 mg/kg	>5000 mg/kg

22/23/24.4.1.2 Chronic and Subchronic Toxicity In 2-year feeding studies of benomyl (2500 ppm, the highest dietary level), the no observable effect level (NOEL) was 2500 ppm for rats and 500 ppm for dogs. In dogs fed 2500 ppm, there was biochemical evidence of impaired liver function and histological evidence of liver cirrhosis. No oncogenic effects were observed in rats.

In a 2-year feeding study with mice, the NOEL was 500 ppm except for changes in the liver. This NOEL was based on reduced body weights, weight effects in the liver and testis, and microscopic changes in these tissues at 1500 and 5000 ppm. Oncogenic effects were observed in the liver of male and female mice at all dietary levels (500 to 5000 ppm). Other studies of the active metabolite of benomyl in similar mouse strains produced similar results; however, oncogenicity was not observed at exposures below 500 ppm. When an unrelated strain of mice was used, that is, one with a much lower background of liver tumor incidence among untreated animals, an oncogenic response was not produced. This was true for exposures up to and including 5000 ppm (438).

For MBC, toxic effects described in animals from exposures by inhalation, ingestion, or skin contact include liver, bone marrow, and testicular effects (436).

Thiophanate-methyl was not irritating or toxic in a 30-day skin absorption study of guinea pigs. The material was applied daily to the abraded dorsum at 2, 20, and 200 mg/kg (414). Mice (CR-SCL strain) were fed thiophanate-methyl for 2 years at doses of 10, 40, 160, and 640 ppm in their diet. Except for slightly retarded growth in males at 640 ppm, no effects were detected (414).

22/23/24.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms As stated previously, MBC is the major metabolite of benomyl and thiophanate-methyl in plants. Subsequent metabolic products are hydroxylated derivatives and 2-aminobenzimidazole.

Benomyl and MBC are rapidly metabolized and eliminated in urine of rats and dogs as methyl 5-hydroxy-2-benzimidazolecarbamate (5HBC) (439). Residue data on dog and rat tissues from 2-year feeding studies indicate that benomyl and MBC and/or metabolites do not accumulate in animal tissue. Data on the metabolism of thiophanate-methyl in animals were not available.

22/23/24.4.1.4 Reproductive and Developmental Benomyl was not embryotoxic or teratogenic to rats by dietary administration at levels as high as 5000 ppm (equivalent to approximately 373 mg/kg/day). No teratogenic effects were found in studies with rabbits fed 500 ppm in the diet (equivalent to approximately 20 mg/kg/day). By gavage administration, a statistically significant teratogenic response was obtained at dose levels of 62.5 mg/kg/day and higher, but not at 30 mg/kg/day and less (438).

Excessive exposure of laboratory animals to benomyl has produced testicular weight, lowered sperm counts, and reduced fertility. These effects were accompanied by other indicators of general toxicity and were reversible in studies that evaluated effects after exposure was discontinued. In two- and three-generation dietary studies of rats, the overall NOEL for parents and their offspring was 500 ppm (20 to 30 mg/kg/day). Reduced body weights, testicular weights, and sperm counts were observed at 3000 and 10,000 ppm. However, there were no compound-related effects on fertility, mating behavior, or length of gestation. Benomyl is not considered to have selective effects on the reproductive system. The effects occur at doses that also produce general toxicity in laboratory animals (438, 440).

The developmental toxicity of MBC was observed in animals dosed by stomach tube; however, when higher doses were administered in the animals' feed, developmental toxicity was observed only at dose levels that were also toxic to pregnant animals. MBC produced reproductive toxicity in studies of male rats and mice; however, the reproductive ability of females was not affected by this material (436).

Groups of pregnant rats were administered MBC by gavage on days 6 to 15 of gestation at dose levels up to 80 mg/kg/day. Groups of pregnant rabbits were similarly administered up to 160 mg/kg/day on days 6 to 18 of gestation. In the rats, dead and resorbed fetuses accounted for 29% of conceptions in controls, 48% at 20 mg/kg of MBC, 64% at 40 mg/kg, and 73% at 80 mg/kg. In rabbits, no dead or resorbed fetuses were seen in controls whereas 15 to 33% were found in MBC-treated rabbits. There were no differences among groups of rats or rabbits in mean weight of live fetuses, and there were no malformations (441).

MBC was administered by gavage to pregnant rats at doses of 25, 50, 100, 200, 400, or 1000 mg/kg/day on days 1 through 8 of gestation. When MBC doses of up to 400 mg/kg/day were administered during early pregnancy, MBC had no significant effect on the number of implantation sites, body weight gain, uterine weight, implantation site size, and serum ovarian and pituitary hormone activity; however, a trend toward increased resorptions was evident. At 100 mg/kg/day, MBC produced reductions in body weight gain, implantation site weights, and serum luteinizing hormone and an increase in serum estradiol. When administered during pseudopregnancy, 400 mg/kg/day of MBC partially reduced uterine decidual growth but affected no other parameter (442).

MBC was orally administered by gavage to male rats at 400 mg/kg/day for 10 days. On the third day of treatment they were mated with unexposed females. Testicular weights were 58% less than those of the control rats. Sixteen of the 24 males in the treatment group were infertile by the fifth week after exposure, and 12 of the 16 never regained fertility. Most of the male rats exposed to MBC had testes that showed atrophy of the seminiferous tubules, which were lined by Sertoli cells and contained spermatogonia (443).

Groups of male and female rats were administered by gavage 50, 100, 200, or 400 mg/kg/day of MBC from weaning through puberty, gestation, and lactation. A similar study was conducted with hamsters administered 400 mg/kg/day. The growth, viability, and reproductive function of the offspring (FI) were observed during a 4-month period of continuous breeding. MBC did not alter pubertal development, growth, or viability.

The reproductive function of rats administered 200 or 400 mg/kg/day of MBC was reduced due to effects on sperm production and fetal viability. In the male rats, MBC markedly altered sperm morphology, testicular and epididymal weights, sperm numbers, and testicular histology. Fertility, sperm motility, and hormone levels were altered primarily in the males that had low sperm counts. The ability to conceive did not involve a female factor. In the female rats, MBC administration caused postimplantation losses in the high-dose group, and a few malformed rat pups were found in the litters from the 100- and 200-mg/kg/day groups. MBC was less toxic to the hamster than the rat, and the only reproductive effects induced by MBC administration were sperm measures. Fetal and

neonatal (F1) viability were not affected (444).

Thiophanate-methyl was fed to CR rats (10 males, 20 females/group) at 0, 40, 160, and 640 ppm in a three-generation (two litters/generation) reproductive study. There was an effect on growth at 640 ppm, but no apparent effects were noted on reproduction parameters. Tissues and organs of 3-week-old F3b animals were examined histopathologically. Cleared specimens were also examined for skeletal anomalies. No effects were detected (414).

22/23/24.4.1.5 Carcinogenesis Long-term testing for the carcinogenic potential of benomyl and MBC is discussed in the section on Chronic and Subchronic Toxicity. Those long-term studies evaluated a variety of toxicity end points including carcinogenicity. Both benomyl and MBC were weak carcinogens in some *in vivo* studies.

Two-year feeding studies with thiophanate-methyl in ICR-SCL mice (see Chronic and Subchronic Toxicity, earlier) a strain of mouse especially susceptible to tumors, showed a variety of tumors in all groups, including controls, but the compound was not considered carcinogenic (414).

22/23/24.4.1.6 Genetic and Related Cellular Effects Studies Benomyl has been evaluated in numerous tests for mutagenicity and genotoxicity. The vast majority of these tests were negative. The weight of evidence from all studies indicates that benomyl is not a heritable gene mutagen. It does not interact with cellular DNA nor induced point or germ cell mutations. Benomyl is not considered clastogenic. The only genotoxic end point for which benomyl produces specific responses is numerical chromosomal aberrations or aneuploidy. This is the mechanism by which benomyl exerts its fungicidal activity (438).

Dominant lethal studies were conducted for all three compounds. Benomyl was fed to male rats for 7 days at 250, 1250, and 2500 ppm in the diet. The rats were bred to three females each week for six of the 10 weeks required for spermatogenetic processes. No toxicity was observed in the males. The control group had higher incidences of preimplantation losses and early resorptions. Benomyl was not mutagenic in the dominant lethal assay (440).

MBC was administered in single doses to male mice at 1280 mg/kg (intraperitoneally). These mice were bred to three females each week during an 8-week period. Except for slight growth depression the first week, no effects on the males were noted. MBC was not mutagenic in this dominant lethal assay (414).

Thiophanate-methyl was administered intraperitoneally in single doses to groups of 10 male ICR-strain mice at 8 to 500 mg/kg. The animals were then mated during an 8-week period. No mutagenic effects were noted (i.e., no increased early fetal death or preimplantation losses) (445).

Tests in bacterial or mammalian cell cultures and in animals indicate that MBC does not interact with DNA. This material does cause an increase in chromosomal numbers (aneuploidy). Currently available animal data indicate that this material does not cause permanent genetic damage in the reproductive cells of mammals.

22/23/24.4.1.7 Other: Neurological, Pulmanary, Skin Sensitization No other human experience data or epidemiology studies were found for these fungicides.

22/23/24.4.2 Human Experience There is no evidence of adverse long-term health effects in humans from exposure to these chemicals. Temporary allergic skin reactions in a few susceptible persons are mentioned in the benomyl material safety data sheet (MSDS) from Du Pont (438).

Ten strawberry harvesters were monitored during working hours for dermal exposure, and the average exposure was 5.39 mg/h/person (446).
22/23/24.5 Standards, Regulations, or Guidelines of Exposure

These three compounds are considered nuisance dust particulates. Benomyl has an ACGIH TLV of 10 mg/m^3, and the OSHA PEL TWA is 15 mg/m^3 for total and 5 mg/m^3 for respective benomyl. There are no occupational exposure standards for carbendazim and thiophanate-methyl.

22/23/24.6 Studies on Environmental Impact

Benomyl released to soil does not leach, but volatilization of benomyl from soil can occur. Hydrolysis of benomyl in soil is probably the most significant removal process although biodegradation may also be significant, especially for the benomyl hydrolytic products. When applied to turf, benomyl has a half-life of 3 to 6 months and up to twice that in bare soil. Benomyl released to water has a low to moderate tendency to adsorb to sediments, suspended sediments, and biota and does not bioconcentrate to any significant extent. Volatilization of benomyl from water is probably insignificant. Hydrolysis is probably the most significant removal process for benomyl from water ($t_{1/2}$ < 1 week), although biodegradation and photolysis may also be important. A computer estimated half-life for the reaction of benomyl in the vapor phase with photochemically produced hydroxyl radicals in the atmosphere is 1.6 hours. The half-life of carbendazim is in the 1-to-2 month range, depending upon media (20).

No significant information was found for thiophanate-methyl.

Aliphatic and Aromatic Nitrogen Compounds

Henry J. Trochimowicz, Sc.D., Gerald L. Kennedy, Jr., Ph.D., CIH, Neil D. Krivanek, Ph.D.

25.0 Benzotriazole

25.0.1 CAS Number:

[*95-14-7*]

25.0.2 Synonyms:

1,2,3-Benzotriazole

25.0.3 Trade Name:

NA

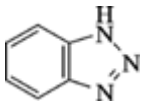
25.0.4 Molecular Weight:

119.12

25.0.5 Molecular Formula:

$C_6H_5N_3$

25.0.6 Molecular Structure:



25.1 Chemical and Physical Properties

25.1.1 General

Physical Form	White to lighten crystals
Boiling Point	350°C
Melting Point	98.5°C
Water Solubility	0.1–0.5 g/100 mL at 23.7°C
Other	May explode during vacuum distillation
Vapor Density	4.1

25.1.2 Odor and Warning Properties None.

25.2 Production and Use

1-H-Benzotriazole is manufactured in the United States. Its main use is as an anticorrosive in metalworking, in art restoration, and as a tarnish remover and protective coating in the construction industry. It is used as a corrosion inhibitor in water-cooling systems and in dry-cleaning equipment. It is also used in some formulations of automatic dishwasher detergents to prevent tarnishing of metal utensils. 1-*H*-Benzotraizole forms covalent linkages with metals thereby preventing attack by corrosive agents. It is used in other capacities in electrolytic and photographic processing.

25.3 Exposure Assessment

To analyze for 1-*H*-benzotraizole, HPLC, thin-layer chromatography, and nonaqueous titration of the amine function with perchloric acid are acceptable (447). One or more of these methods could be adapted to analyze for 1-*H*-benzotriazole in air.

ind59-108 Toxic Effects

25.4.1 Experimental Studies 25.4.1.1 Acute Toxicity The acute toxicity of 1-*H*-benzotriazole is moderate to slight.

Oral ALD (rats)	500 to 670 mg/kg (448, 449)
Intraperitoneal LD_{50} (mice)	1000 mg/kg (450)
Intravenous LD_{50} (mice)	238 mg/kg (451)
Inhalation LC_{50} (rats), 3 hr.	1900 mg/m^3 (452)

In a test for primary skin irritation and sensitization on guinea pigs, 1-*H*-benzotriazole was at most, mildly irritating in concentrations up to 50% in ethanol and was not a sensitizer. The dry powder is severely irritating to rabbit eyes (0.1 mL, unwashed) but prompt water washing reduces irritation considerably (448).

25.4.1.2 Subchronic and Chronic Toxicity A 56-day feeding study was conducted in rats and mice to determine maximum tolerated doses for the bioassay of 1-*H*-benzotriazole (447). Toxicity (i.e., weight depression) was observed in rats at 300 to 30,000 ppm, but not in mice, except at 30,000 ppm (not at 10,000 ppm).

25.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 1-*H*-Benzotriazole was metabolized by rat liver microsomes *in vitro* to 4-hydroxybenzotriazole and 5-hydroxybenzotriazole (453).

No data for absorption, distribution, metabolism, or excretion of benzotriazole in mammals were found.

25.4.1.4 Reproductive and Developmental No relevant studies were found.

25.4.1.5 Carcinogenesis Chronic (2-year) feeding studies were conducted. Rats were given 0, 6,700, or 12,000 ppm in feed for 78 weeks and held for an additional 26 weeks. Mice were given 0, 11,700, or 23,500 ppm in feed in 104 weeks. The authors concluded that under the conditions of this study, there were no convincing evidence that 1-H-benzotriazole was carcinogenic in rats or mice (447).

25.4.1.6 Genetic and Related Cellular Effects Studies 1-H-Benzotriazole was positive in the *S. typhimurium* and in *E. coli* mutagenicity assays (454).

25.4.2 Human Experience A report showed that two metalworkers developed contact dermatitis from exposure to lubricating oil that contained 1-*H*-benzotriazole (455).

No other human experience data, case histories, or epidemiology studies were found for benzotriazole.

25.4 Standards, Regulations, or Guidelines of Exposure
No occupational exposure standards have been established.
25.6 Studies on Environmental Impact
No information was found.

Aliphatic and Aromatic Nitrogen Compounds

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Alkylpyridines and Miscellaneous Organic Nitrogen Compounds

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A. Alkylpyridines

Table 60.1. Acute Toxicity of Five Alkylpyridines (36)

	Approximate Oral LD_{50} (mg/kg)		Approximate Dermal LD_{50} (mg/kg)	Inhalation Toxicity in Rats		
Pyridine	**Rats**	**Mice**	**Guinea Pigs**	**Concn (ppm)**	**Time (h)**	**Mortality**
2-Ethyl	—	—	—	5400	3	100
4-Ethyl-	—	—	—	2500	5	100
2-Methyl-5-Ethyl	800–1600	800–1600	2,500–5,000	1700	3.7	100
2-*n*-Amyl	100–200	200–400	5,000–10,000	400	6	0
4-*n*-Amyl	200–400	200–400	5,000–10,000	300	6	0

Table 60.2. Acute Toxicity of Vinylpyridines (36)

	Approximate Oral LD_{50} (mg/kg)		Approximate Dermal LD_{50} (mg/kg)	Inhalation Toxicity in Rats	
				Concn	**Time**

Pyridine	Rats	Mice	Guinea Pigs	(ppm)	(h)	Mortality
2-Vinyl	100–200	400–800	<500	160	6	0
		Rabbits	300 (56)	5500	1.5	100
4-Vinyl	100–200	200–400	<500	150	6	0
				2000	2	100
2-Methyl-5-vinyl	1167 (57)	775 (58)	718 (57)	1000	4.5	0
			Rabbits	6000 (52)	3–5	100

Note: Numbers in parentheses are references.

Table 60.3. Acute Toxicity of Nicotine

Species	Route	Dose (mg/kg)	Response	Ref.
Cat	i.v.	2	LD_{50}	108
	i.v.	1.3	LD_{50}	109
	i.m.	9	Paralysis, convulsions, ataxia	98
Dogs	i.v.	15 (over 8 h)	Respiratory failure	110
	i.v.	5	LD_{50}	108
Mouse	Oral	24	LD_{50}	111
	s.c.	16	LD_{50}	111
	i.v.	7.1	LD_{50}	108
	Oral	50–60	Approx. LD_{50}, convulsions, paralysis	98
	i.p.	5.9	LD_{50}	112
Monkey	i.m.	6	Convulsions, paralysis	98
Rabbit	i.v.	9.4	LD_{50}	108
	Dermal	50	LD_{50} (estd.)	113
	i.p.	14	LD_{50}	114
	i.m.	30	Convulsions, paralysis	98
Rat	Oral	50–60	Convulsions, paralysis	115
	i.p.	14.6	LD_{50}	116
	Dermal	140	LD_{50}	117
	i.v.	7	LD_{50}	118
	Intratracheal	19.3	LD_{50}	119
Human	Rectal	1.4	Hallucinations, nausea	120

Table 60.4. Acute Toxicity of Three Substituted Uracils[a]

Test	Bromacil	Lenacil	Terbacil
Oral LD_{50}			
Rat (mg/kg)	5200 (167)	>11,000 (168)	>5000 (169) >7500 (170)
Dog (mg/kg)	>5000 (170)	—	>5000 ALD (170)
Skin ALD			
Rabbit (mg/kg)	>5000 (171) >2000 (174)	>5000 (172)	>5000 (173)
Skin irritation			
Rabbit	None (175) Slight (174, 176)	None (172)	None (173)
Guinea pig	Mild (177)	Mild to moderate (171)	None (173)
Sensitization			
Guinea pig	None (178, 179)	None (178, 180)	Mild (173)
Eye irritation			
Rabbit	Mild (181)	Mild (171)	Mild (182)
Inhalation			
LC_{50} (4 h)	>4.8 (183)	>5.2 (184)	>4.4 (185)
Rat (mg/L)	>5.2 (186)		

[a] Numbers in parentheses are references.

Table 60.5. Genetic Toxicity Tests on Substituted Uracils[ab]

Assay/End Point	Bromacil	Lenacil	Terbacil
Salmonella typhimurium	–(214–218) +(219, 220)	–(221)	–(215, 216, 222, 223)
Escherichia coli	–(218, 222, 224, 225)		–(216, 222)
Saccharomyces cerevisiae	–(217, 225–227)		
Drosophila melanogaster	+(205, 217, 218, 224, 225) –(220, 238)		–(206, 229)
Mouse lymphoma assay	+(217, 218, 224,		

	225)	
Chinese hamster ovary	–(224, 225, 230)	–(229, 231)
Unscheduled DNA/human fibroblasts	–(225, 230)	
in vivo mouse micronucleus	–(224, 225, 232)	
in vivo mouse dominant lethal	–(217, 225, 233–235)	

[a] + = positive result; – = negative result.
[b] Reference numbers in parentheses.

Table 60.6. Acute Toxicity of Quaternary Herbicides in Various Species[a] (240, 241)

	Oral LD_{50} (mg/kg)			Dermal LD_{50} (mg/kg)			Inhalation LC_{50} (mg/m^3)		
	PQ	**DQ**	**DFQ**	**PQ**	**DQ**	**DFQ**	**PQ**	**DQ**	**DFQ**
Rat	100–200	130–400	270	80–350	650	—	1–10	35–83	—
Mouse	—	125–170	31–44	62	430	—	—	—	—
Rabbit	—	101–190	470	236–500	>400	3540	—	—	—
Guinea pig	22–80	100–123	—	319	400	—	4	38	—
Monkey	50	100–300	—	—	—	—	—	—	—

[a] PQ = paraquat; DQ = diquat; DFQ = difenzoquat; — = No data.

Alkylpyridines and Miscellaneous Organic Nitrogen Compounds
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B *s*-Triazine Herbicides

Alkylpyridines and Miscellaneous Organic Nitrogen Compounds

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Cyanides and Nitriles

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A. Cyanides

Table 61.1. Physical and Chemical Properties of Cyanides a

Compound	CAS Number	Molecular Formula	Physical Formula	Molecular Weight	Boiling Point (°C)	Melting Point (°C)
			Cyanides			
Hydrogen cyanide	[*74-90-8*]	HCN	Colorless liquid	27.03	25.7	–13.2
Sodium cyanide	[*143-33-9*]	NaCN	White crystals	49.01	—	563
Potassium cyanide	[*151-50-8*]	KCN	White crystals	65.12	—	634
Calcium cyanide	[*592-01-8*]	$Ca(CN)_2$	White powder	92.11	—	—
Cyanamide	[*420-04-2*]	CH_2N_2	Elongated tablets	42.04	—	—
Calcium Cyanamide	[*156-62-7*]	$CaCN_2$	White crystals	80.11	—	1300
Cyanogen	[*460-19-5*]	C_2N_2	Colorless gas	52.04	–27.17	–27.9
Cyanogen chloride	[*506-77-4*]	ClCN	Colorless liquid or gas	61.47	13.8	–6
Cyanogen bromide	[*506-68-3*]	BrCN	Colorless crystals	105.9	61.6	52
Dimethyl cyanamide		$(CH_3)_2CN_2$	Colorless liquid	70.1	—	–41
			Nitriles			
Acrylonitrile	[*107-13-1*]	$CH_2{=}CHCN$	Colorless liquid	53.06	77.5–77.9	–83.5
Methyl acrylonitrile	[*126-98-7*]	$CH_2{=}C(CH_3)CN$	Colorless liquid	67.09	90.3	–35.8
Acetonitrile	[*75-05-8*]	CH_3CN	Colorless liquid	41.05	81.6	–43
Propionitrile	[*107-12-0*]	CH_3CH_2CN	Colorless liquid	55.08	97.1	–98
n-Butyronitrile	[*109-74-0*]	$CH_3CH_3CH_2CN$	Colorless liquid	69.11	116	–112.6
Isobutyronitrile	[*78-82-0*]	$(CH_3)_2CHCN$	Colorless liquid	69.11	107	–75
3-Hydroxypropionitrile	[*109-78-4*]	$HOCH_2CH_2CN$	Colorless or straw liquid	71.08	221	–46
Lactonitrile	[*78-97-7*]	C_3H_5NO	Colorless or straw liquid	71.08	103	–40
2-Methyllactonitrile	[*75-86-5*]	C_4H_7NO	Liquid	85.11	95	–20
Glycolonitrile	[*107-16-*		Colorless	57.05	183	

	4]	$HOCH_2CN$	oily liquid			
Succinonitrile	[*110-61-2*]	$CNCH_2CH_2CN$	Colorless waxy solid	80.09	265–267	57–57.
Adiponitrile	[*111-69-3*]	$CN(CH_2)_4CN$	Colorless liquid	108.1	295	1–3
Glycolonitrile	[*107-16-4*]	$HOCH_2CN$	Clear pale yellow liquid	57.05	183	<–72
3-Dimethylaminopropionitrile	[*1738-25-6*]	$(CH_3)_2NCH_2CH_2CN$	Colorless liquid	98.15	172	–44.2
3-Isopropylaminopropionitrile	[*7249-87-8*]	$(CH_3)_2CH_2NHCH_2CN$	Liquid	112.2	87	–20
3-Methoxypropionitrile	[*110-67-8*]	$CH_3OCH_2CH_2CN$	Colorless liquid	85.1	160	–62.9
3-Isopropoxypropionitrile	[*110-47-4*]	$(CH_3)_2CH_2OCH_2$	Liquid	113.2	177	–67
3-Chloropropionitrile	[*542-76-7*]	$ClCH_2CH_2CN$	Colorless liquid	89.52	132	–51
3-Aminopropionitrile	[*151-18-8*]	$NH_2CH_2CH_2CN$	Liquid solid	70.09	79–81	—
3,3'-Iminodipropionitrile	[*111-94-4*]	$HN(CH_2CH_2CN)_2$	Colorless liquid	123.6	173	–5.5
Malononitrile	[*109-77-3*]	$CH_2(CN_2)_2$	White powder	66.06	218	32
Cyanoacetic acid	[*372-09-8*]	$CNCH_2COOH$	White cystals	85.06	108	66
2-Cyanoacetamide	[*107-91-5*]	$CNCH_2CONH_2$	White powder	84.08	Decomposes	119
Chloroacetonitrile	[*107-14-2*]	C_2H_2ClN	Colorless liquid	75.5	1.193	—
Methyl cyanoacetate	[*105-34-0*]	CH_3OOCCH_2CN	Liquid	99.09	203	–22.5
Ethyl cyanoacetate	[*105-56-6*]	$CH_2(CN)COOC_2H_5$	Colorless liquid	113.1	205	–22.5
Methyl cyanoformate	[*17640-15-2*]	$CNCOOCH_3$	Colorless liquid	85.03	97	—
Ethyl cyanoformate	[*623-49-4*]	$CNCOOC_2H_5$	Colorless liquid	99.05	116	—
Methyl isocyanate	[*624-83-9*]	CH_3NCO	Colorless liquid	57.05	39–40	–80
Cyanuric chloride	[*108-77-0*]	$(CNCl)_3$	Colorless crystals	184.4	190	145.8
Bromophenylacetonitrile	[*5798-79-8*]	C_6H_5BrCN	—	196.1	225	25

Toluene-2,4-diisocyanate	[*584-84-9*]	$C_9H_2N_2O_2$	White liquid	174.2	250	—
Sodium dicyanamide	—	$NaN(CN)_2$	Colorless crystals	89.04	—	315
Dicyanodiamide	[*461-58-5*]	$C_2H_2N_4$	Crystal solid	84.08	Decom-poses	209
Sodium cyanate	[*917-61-3*]	NaOCN	Colorless solid	65.01	—	—
Potassium cyanate	[*590-28-3*]	KOCN	White solid	81.11	—	315
Potassium ferricyanide	[*13746-66-2*]	$K_2Fe(CN)_6$	Red solid	329.2	—	—
Potassium ferrocyanide	[*13943-58-3*]	$K_4Fe(CN)_6 \cdot 3H_2O$	Yellow solid	422.4	—	Loses H_2O a 60°C
Sodium nitroprusside	[*14402-89-2*]	$Na_2[Fe(CN)_5NO]$ H_2O	Red crystals	280.92	—	

Table 61.2. Physiological Response to Various Concentrations of Hydrogen Cyanide in Air—Animals[a]

	Concentration		
Animal	**mg/L**	**ppm**	**Response**
Mouse	1.45	1300	Fatal after 1–2 min
Mouse	0.12	110	Fatal after 45 min exposure
Mouse	0.05	45	Fatal after 2.5–4 h exposure
Cat	0.350	315	Quickly fatal
Cat	0.20	180	Fatal
Cat	0.14	125	Markedly toxic in 6–7 min
Dog	0.350	315	Quickly fatal
Dog	0.0125	115	Fatal
Dog	0.1	90	May be tolerated for hours; death after exposure
Dog	0.07–0.04	65–35	Vomiting, convulsions, recovery; may be fatal
Dog	0.035	30	May be tolerated
Guinea pig	0.035	315	Fatal
Guinea pig	0.23	200	Tolerated after 1.5 h without symptoms
Rabbit	0.350	315	Fatal
Rabbit	0.13	120	No marked toxic symptoms
Monkey	0.14	125	Distinctly toxic after 12 min

Rat	0.12	110	Fatal after 1.5-h exposure

[a] Refs 46, 47.

Table 61.3. Physiological Response to Various Concentrations of Hydrogen Cyanide in Air—Humans[a]

	Concentration	
Response	**mg/L**	**ppm**
Immediately fatal	0.3	270
Estd. human LC_{50} after 10 min (18)	0.61	546
Fatal after 10 min	0.2	181
Fatal after 30 min	0.15	135
Fatal after 0.5–1 h or later, or dangerous to life	0.12–0.15	110–135
Tolerated for 0.5–1 h without immediate or late effects	0.05–0.06	45–54
Slight symptoms after several hours	0.02–0.04	18–36

[a] Refs 46, 47.

Table 61.4. Toxicity of Cyanogen in Air for Various Animal Species[a]

	Concentration			
Animal	**mg/L**	**ppm**	**Duration**	**Response**
Mouse	0.5	235	15 min	Recovered
Mouse	5.5	2,600	12 min	Fatal
Mouse	31.5	15,000	1 min	Fatal
Rat	0.59	350	1 hr	LC_{50} (74a)
Rabbit	0.21	100	4 hr	Practically no effect
Rabbit	0.42	200	4 hr	Slight symptoms
Rabbit	0.63	300	3.5 hr	Severe symptoms; delayed death
Rabbit	0.84	400	1.8 hr	Fatal
Cat	0.1	50	4 hr	Severe symptoms but recovered
Cat	0.21	100	2–3 hr	Fatal
Cat	0.42	200	0.5 hr	Fatal

Cat	4.26	2,000	13 min	Fatal

[a] Ref. 47

Table 61.5. Effects of Cyanogen Chloride Inhalation on Various Animal Species (13)

	Concentration			
Animal	**mg/L**	**ppm**	**Duration**	**Response**
Mouse	0.2	80	5 min	Tolerated by some animals
Mouse	0.3	120	3.5 min	Fatal to some animals
Mouse	1.0	400	3 min	Fatal
Rabbit	3.0	1200	2 min	Fatal
Cat	0.1	40	18 min	Delayed fatalities after 9 days
Cat	0.3	120	3.5 min	Fatal
Cat	1.0	400	1 min	Fatal
Dog	0.05	20	20 min	Recovered
Dog	0.12	48	6 hr	Fatal
Dog	0.3	120	8 min	Severe injury, recovered
Dog	0.8	320	7.5 min	Fatal
Goat	2.5	1000	3 min	Fatal after 70 h

Table 61.6. Effects of Varying Concentrations of Cyanogen Chloride in Air or Humans[a]

Concentration		
mg/L	**ppm**	**Response**
0.4	159	Fatal after 10 min
0.12	48	Fatal after 30 min
0.05	20	Intolerable concentration, 1-min exposure
0.005	2	Intolerable concentration, 10-min exposure
0.0025	1	Lowest irritant concentration, 10-min exposure

[a] Ref. 41, 47

Table 61.7. Response of Animals to Various Concentrations of Cyanogen Bromide in Air[a]

Concentration		Response	
mg/L	**ppm**	**Mice**	**Cats**
1	230	Fatal	Fatal
0.3	70	Paralysis after 3-min exposure	Paralysis after 3-min exposure
0.15–0.05	35–12	—	Severe injury; fatal on prolonged inhalation

[a] Ref. 47

Table 61.8. Response of Humans to Various Concentrations of Cyanogen Bromide in Air[a]

Concentration		
mg/L	**ppm**	**Response**
0.4	92	Fatal after 10 min
0.085	20	Intolerable concentration, 1-min exposure
0.035	8	Intolerable concentration, 10-min exposure
0.006	1.4	Lowest irritant concentration, 10-min exposure

[a] Ref. 47, 73

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B. Nitriles

Nitriles are often considered derivatives of carboxylic acids and are named according to the carboxylic acid that is produced upon hydrolysis of the nitrile. For example, cyanomethane (methyl cyanide) is named acetonitrile because hydrolysis of its cyano group yields acetic acid. Nitriles

which contain additional functional groups are typically named as cyano-substituted compounds (e.g., cyanoacetic acid). Nitriles that contain a hydroxy (—OH) group on the carbon atom that is bonded to the cyano moiety are known as *cyanohydrins*. According to *Chemical Abstracts*, aliphatic nitriles are named as derivatives of the longest carbon chain and the carbon of the nitrile is included.

Table 61.9. Physiological Response to Various Concentrations of Acrylonitrile in Air—Animals

	Concentration		
Animal	**mg/L**	**ppm**	**Response**
Rat	1.38	636	Fatal after 4 h exposure
Rat	0.28	129	Slight transitory effect
Rat	0.21	97	Slight transitory effects
Rabbit	0.56	258	Fatal during or after exposure
Rabbit	0.29	133	Marked transitory effects
Rabbit	0.21	97	Slight transitory effects
Cat	0.60	276	Markedly toxic
Cat	0.33	152	Markedly toxic, sometimes fatal
Guinea pig	1.25	576	4 hr LC_{50}
Guinea pig	0.58	267	Slight transitory effect
Dog	0.24	110	Fatal to 75% of the dogs
Dog	0.213	98	Convulsions and coma; no death
Dog	0.12	55	Transitory paralysis; 1 dog died
Dog	0.063	29	Very slight effects

Table 61.10. Acute Toxicity of Acetonitrile in Animals

Route of Administration	**Species**	**LD_{50} or LC_{50}**	**Remarks**	**Ref.**
Oral	Rat	3.8 g/kg		116
Oral	Rat	2.45 g/kg		117
Oral	Rat	0.16–3.5 g/kg	Young more sensitive	118
Dermal	Rabbit	3.9 g/kg		116
Inhalation	Rat	16,000 ppm	4 h	119
Inhalation	Guinea pig	5,655 ppm	4 h	119
Inhalation	Rabbit	2,828 ppm	4 h	119

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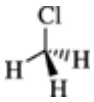
Saturated Methyl Halogenated Aliphatic Hydrocarbons
Jon B. Reid, Ph.D., DABT

1.0 Methyl Chloride
1.0.1 CAS Number:
[*74-87-3*]
1.0.2 Synonyms:
Chloromethane; monochloromethane
1.0.3 Trade Names:
Artic; RCRA Waste Number U045; R40, Refrigerant R40, R-40; UN 1063
1.0.4 Molecular Weight:
50.49
1.0.5 Molecular Formula:
CH_3Cl
1.0.6 Molecular Structure:



1.1 Chemical and Physical Properties

Physical state	Colorless gas
Melting point	–97°C
Boiling point	–24.2°C
Solubility	0.9 g/100 mL water at 20°C; 7.8 g/100 mL ethanol at 20°C; soluble in ethyl ether, chloroform, acetone
Autoignition temperature	634°C
Flash point	< 0°C
Flammability limits	8–19% in air 1 mg/L = 484 ppm and 1 ppm = 2.06 mg/m^3 at 25°C, 760 torr

1.1.1 General Methyl chloride is a natural and ubiquitous constituent of the oceans and atmosphere. It is a product of biomass combustion and also created from biogenic emissions by wood-rotting fungi. It has been detected in surface waters, drinking water, groundwater, and soil as well as in industrial leachate. It is an impurity in vinyl chloride.

1.1.2 Odor and Warning Properties Methyl chloride has a faint sweet odor. Charcoal used in most organic respirator cartridges and canisters is not totally effective as a sorbent.
1.2 Production and Use
Methyl chloride has been used in rubber adhesives and other rubber solutions; in the pharmaceutical industry; as a paint and varnish remover, in solvent degreasing; in aerosol formulations; in food and drug processing; in the plastics industry; in hairsprays, insecticides, and spray paints; as a cosolvent or vapor pressure depressant; as a blowing agent for flexible polyurethane foams; as a cleaning solvent for printed-circuit boards; as a stripper solvent for photoresists; as a solvent for cellulose acetate fiber; in plastic film; in protective coatings; in chemical processing; as a carrier solvent for herbicides and insecticides; to extract heat-sensitive, naturally occurring substances such as cocoa, edible fats, spices, and beer hops; for decaffeinating coffee; as a refrigerant; in oil dewaxing; as a dye and perfume intermediate; in the textile industry; as a postharvest fumigant for strawberries; as a grain fumigant; for degreening citrus fruits; as an industrial solvent; in low temperature extraction; as

a solvent for oil, fats, bitumen, esters, resins, and rubber; in coating photographic films; as a food additive; in synthetic fibers and leather coatings; as a spotting agent; and in organic synthesis.

Methyl chloride is a ubiquitous environmental contaminant because it is produced in very large quantities by fire, fungi, terrestrial plants, seaweed, algae, and possibly other organic processes. An estimated 5×10^6 tons are produced annually by global biologic processes (9). Less than 1% of environmentally occurring methyl chloride is the result of industrial processes.

Most industrially produced methyl chloride is consumed as a chemical intermediate, primarily in methylating reactions. However, published reports of human exposure have primarily been the result of its previous use as a refrigerant gas and as a blowing agent for plastic foams. Both of these uses have virtually disappeared, although it is possible that some methyl chloride may be present in old refrigeration systems and foams.

Because methyl chloride has a sweet odor which is not noticeable at dangerous concentrations, it must be used in closed or well-ventilated systems, preferably with continuous monitoring to prevent excessive exposure. Inhalation is the only significant route of toxic exposure. Respirators containing activated charcoal have been shown to have only limited capacity for removing the gas.

Methyl chloride has been identified in at least 172 of the 1467 current or former EPA National Priorities List (NPL) hazardous-waste sites.

1.3 Exposure Assessment

Numerous analytical methods are given in the ATSDR Toxicological Profile Update (10).

1.3.1 Air As discussed in the ATSDR Profile for methyl chloride (10), in air, methyl chloride can be analyzed by NIOSH method 1001, using gas chromatography (GC) with flame ionization detector, for a range of 66–670 mg/m^3 (11). Methyl chloride can also be trapped cryogenically from an aliquot of air collected into an evacuated canister followed by determination using GC with either electron capture or mass spectrometric detection (12). Extreme care must be taken to ensure that no contamination is introduced into the sampling and analysis method and correction for loss of the compound from air samples stored in canisters. See Section 1.3.3.

1.3.2 Background Levels: NA

1.3.3 Workplace Methods NIOSH Method 1001 is recommended for determining workplace exposures to methyl chloride (11).

1.3.4 Community Methods: NA

1.3.5 Biomonitoring/Biomarkers The ATSDR profile (10) indicates several analytical methods in the analytical section. Several studies have unsuccessfully attempted to correlate exposure levels in air with urinary excretion of *S*-methylcysteine. Use of blood and breath analysis to monitor exposure levels immediately after exposure were of limited value.

1.3.5.1 Blood No analytical methods were found for blood.

1.3.5.2 Urine *S*-Methylcysteine may be a urinary metabolite of methyl chloride in some humans (13, 14). *S*-Methylcysteine can also be analyzed as methanethiol following alkaline hydrolysis and acidification (14).

1.3.5.3 Other Breast milk can be analyzed for chloromethane, after suitable preparation using gas chromatography and mass spectroscopy (15).

1.4 Toxic Effects

Methyl chloride is poisonous intravenously; moderately toxic by ingestion, subcutaneous, and

intraperitoneal routes; mildly toxic by inhalation. It is an experimental carcinogen and tumorigen, an experimental teratogen, produces experimental reproductive effects, an eye, respiratory tract, and skin irritant, and it is mutagenic to humans. When heated to decomposition it emits toxic fumes of chlorine, hydrogen chloride gas, carbon monoxide, carbon dioxide, and phosgene.

Chronic and subacute exposure predominantly affect the nervous system. Symptoms observed are ataxia, staggering gait, weakness, tremors, vertigo, drowsiness, confusion, personality changes, loss of memory, difficulty in speech, and blurred vision. In severe acute poisoning, GI disturbances such as nausea, vomiting, abdominal pain, and diarrhea may be observed. Acute animal experiments have indicated pulmonary congestion and edema. Histopathological changes of the internal organs are not common and laboratory values are unaffected.

In a practical sense, the major problem encountered in mild exposure is “drunkenness” or inebriation. The resulting incoordination and impaired judgment may lead to unsafe manual manipulation. The employee may be injured or endanger others by mechanical misoperation. Because this condition may persist for some time, the employee is a hazard if he or she drives a vehicle after such exposure. The symptoms may be delayed in onset. They may also continue for some hours after the exposure has stopped.

Although most experience would indicate complete recovery in a matter of hours following acute exposure, symptoms may persist for several months and chronic effects following a massive, almost lethal, exposure have been reported to last as long as 5–13 years.

Studies in laboratory animals have shown adverse effects on the brains, kidneys, liver, testes, spleen, and sperm in several species. Kidney tumors have been produced in male mice but not female mice or rats of either sex. These effects have generally been at neurotoxic levels of exposure, and a threshold of about 50 to 100 ppm appears to exist for adverse effects following repeated 6–7 h inhalation exposures of animals.

Because methyl chloride is a gas, ingestion is not of practical concern.

1.4.1 Experimental Studies 1.4.1.1 Acute Toxicity In an unpublished study, Sprague Dawley rats were exposed to 99.5% chloromethane at 0, 200, 500, 1000, or 2000 ppm for 48 or 72 h. At 2000 ppm at 48 h, rats were either lethargic, moribund, or dead. At 2000 ppm rats were all dead or moribund. The cause of death was thought to be kidney failure (16).

Morgan et al. (17) studied lesions induced by inhalation exposure of methyl chloride in C3H, C57BL/6, and B6C3F1 mice and Fischer 344 rats. In mice exposed to 2000 ppm, all male B7C3F1 mice were moribund or died by day 2, one C576BL/6 male died on day 2, and others were moribund by day 5. All other mice survived except one male C3H exposed to 1000 ppm, which died by day 11. This study confirmed the existence of species, sex, and strain differences in susceptibility. Deaths are due to effects on the central nervous system (CNS). Histological effects have been shown to occur in the cerebellum of animals exposed to concentrations causing obvious CNS changes, including ataxia, severe diarrhea, incoordination of fore-limbs and in some cases the hind limbs, and convulsions. In addition, lesions have been reported in the liver, kidneys, adrenals, spleen, testes, and epididymis particularly on repeated exposure.

Dogs exposed acutely to 15,000 ppm died within 4–6 h after an initial rise in heart rate and blood pressure, followed by reduced respiration, decreased heart rate, and progressive fall in blood pressure (18, 19).

1.4.1.2 Chronic and Subchronic Toxicity In an unpublished study with Fischer 344 rats and B6C3F1 mice (20), 120 animals per sex per exposure level were exposed in whole body chambers to 0, 50, 225, or 1,000 ppm, 6 h/day, 5 days/week. During the acute exposure (< = 14 days), there was no effect on survival curves of male or female rats or mice. During the intermediate time (15–364 days)

there was some increased mortality in female mice at 1,000 ppm, but no effect on survival of male mice or male or female rats. During the chronic period (> = 365 days), there was increased mortality in 1000 ppm exposed male mice. There was no effect on survival of male or female rats. See Section 1.4.1.5 for the carcinogenicity aspects of this study.

Although old reports suggest no effect after 6 months of 6-h daily exposure to 300 ppm (21), newer studies suggest that 50 ppm is the NOEL in rats and mice after 2 years of repeated exposure (22). The seminiferous tubules of the testes of rats were severely affected by exposure to 1000 ppm after 6 months or more. Exposure to 250 or 50 ppm caused no adverse effect in either male or female rats except for a questionable decrease in growth of female rats at 250 ppm. $B6C3F_1$ mice were in general much more severely affected than rats, but 50 ppm was considered to be without effect after 2 years of exposure. At 1000 ppm, severe neurofunctional impairment (tremors and paralysis) with supporting histopathological injury was observed, as were splenic atrophy and hepatocellular necrosis and degeneration in the livers of male mice. Renal tubuloepithelial hyperplasia and karyomegaly were seen in mice after 12 months of exposure to 1000 ppm as well as kidney tumors in male mice only.

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The 1998 ATSDR Toxicological Profile (10), in the section on metabolism, indicates that methyl chloride is rapidly absorbed from the lungs and rapidly reaches equilibrium with levels in blood and expired air approximately proportional to the exposure concentrations. At high concentrations, kinetic processes such as metabolism or excretion may become saturated, limiting the rate of uptake. Animal studies show that methyl chloride is absorbed from the lungs and extensively distributed througout the body. Methyl chloride is metabolized by conjugation with glutathione to yield *S*-methylglutatione, *S*-methylcysteine, and other sulfur-containing compounds that are excreted in the urine or further metabolized to methanethiol. Cytochrome P450–dependent metabolism of methanethiol may yield formaldehyde and formic acid, whose carbon atoms are then available to the one-carbon pool for incorporation into macromolecules or for formation of CO_2. Alternatively, formaldehyde may be directly produced from chloromethane via a P450 oxidative dechlorination.

The conjugation of chloromethane with glutathione is primarily enzyme-catalyzed. In contrast to all other animal species investigated (rats, mice, bovine, pigs, sheep, and rhesus monkeys), human erythrocytes contain a glutathione transferase isoenzyme that catalyzes the conjugation of glutathione with methyl chloride. There are two distinct human subpopulations based on the amount or forms of this transferase.

Considerable variation in toxic response related to sex, species, and strain in animal studies may be due to qualitative and quantitative differences in metabolism. Differences in individual metabolism are also apparent in controlled human exposure studies, with two distinct subpopulations identified in several studies. Methyl chloride does not appear to methylate directly, and incorporation into macromoleculars such as RNA, DNA, protein, and lipid is due to rapid conversion to formate and metabolism as part of the one carbon pool.

The metabolism scheme presented in the previous edition is still appropriate (23) and is shown in Figure 62.1.

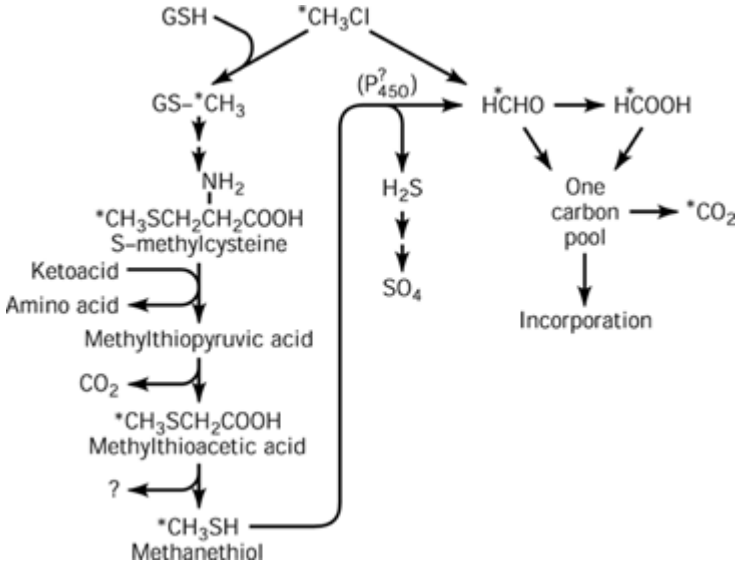


Figure 62.1. Proposed metabolism of methyl chloride in the rat (From Ref. 23).

Conjugation with glutathione is the major pathway. In discussing this diagram the authors state "The metabolic scheme depicted ... accounts for the present as well as previous findings on the metabolism of methyl chloride." The reaction of CH_3Cl with glutathione was previously demonstrated both *in vitro* (24) and *in vivo* (25). The reaction appears to be primarily enzyme-catalyzed, probably by glutathione-transferase, as has been demonstrated for methyl iodide (26). The product of this reaction, methylglutathione, may be metabolized by transpeptidases to *S*-methylcysteine, which has been detected in the urine of rats (27) and humans (28) exposed to methyl chloride.

However, no relationship between urinary *S*-methylcystine excretion and 6 h of exposure to 50 or 10 ppm of methyl chloride was found in human studies (13); nor was *S*-methylcystine a sensitive indication of exposure in beagle dogs, although the metabolite did occur in rats (27).

Peters et al. (29) have shown that erythrocyte cytoplasm from rats, mice, bovines, swine, sheep, and rhesus monkeys did not convert methyl chloride. However, 60% of human blood samples showed conversion to *S*-methylglutathione whereas 40% did not. An enzyme, glutathione-*S*-transferase, present in some blood samples and not in others, accounted for the differences. This is consistent with the observation by Landry et al. (27) that human blood samples being analyzed for methyl chloride *per se* had to be quickly heated to 100°C for 1 min to stop enzymatic reactions whereas rat blood samples were stable for several hours.

Because the major metabolic pathway involves conjugation with reduced glutathione, possibly leading to production of potent vasoconstrictors (leukotrienes), it has been postulated that the toxic action on sperm, the subsequent "dominant lethal affect," as well as effects in the liver, kidneys, and brain, are the result of these inflammatory responses (30).

In a study comparing biochemical effects in rat and mice livers and kidneys, it was concluded that renal tumors observed in male mice at 1000 ppm are probably not evoked by intermediates or *in situ*–produced formaldehyde (31).

1.4.1.4 Reproductive and Developmental Reproduction studies in animals have been conducted and the specific action of methyl chloride on the epididymis clearly influenced the results. Exposures that did not cause inflammation of the epididymis did not affect reproduction in rats.

NIOSH (32) reviewed studies on the reproductive and/or developmental effects from exposure to

methyl chloride. Pregnant mice were exposed via inhalation at concentrations of 0, 100, 250, 500, 750, or 1500 ppm methyl chloride on days 6–18 of gestation. Exposure at 1500 ppm was terminated due to excessive maternal morbidity. Exposure at 500 or 750 ppm caused a statistically significant increase in the numbers of cardiac malformations. Exposure at concentrations of 250 or 100 ppm was considered to be nonteratogenic. Offspring of rats exposed similarly to methyl chloride showed no terata.

Daily exposure of male F344 rats at 1500 ppm for 10 weeks by Hamm et al. (33) caused severe testicular degeneration; no males sired litters during a subsequent 2-week breeding period. The highest no-observed-adverse-effect level (NOAEL) concentration was 150 ppm; however, the authors stated that the actual no-effect concentration was more likely 475 ppm.

In a study by Wolkowski-Tyl et al. (34), the authors concluded that in $B6C3F_1$ mice, an inhalation exposure to 1492 ppm chloromethane resulted in severe maternal toxicity; exposure to 102 and 479 ppm chloromethane resulted in severe maternal toxicity. No deaths were observed in female rats. In a reproductive and developmental effects study of methyl chloride inhalation Wolkowski-Tyl et al. (35) concluded that an inhalation exposure to methyl chloride during Gd 6-17 resulted in maternal toxicity at 750 ppm, but not 500 ppm. Exposure to pregnant mice to 250 ppm chloromethane produced neither maternal nor fetal toxicity nor teratogenicity. Although teratological studies in rats have been negative and at most questionable in mice, methyl chloride has been shown in longer studies to have a severe effect on epididymis and sperm, with significantly altered reproductive capability. Furthermore, fetal toxicity, possibly secondary to maternal toxicity, has been shown to be severe at neurotoxic concentrations.

1.4.1.5 Carcinogenesis Classifications are

IARC	Group 3, Not classifiable as to its carcinogenicity to humans.
MAK	Group 3, Possible human carcinogen.
NIOSH	Carcinogen, with no further categorization.
TLV	A4, Not classifiable as a human carcinogen.

The National Institute for Occupational Safety and Health (NIOSH) (36) reviewed the final report from an inhalation carcinogenesis bioassay by Pavkov (37) in which $B6C3F_1$ mice and F344 rats of both sexes were exposed at methyl chloride concentrations of 0, 50, 225, or 1000 ppm for 6 h/day, 5 days/week for 2 years. This study showed renal degenerative changes (cortical tubular epithelial hypertrophy and hyperplasia with or without karyomegaly) and hepatocellular degeneration. A statistically significant increase in both malignant and nonmalignant renal tumors occurred in only the male mice exposed at 1000 ppm, including renal cortical adenomas and adenocarcinomas, papillary cystadenomas and cystadenocarcinomas, and tubular cystadenomas. Additionally, chronic inhalation of 1000 ppm methyl chloride induced functional limb muscle impairment and degeneration and atrophy of the internal granular layer of the cerebellum in male and female mice. Male and female mice exposed at 1000 ppm also exhibited atrophy of the spleen. Male and female rats exposed to methyl chloride failed to exhibit a significant increase in neoplastic lesions or to develop the other gross and histopathologic lesions observed in mice. Male rats developed bilateral atrophy of the testicular seminiferous tubules; no such change occurred in the male mice, indicating that male mice were more sensitive to the toxic effects of inhaled methyl chloride than female mice and that both sexes of mice were more sensitive than were male or female F344 rats.

In a 2-year oncogenicity study by CIIT (20), a high incidence of renal tumors was found in male mice exposed to 1000 ppm methyl chloride, no evidence of carcinogenicity was found in male or female rats exposed to concentration of 1000 ppm in this study.

In 1986 IARC concluded that there was inadequate evidence for the carcinogenicity of methyl

chloride in animals; however, NIOSH (36) has classified methyl chloride as a potential occupational carcinogen.

1.4.1.6 Genetic and Related Cellular Effects Studies When studied in rats, there has been no evidence of alkylation of DNA, even in a study designed to maximize analytic sensitivity (38). However, in certain *in vitro* and *in vivo* studies, methyl chloride appears to be a weak, direct-acting mutagen for bacteria, *Drosophila*, and mammalian cells. Although positive in a dominant lethal study in rats, the effect appears to be secondary to injury of a specific area of the epididymis.

Dominant lethal mutations were indicated by increased preimplantation loss in male F344 rats exposed 6 h/day at 3000 ppm administered for 5 consecutive days throughout the 8 weeks following exposure (*i.e.*, after treatment of spermatogonia, spermatocytes, spermatids, and spermatozoa), and a slight increase in postimplantation loss was found only during the first week after exposure (*i.e.*, after treatment of spermatozoa) (39). Subsequently the authors indicated that the postimplantation loss was a secondary effect due to methyl chloride-induced inflammation of the epididymis (40).

1.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Exposure to animals results in neurological effects. Rats, mice, rabbits, guinea pigs, dogs, cats, and monkeys exposed to chloromethane until death all displayed signs of severe neurotoxicity (41, 42).

A limited number of animal (not human) studies report ocular effects but the results are mixed.

1.4.2 Human Experience Since the mid-1960s or so, methyl chloride was used as a refrigerant, and many human deaths resulted from exposure to methyl chloride vapors from leaks in home refrigerators and industrial cooling and refrigeration systems (43).

The principal route of absorption is by inhalation, but methyl chloride can be absorbed through the skin. Symptoms may include headache, elevated blood concentrations of carboxyhemoglobin, nausea, and irritation of the skin and eyes. Central nervous system depression, pulmonary edema, hemolysis, chronic intoxication, and paresthesia may also occur. Other symptoms include narcosis, temporary neurobehavioral effects, increase in serum bilirubin, increased urinary formic acid concentrations, and increased risk of spontaneous abortion. In addition, intravascular hemolysis, unconsciousness, lack of response to painful stimuli, rapid followed by slowed respiration, erythema, blistering, toxic encephalopathy, painful joints, swelling of the extremities, mental impairment, diabetes, skin rash, aspiration pneumonia, gross hematuria, reduction of blood pH, gastrointestinal injury, and narrowing of the intestinal lumen may also occur. Symptoms may include upper respiratory tract irritation, giddiness, stupor, irritability, numbness, tingling in the limbs, and hallucinations. A dry, scaly, and fissured dermatitis, skin burns, coma and death may also result. Other symptoms may include dizziness, sense of fullness in the head, sense of heat, dullness, lethargy, and drunkenness. In addition, mental confusion, lightheadedness, vomiting, weakness, somnolence, lassitude, anorexia, depression, fatigue, vertigo, liver damage, nose and throat irritation, anesthetic effects, smarting and reddening of the skin, blood dyscrasias, acceleration of the pulse, and congestion in the head may result. Staggering may also occur. Symptoms of exposure may include neurasthenic disorders, digestive disturbances and acoustical and optical delusions. Arrhythmias produced by catecholamines may also result. Additional symptoms include edema, faintness, loss of apetite, and apathy. Hyporeflexia, gross hemoglobinuria, epiglottal edema, metabolic acidosis, GI hemorrhage, ulceration of the duodenojejunal junction, and diverticula may also occur. Other symptoms may include kidney damage, lung damage, corneal injury, abdominal pain, and an increase in salivary gland tumors. Cyanosis may also occur. Exposure may also cause altered sleep time, convulsions, euphoria and a change in cardiac rate.

1.4.2.1 General Information Generally, case reports do not describe respiratory effects in human exposures. No effects on pulmonary function were observed in volunteers who were exposed to 150 ppm (44).

Cardiovascular effects (electrocardiogram abnormalities, tachycadia, increased pulse rate, and decreased blood pressure) have been described in case reports of humans exposed occupationally or accidentally to refrigerator leaks (45).

In an extensive study with human subjects, Stewart et al. (46) gave males single or repeated exposures to 0, 20, 100, or 150 ppm and females to 0 or 100 ppm. Exposures were generally held at a constant level, but in one case were allowed to range from 50 to 150 ppm, averaging 100 ppm. Exposures were for 1, 3, or 7 h/day, 5 days/week. Using a wide battery of behavioral, neurological, electromyographic, and clinical chemical tests, no significant decrements were found. No increase in methyl alcohol was found in the urine, and methyl chloride in expired air dropped so rapidly as to be of little or no value in quantifying exposure. There was a remarkable difference in individual responses, with some subjects consistently showing several times the blood and expired air concentrations found in others. This bimodal distribution has also been reported by Putz et al. (47).

Kegel et al. (48) and McNally (49) reported clinical cases of acute poisoning from leaking refrigerators.

Hansen et al. (50) observed the effects of excessive exposure after a spill. Fifteen workers manifested signs of dizziness, blurred vision, incoordination, and GI complaints. Recovery was complete in 10–30 days. Although rarely in the United States, some methyl chloride may still be used as a refrigerant in other countries. A 1976 report describes poisoning of four members of a family due to a leaking refrigerator (45).

Klimkova-Dentschova (51) observed the neurological pictures in 100 workers. The report stated: “Involvement of the internal organs (kidney, optic disturbances) was absent even where nervous and mental changes indicated a severe form of poisoning.” Levels of exposure were not indicated.

Numerous other studies described the effect of acute exposure, but reports of chronic low level exposure are less common. One report described the nonspecific nature of six cases and reports many of the symptoms discussed earlier (52). Recovery seemed to occur in all subjects, but often several months were required. Another report of eight cases is given by MacDonald, who described similar effects, ascribing them to exposure below 100 ppm in one subject, and to have resulted in permanent injury in another. However, there is uncertainty in the exposure estimates.

Exposure to methyl chloride in excess of 200 ppm resulted in serious disturbances in CNS function in a husband and wife who stored foamed plastic panels in their new house (53). The house was of tight, energy-efficient construction (0.06 air changes/h), and the foam sheets were being stored prior to installation. After several days, complete exhaustion, labyrinthitis, and unsteadiness of gait were observed. Recovery appeared to have been complete. It was concluded that the foam panels had not offgassed adequately before being placed in the house.

An epidemiological study by Holmes (54) is discussed in Section 1.4.2.3.5.

1.4.2.2 Clinical Cases Numerous case reports of humans exposed to methyl chloride vapors as a result of industrial leaks describe neurological effects (43). In general, symptoms develop within a few hours after exposure and include fatigue, drowsiness, staggering, headache, blurred and double vision, mental confusion, tremor, vertigo, muscular cramping and rigidity, sleep disturbances, and ataxia. The symptoms may persist for several months, and depression and personality changes may develop. In some cases, complete recovery occurs, but in severe poisoning, convulsion, coma, and death are possible. Microscopic examination of the brain of an individual who died following an exposure showed accumulation of lipoid-filled histiocytes in the leptomeninges of the hemispheres, hyperemia of the cerebral cortex, and lipoid droplets in the adventitia cells of the capillaries throughout the brain (55). Exposure to animals also results in neurological effects. Rats, mice, rabbits, guinea pigs, dogs, cats, and monkeys exposed to chloromethane until death all displayed signs of severe neurotoxicity (41, 42).

Exposure to high concentrations of methyl chloride can result in moderate to severe neurological effects. Refrigerator repairmen developed neurological symptoms after exposure from leaks at concentrations as high as 600,000 ppm, but there were no deaths (56).

Numerous case reports of humans exposed to methyl chloride describe symptoms of nausea and vomiting, but these symptoms may be associated with the concomittant CNS toxicity (43). Generally animal studied do not support gastrointestinal damage.

Case reports of humans exposed to methyl chloride describe indicators of renal toxicity, such as albuminuria, increased serum creatinine and blood urea nitrogen, proteinuria, and anuria (45). Animal studies generally support kidney injury.

1.4.2.3 Epidemiology Studies A retrospective epidemiologic study of workers exposed in a butyl rubber manufacturing plant found no statistical evidence that the rate of death due to diseases of circulatory system was increased when compared to U.S. mortality rates (54) discussed in the next section.

1.4.2.3.5 Carcinogenesis A retrospective epidemiology study of male workers exposed to chloromethane in a butyl rubber manufacturing plant produced no statistical evidence of cancer deaths (54).

Rafnsson and Gudmundsson (57) reported excess mortality from cancer in a long-term follow-up after an acute high level exposure of crew members to a leaking refrigerator. The authors reported an excess mortality from all causes associated with chloromethane exposure, including an elevated mortality from all cancers and lung cancer, but conclusions from the study are limited because of possibly faulty assumptions with regard to matching the control group.

The USEPA has not assigned a carcinogenicity classification. Health advisories published by the EPA Office of Water assign chloromethane to cancer group C, which indicates that the substance is a possible human carcinogen. IARC has classified chloromethane as group 3 (not classifiable). The NTP has not classified the chemical with regard to carcinogenicity. NIOSH recommends that methyl chloride be treated as a potential occupational carcinogen.

1.4.2.3.6 Genetic and Related Cellular Effects Studies Uniquely, human erythrocytes contain a glutathione transferase isoenzyme that catalyzes the conjugation of glutathione with methyl chloride. There are two distinct human subpopulations based on the amount or forms of this transferase. They are known as “fast metabolizers” and “slow metabolizers” or *conjugators* and *nonconjugators*. There is considerable variation among ethnic groups and this aspect has significant effect on toxicity.

1.5 Standards, Regulations, or Guidelines of Exposure

ACGIH TLV TWA is 50 ppm (103 mg/m^3) and the ACGIH TLV STEL is 100 ppm (207 mg/m^3).

NIOSH considers methyl chloride a carcinogen and recommends that exposures be limited to the lowest feasible concentration; NIOSH IDLH is 2000 ppm. The OSHA PEL is 100 ppm, the ceiling is 200 ppm and 300 ppm is 5-min the maximum peak in any 3 hours.

In the provisions of the Clean Air Act Amendments (CAAAs) of 1990, methyl chloride is among 189 compounds designated as hazardous air pollutants.

Regulations in other countries include Australia—50 ppm, STEL 100 ppm (1990); (Former Federal Republic of) Germany—50 ppm, short-term level 100 ppm, 30 min, 4 times per shift, group 3, Possible human carcinogen, pregnancy group B, a risk of damage to the developing embryo or fetus must be considered to be probable and cannot be excluded when pregnant women are exposed under conditions where MAK and BAT values are observed (1998); Sweden—50 ppm, 15-min short-term

value 100 ppm (1990); United Kingdom—50 ppm, 10-min STEL 100 ppm (1991); U.S. NIOSH—lowest feasible concentration, carcinogen, IDLH 2000 ppm.
1.6 Studies on Environmental Impact:
NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons
Jon B. Reid, Ph.D., DABT

2.0 Methyl Bromide
2.0.1 CAS Number:
[*74-83-9*]
2.0.2 Synonyms:
Monobromomethane; bromomethane
2.0.3 Trade Names:
Dowfume MC-2; Dowfume MC-33; Edco; Embafume; Halon 1001, Iscobrome; MB, MBX, MEBR; Metafume; Methogas; Pestmaster; Profume; Rotox; Terr-O-Gas 100; Zytox
2.0.4 Molecular Weight:
94.95
2.0.5 Molecular Formula:
CH_3Br
2.0.6 Molecular Structure:

2.1 Chemical and Physical Properties

2.1.1 General

Physical state	Colorless gas
Specific gravity	1.732 (0/0°C)
Melting point	–93.66°C
Boiling point	3.56°C
Solubility	0.09 g/100 mL water at 20°C; soluble in ethyl ether, ethanol, benzene, carbon tetrachloride
Flammability	Practically nonflammable; flame propagation is in the narrow range of 13.5–14.5% by volume in air; ignition temperature is 537°C

1 mg/L = 257 ppm and 1 ppm = 3.89 mg/m^3 at 25°C, 760 torr

2.1.2 Odor and Warning Properties Methyl bromide has practically no odor or irritating effect and therefore no warning, even at physiologically hazardous concentrations. At high concentrations it has a chloroform odor. Some mixtures of methyl bromide used for fumigation contain chloropicrin as another active ingredient or as a warning agent. The chloropicrin may give warning of significant concentrations of methyl bromide from leaking containers; however, experience has shown that chloropicrin vapor may disappear before methyl bromide vapor and therefore the warning properties are lost. Charcoal-gas mask canisters also preferentially remove chloropicrin. With prolonged use,

methyl bromide may penetrate the charcoal in harmful concentrations with no odor of chloropicrin.
2.2 Production and Use
Methyl bromide is used in ionization chambers, refrigerants, fire extinguishing agents, organic synthesis as an methylating agent, preparation of quarternary ammonium compounds, organotin derivatives, and antipyrine. It is also used as a soil and space fumigant; in the disinfestation of potatoes, tomatoes, and other crops; as an acaricidal fumigant; as an industrial solvent for extraction of plant oils; as a fungicide, herbicide, nematocide, rodenticide, and insecticide; and in degreasing wool, nuts, seeds, and flowers. Other uses include food sterilization for pest control in fruits, vegetables, and dairy products.

Much environmentally occurring methyl bromide is the result of biologic activity, particularly by seaweed (58). Automobile exhaust from leaded gasoline was formerly a significant source.

The largest single industrial use for methyl bromide is as a fumigant used to treat soil, a wide range of grains, and other commodities, mills, warehouses, and houses. The principal problems have been associated with the fumigating personnel and control of other people who may enter the area being fumigated.

Some methyl bromide is used as a chemical intermediate. In the United States use as a refrigerant is no longer significant. It once was used as a fire-extinguishing agent, particularly in automatic equipment for the control of engine fires on aircraft, but because of the toxicity of this material, its use as a fire extinguisher must be limited to specialized applications. A number of reports of injury from use as a fire extinguisher can be found in the European literature.
2.3 Exposure Assessment
Because methyl bromide is a gas at ordinary temperatures and has essentially no warning properties, dangerous concentrations may rapidly accumulate in a work area without warning to the operator. Owing to the high volatility, one can readily attain high concentrations in a work atmosphere. Such high concentrations can be attained without recognition. These factors and the fact that methyl bromide is quite toxic create a potentially high hazard. It must be used only by individuals who are well acquainted with proper methods of handling and fully cognizant of the consequences of exposure to excessive amounts. In industrial operations regularly using methyl bromide, it is advisable to have some kind of warning or monitoring system for continuous analysis of the air. In fumigation operations, suitable analytic equipment is required and personnel must have proper protective equipment for the operation. Charcoal used in respiratory protective devices has limited capacity to remove methyl bromide. A survey by NIOSH estimated that between 1981 and 1983, about 105,000 workers were exposed to methyl bromide. The primary route of potential occupational exposure is inhalation, although some intoxications have also been reported after dermal exposure.

2.3.3 Workplace Methods NIOSH Method 2520 is recommended for determining workplace exposures to methyl bromide (11).

2.3.5 Biomonitoring/Biomarkers Blood bromide levels in humans are elevated by exposure to methyl bromide and may be useful in establishing whether exposure to methyl bromide has occurred, but bromide ion determination is not totally satisfactory for quantifying exposure. Numerous other sources of bromide, such as food, water, and medications, may interfere, particularly at the low blood levels that result from repeated exposure to concentrations considered acceptable for occupational exposure. “Normal” bromide ion concentration is below 1 mg/100 mL of blood serum, in the absence of the above dietary sources. A concentration of 5 mg/100 mL may be considered evidence that exposure to methyl bromide has occurred; 15 mg/100 mL of blood is consistent with toxic symptoms. Because bromide from ingested drugs may reach 150 mg/100 mL% or more, it is obvious that the source of the bromide must be considered in interpreting the analytic results
2.4 Toxic Effects
Methyl bromide is toxic by inhalation, by ingestion, or through skin absorption. It is readily absorbed through the skin. It is irritating to the eyes, skin, mucous membranes, upper respiratory tract, and lungs. It is narcotic at high concentrations. It may cause lacrimation from irritation of the eyes. When

heated to decomposition it may emit toxic fumes of carbon dioxide. It may also emit toxic fumes of hydrogen bromide.

Methyl bromide is one of the most toxic of the common organic halides and is reported to be 8 times more toxic on inhalation than ethyl bromide. Moreover, because of its greater volatility, it is a much more frequent cause of poisoning. Fatal poisoning has always resulted from exposure to relatively high concentrations of methyl bromide vapors (8600–60,000 ppm). Nonfatal poisoning has resulted from exposure to concentrations as low as 100–500 ppm.

Inhalation is by far the most significant route of exposure, although serious skin burns may occur from confined contact, especially under clothing or in shoes and gloves. Absorption through the skin has been reported, but very high vapor concentrations were involved, and some inhalation may have occurred as leakage around the respirators. Unless the concentration is high enough to cause rapid narcosis and death from respiratory failure, the most striking response to exposure at high concentrations will be lung irritation with congestion and edema. These symptoms are observed in both animals and humans and often develop into a typical confluent bronchial pneumonia. At lower levels of exposure, this lung condition may account for delayed deaths. If it leads to secondary infection, the delay may be a matter of days. At threshold concentrations, this lung condition is not observed. The response is almost entirely referable to the nervous system and usually shows up only after prolonged and repeated exposures. Excitation and even convulsions have been observed in animals; but if they survive repeated exposures, the later signs are paralysis of the extremities. Paralysis of the extremities is most typical of threshold toxic response from repeated exposures over a long period of time. Animals that have been seriously paralyzed have recovered, although the recovery is somewhat slow. Human experience indicates that there is a high probability of complete recovery although the time necessary may be quite long, even months. Several reviews are available (59–61).

2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity Because methyl bromide is a gas at 4°C, oral toxicity is of minor concern. Nevertheless oral doses of 60–65 mg/kg were reported to be the minimal amount lethal to rabbits (62); a dose of 100 mg/kg, to be lethal to rats 5–7 h after exposure (63); and 214 mg/kg, to be an oral LD_{50} (64).

Toxic response appears to differ significantly between test animal strains and species (65). The 8 h survival dose for rats was reported to be approximately 1 mg/L (260 ppm). Rats survive 5200 ppm for 6 min and 2600 ppm for 24 min. The 6-h survival dose for rabbits is approximately 2 mg/L (520 ppm). The authors studied rats, rabbits, guinea pigs, and monkeys. They described the response of most animals as typically one of lung irritation. If the exposure was severe enough, this resulted in lung edema and usually a typical confluent bronchial pneumonia.

An 8 h LC_{50} of 302 ppm (267–340 ppm) was determined for male rats. (Sprague–Dawley/Charles River Japan) (66). Deaths were accompanied by lung hemorrhages and convulsions.

Mice were exposed for 1 h to concentrations of 0.87–5.93 mg/L (220–1500 ppm). An LC_{50} of 1200 ppm was determined for the 1 h exposures. At ≤1.72 mg/L no toxic response was noted. Exposure for 1 h to 2.2–2.7 mg/L was reported to cause decreased lung and liver weight. Above 3.5 mg/L kidney lesions were observed. Mortality occurred above 3.82 mg/L (980 ppm) accompanied by weight loss and other clinical signs. At still higher concentrations, liver lesions, decreased motor coordination, tremors, seizures, paralysis, and other effects also occurred. Gluthathione depletion and an increase in blood bromide were observed and related to exposure concentration (67).

Rats were exposed 6 h/day for 5 days to 0, 90, 175, 250, or 325 ppm in order to study histopathology (68). Exposure to 325 ppm required premature sacrifices after 4 days, but the other groups were anesthesized and perfused 1–2 h after their fifth exposure. Clinical signs confined to the 250- and

325-ppm groups were diarrhea, hemoglobinuria, gait disturbances, and convulsions. At all concentrations except 90 ppm there were degenerative changes in the adrenals, cerebellar granular cells, and nasal olfactory epithelium. Hepatocellular degeneration was confined to the 250- and 325-ppm groups. The kidneys and epididymides were not affected, but cerebral cortical degeneration and minor testicular changes were seen in the 325-ppm group.

Male rats were exposed 4 h/day to four different concentrations of methyl bromide gas, 150 ppm for 5 days/week, 11 weeks (55 times), and to 200, 300, or 400 ppm for 6 weeks (30 times) (69). Body weight, hematology, organ weight, residual bromide concentrations, and histopathology of several organs were studied. In addition, a 4 h acute LC_{50} was determined to be 780 ppm with 95% confidence limits of 760–810 ppm. As in other studies, a remarkably steep dose response was observed with 0 and 100% lethal concentrations of 650 and 900 ppm. Neurological signs were manifest at 300 and 400 ppm with necrosis of the brain at 400 ppm. Necrosis of the heart was apparent at all concentrations with little response in other organs. Certain blood enzyme levels generally considered to be associated with pathological changes in the heart were not changed at either 150 or 200 ppm, but at 300 and 400 ppm aspartic transaminase, lactic dehydrogenase, LAP (not defined by the authors), and hydroxybutyrate dehydrogenase were elevated.

2.4.1.2 Chronic and Subchronic Toxicity Oral Exposure According to IRIS (online), the USEPA determined critical effect for oral exposure as epithelial hyperplasia of the forestomach with an NOAEL of 1.4 mg/kg/day [LOAEL: 7.1 mg/kg/day] and a RfD of 1.4×10^{-3}. The previous *oral* RfD [4.0×10^{-4} mg/kg/day] was based on the inhalation studies by Irish et al. (65). According to the EPA (IRIS), inhalation studies are inappropriate for oral risk assessment extrapolation for bromomethane because portal-of-entry effects are observed for both the inhalation route (lung pathology) and oral route (stomach hyperplasia). In addition, neurological effects reported after inhalation exposures have not been reported after oral exposures.

The current EPA reference dose (RfD) for oral exposure is based on the Danse et al. (64) study, on carcinogenic effects in the rat forestomach for the oral route of exposure. Treatment of groups of 10 male and 10 female Wistar rats by gavage 5 days/week for 13 weeks with bromomethane at 0, 0.4, 2, 10, or 50 mg/kg resulted in severe hyperplasia of the stratified squamous epithelium in the forestomach at a dose of 50 mg/kg/day and slight epithelial hyperplasia in the forestomach at a dose of 10 mg/kg/day. At the 50-mg/kg/day dose level, decreased food consumption, body weight gain, and anemia were observed in the male rats. Slight pulmonary atelectasis was observed, at the two higher dose levels, in both male and female rats; however, the investigators stated that the possible inhalation of bromomethane-containing oil during the gastric intubation procedure might have been responsible for this effect. No neurotoxic effects were observed at any dose level tested. Renal histopathology was not evaluated. Adverse effects were not observed at 0.4 or 2 mg/kg. This 90-day gastric intubation study was conducted in groups of Wistar rats (10 of each sex) given 0, 0.4, 2, 10, or 50 mg/kg methyl bromide in peanut oil. Findings included squamous cell papillomas (2 males) and carcinomas (7 males and 6 females) of the forestomach at the 50-mg/kg dose level.

In a similar study by Boorman et al. (70) 6-week-old male Wistar rats were gavaged 5 times/week at 50 mg/kg, either for 13 weeks with a 12-week recovery period or continuously for a period of 25 weeks. At week 13, inflammation, acanthosis, fibrosis, and a high incidence of pseudoepitheliomatous hyperplasia of the forestomach were observed. At week 25, rats previously treated with methyl bromide still exhibited more severely perplastic lesions than vehicle controls. One of 15 rats showed malignancy, which was considered an early carcinoma. However, there was a clear regression of the overall incidence of proliferative lesions at the end of the recovery period.

Mitsumori et al. conducted a 2-year oral chronic toxicity/carcinogenicity study (71) in F344 rats fed a diet containing 80–500 ppm total bromide following fumigation with methyl bromide. Of 60 male and 60 female rats per dosage group, 10 were sacrificed at 52 and 104 weeks, respectively, in order to perform urine analysis, hematology, blood chemistry, and pathology. Rats killed in moribund

condition or found dead and all survivors sacrificed at the end of the 2-year dosing period were examined for pathologic lesions. No marked toxic effects were observed at any of the dose levels administered except for a slight decrease in body weight gain in males fed the 500-ppm methyl bromide-containing diet at week 60 onward. The conclusion was that residues of ≤ 500 ppm total bromide in the diet fumigated with methyl bromide are *not carcinogenic* in F344 rats of either sex. The NOEL in males was given as 200 ppm [6.77 mg total bromide/kg/day]. None was determinable from the data in females because they showed slightly higher incidence of focal fatty change of the adrenal cortex than controls. However, control values in this study were lower than historical controls with regard to this very common lesion in aging female F344 rats.

Inhalation Exposure For inhalation, the EPA (IRIS) considers the *critical effect* for chronic inhalation to be degenerative and proliferative lesions of the olfactory epithelium of the nasal cavity with a LOAEL of 11.7 mg/m^3 (3 ppm), adjusted to 2.08 mg/m^3, giving a RfC of 5.0×10^{-3} based on a 29-month rat inhalation study by Ruezel in 1987 and 1991 (72, 73) where a series of inhalation toxicity studies of bromomethane were conducted under the sponsorship of the National Institute of Public Health and Environmental Hygiene of the Netherlands. In a chronic inhalation study, 50 male and 60 female Wistar rats were exposed to 0, 3, 30, or 90 ppm (0, 11.7, 117, or 350 mg/m^3, respectively) 98.8% pure bromomethane 6 h/day, 5 days/week (duration-adjusted concentrations are 0, 2.08, 20.9, or 62.5 mg/m^3, respectively) for up to 29 months. Three satellite groups of 10 animals/sex/exposure level were sacrificed at 14, 53, and 105 weeks of exposure. Animals were observed daily, and body weight was recorded weekly for the first 12 weeks and monthly thereafter. Hematology, clinical chemistry, and urinalyses were conducted at 12–14 weeks and 52–53 weeks in the satellite groups. Eleven organs were weighed at necropsy, and approximately 36 tissues, including the lungs with trachea and larynx; 6 cross sections of the nose; heart; brain; and adrenal glands were examined histopathologically. The test atmosphere was measured by gas chromatography every 30 min during exposure. Males and females exposed to 90 ppm exhibited decreased body weight gains; no treatment-related changes in hematological, biochemical, or urine parameters were observed. A significant concentration-related decrease in relative kidney weights was reported in the 30- and 90-ppm males. A decrease in mean absolute brain weight was reported to occur in the 90-ppm females at weeks 53 and 105, but there was no change in relative brain weight or in brain histology. Microscopic evaluation revealed that the nose, the heart, and the esophagus and forestomach were the principle targets of bromomethane toxicity in this study. Very slight to moderate hyperplastic changes in the basal cells accompanied by degeneration in the olfactory epithelium in the dorsomedial part of the nasal cavity were observed in all exposed groups of both sexes at 29 months of exposure. At the lowest concentration, the lesion is described as very slight. These changes were concentration-related in both incidence and severity and were statistically significant at 29 months. Incidence of basal cell hyperplasia in control, 3-, 30-, and 90-ppm groups were 4/46, 13/48, 23/49, and 31/48 in males and 9/58, 19/58, 25/59, and 42/59 in females, respectively. Slight increases in incidence of basal cell hyperplasia in the 30- and 90-ppm groups (n = 7–10) at 53 and 105 weeks were not statistically significant. Lesions in the heart were statistically significant in the males (cartilaginous metaplasia and thrombus), and the females (myocardial degeneration and thrombus) exposed to 90 ppm. The authors attributed part of the increased mortality in the high concentration animals to the cardiac lesions. A statistically significant increase in hyperkeratosis of the esophagus was observed in the 90-ppm males after 29 months of exposure. Slight increases in forestomach lesions were not statistically significant. No effects were observed in the tracheobronchial or pulmonary regions of the respiratory tract. No other exposure-related effects were noted. Based on these results, a LOAEL of 3 ppm for nasal effects was established.

Male Sprague–Dawley rats were exposed by inhalation for 24 h at 120 ppm or continuously for 3 weeks at 10 ppm methyl bromide, which resulted in a dose-dependent decrease in the concentration of norepinephrine in the hypothalamus, cortex, and hippocampus (74). Typical high dose effects of methyl bromide inhalation in rats (200, 300, or 400 ppm for 6 weeks; 150 ppm for 11 weeks) are liver necrosis with sinusoidal infiltration, degeneration of the kidney tubular epithelium, necrosis of

the excretory pancreas epithelium, focal necrosis of the heart muscle, and necrosis of the brain cortex (69). Additional high dose effects reported were diarrhea, hemoglobinuria, and degeneration of the zona fasciculata of the adrenals and of the olfactory epithelium (68). The latter appeared reversible 10 weeks after cessation of exposure (75). These effects were corroborated by other studies and also in other species (76, 77). Expected similarities between the toxicity profile of methyl bromide and methyl chloride were also noted.

Inhalation by rabbits at 27 ppm methyl bromide for 8 months for a total exposure duration of 900 h resulted in no observable neurotoxic or other adverse signs. At 65 ppm, severe neuromuscular losses were seen. These subsided 6–8 weeks after exposures were terminated (78, 79). Rats exposed at 55 ppm via inhalation of methyl bromide for 36 weeks with a total affective duration of 1080 h showed no signs of a neurologic deficit (79).

In a chronic mouse study, virtually the same lesions were reported as observed in subchronic studies at somewhat lower doses than expected (77). This mouse (77) and rat (73) inhalation bioassay has been performed. These studies show clear mutagenicity but not carcinogenicity under the conditions of the bioasssays. The NTP 2-year inhalation study (77) was carried out with 70 male and female $B6C3F_1$ mice exposed 6 h/day, 5 days/week at 0, 10, 33, or 100 ppm of methyl bromide. After 20 weeks, exposure of the high dose group (100 ppm) was discontinued because of excess mortality (31% in males, 8% in females). Similar lesions were observed as reported in Section 2.4.1.2 of this TLV documentation, without the occurrence of excess neoplastic lesions. A NOEL was not presented in the NTP (77) study, but there were no effects at 33 ppm.

Male and female Wistar rats were exposed by inhalation 6 h/day, 5 days/week for 29 months at 0, 3, 30, or 90 ppm methyl bromide (73). Interim sacrifices were conducted after 3, 12, and 24 months. Excess mortality was first observed at 114 weeks in the high dose group. Dose-dependent increases in the incidences of degenerative and hyperplastic changes of the nasal olfactory epithelium were observed. The lesions were characterized as very slight, slight, or moderate. A statistically significant difference was found between controls and the low dose group (3 ppm) at the end of the exposure period (29 months) in terms of total lesions. At the highest dose level, effects (thrombi, myocardial degeneration, hyperkeratosis of the esophagus and forestomach) were observed.

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Methyl bromide is converted to bromide ion, *in vivo*. At all concentrations that could be tolerated by animals, inhaled methyl bromide was rapidly eliminated (65). Circulating bromide concentrations in untreated rabbits were approximately 10 ppm and those in rabbits with methyl bromide–induced paralysis were approximately 110 ppm (65).

The blood bromide level tends to correlate with the severity of the clinical signs (80).

Although methyl bromide is metabolized to methanol, the quantities of methanol produced are insufficient to account for methyl bromide's toxicity (65, 80). The toxicity of methyl bromide is with the intact molecule. The bromide ion has been shown to be much slower in leaving the body following exposure to methyl bromide. A half-life of 5 days has been reported for rats (66). The investigators also concluded that neither bromide ion nor methanol was involved in the toxicity but rather the parent compound or an incorporation of the methyl group into some other substance was involved. Bonnefoi et al. (81) have shown that glutathione depletion occurs and may be related to subsequent toxic effects.

Methyl bromide showed a significant non-enzymatic conjugation in human erythrocyte cytoplasm. In the majority of the subjects there was also enzymatic conjugation but a minority lack this enzymatic activity. Methyl bromide had a higher affinity for the conjugating enzyme(s) (possibly erythrocyte glutathione transferases) than methyl chloride or methyl iodide (82).

2.4.1.4 Reproductive and Developmental Adult male F344 rats were exposed to 0 or 200 ppm 6 h/day for 5 days and examined after 1, 3, 5, 6, 8, 10, 17, 24, 38, 52, and 73 days. The only effects were a transient decrease in plasma testosterone and testicular nonprotein sulfhydryl. In contrast to the very specific effects of methyl chloride there were no lasting effects on sperm quality or spermatogenesis. However, Eustis et al. (76) reported testicular degeneration in male rats exposed to 160 ppm 6 h/day, 5 days/week for 3–6 weeks, and Kato et al. (69) reported testicular atrophy after 6 weeks of repeated 4 h/day, 5 days/week exposures to 400 ppm but not 300 ppm.

In an abstract reporting preliminary results in the F_0 generation of a two-generation reproduction study in CD rats (83), there were no reproductive effects reported after repeated 6 h/day, 5 day/week exposures to 0, 3, 30, or 90 ppm.

There are little data to indicate anything but extremely low, if any, potency for methyl bromide for teratogenic/reproductive toxicity. Although methyl bromide, acutely and subchronically, causes varying degrees of testicular alterations and transiently reduced plasma testosterone concentrations, inhalation exposure of male Fischer 344 rats for 6 h/day at 200 ppm methyl bromide for 5 days had "no lasting effect on sperm quality or spermatogenesis" in this rat strain (75). In a study by Sikov et al. (84), neither maternal or fetotoxic nor teratogenic effects were observed in Wistar rats exposed by inhalation to methyl bromide 5 days/week at 20 and 70 ppm for 3 weeks prior to mating and during gestation.

2.4.1.5 Carcinogenesis The USEPA consideres the animal data for carcinogenesis as "Inadequate" (IRIS) (5). Bromomethane was administered by gavage to groups of 10 male and female Wistar rats (64). Animals were administered doses of 0, 0.4, 2, 10, or 50 mg/kg/day bromomethane in arachis oil 5 days/week for 13 weeks, at which time the experiment was terminated. There was an apparent dose-related increase in diffuse hyperplasia of the forestomach. The authors reported a forestomach papilloma incidence of 2/10 in the high dose males and forestomach carcinoma incidences of 7/10 and 6/10 in the high dose males and females, respectively. These results were subsequently questioned (85, 86). A panel of NTP scientists reevaluated the histological slides and concluded that the lesions were hyperplasia and inflammation rather than neoplasia.

Rosenblum et al. (87) reported a 1-year study in which beagle dogs (4 per treatment group, 6 per control) were provided diets fumigated to residue levels of 0, 35, 75, or 150 ppm bromomethane. No tumors were observed at any dose level; however, there was no indication that the dogs were examined for tumors. In addition, 1-year observation is considered to be inadequate by the EPA for tumor induction in dogs.

Bromomethane is structurally related to *bromoethane* which, when tested in mice and rats of both sexes, has shown clear evidence of carcinogenicity in some cases and equivocal in others. NTP (88) conducted an inhalation bioassay on bromoethane, and the results were recently released in a draft report. Groups of F344/N rats (50/sex) and B6C3F1 mice (50/sex) were exposed to 0, 100, 200, or 400 ppm bromoethane 6 hours/day for 5 days/week. A statistically significant increase in uterine adenomas, adenocarcinomas, or squamous cell carcinomas was observed in female mice exposed to 200 and 400 ppm, indicating clear evidence of carcinogenic activity. Equivocal evidence of carcinogenic activity was reported for male and female rats and male mice. Although alveolar and bronchiolar adenomas or carcinomas and pheochromocytomas were observed in male rats, the incidences were not dose-related and were within the historical ranges for NTP studies. Granular cell tumors of the brain were also observed in male rats and, although not statistically significant, the incidence was higher than historical incidence in either the study lab or NTP studies. The incidence of alveolar/bronchiolar neoplasms in exposed male mice was marginally greater than control or historical incidence. An increased incidence of gliomas in exposed female rats was significant by the trend test; however, the incidence was not significantly greater when compared with the controls in the study and the controls used in NTP studies.

In a rather short oral gavage study, squamous-cell carcinomas were reported to be produced in 13/20 rats dosed 5 days/week with 50 mg/kg body weight (64). Marked diffuse hyperplasia of the epithelium of the forestomach was reported at this level after only 90 days, with less effect at 10 and 2 mg/kg and none at 0.4 mg/kg. However, in rats similarly exposed in a second study (70) with an extended recovery period, it was found that nearly all lesions regressed, suggesting they were not malignant. Furthermore, the 29-month inhalation study in Wistar rats discussed subsequently failed to support the finding of carcinogenicity in the rat forestomach.

In the 29-month study male and female rats were exposed to 0, 3, 30, or 90 ppm of methyl bromide gas 6 h/day, 5 days/week (47). Ten rats per sex were killed at 13, 52, and 104 weeks for interim information. Mortality was increased at week 114 but only in the 90-ppm group, which also had lowered body weights. Increased incidences of degenerative and hyperplastic changes in the nasal olfactory epithelium were observed in a dose-related manner in all groups. The lesions did not appear to progress with time. Exposure to 90 ppm was associated with an increased incidence of thrombi and myocardial degeneration in the heart and hyperkeratosis in the esophagus and forestomach. There was no indication of a relationship between exposure and tumor incidence.

In the a 2-year oral chronic toxicity/carcinogenicity study, Mitsumori et al. (71) concluded that residues of ≤ 500 ppm total bromide in the diet fumigated with methyl bromide are not carcinogenic in F344 rats of either sex. More information on this study was given in Section 2.4.1.2.

2.4.1.6 Genetic and Related Cellular Effects Studies Bromomethane has been shown to produce mutations in *Salmonella* strains sensitive to alkylating agents and to *Escherichia coli* both with and without the addition of a metabolic activation system (89–92). Bromomethane was also mutagenic in a modification of the standard *Salmonella* assay employing vapor-phase exposure (93–96). Bromomethane was observed to be mutagenic for *Drosophila* and for mouse lymphoma cells (89, 91). Methyl bromide is genotoxic in *in vivo* and *in vitro* tests. Positive results were obtained in the *Salmonella* (90, 91), and *Drosophila* (97), gene mutation assays, the sister chromatid exchange (SCE) test with human lymphocytes (97), the test for SCE induction in female mice, and the micronuclei test (98) (the latter two on peripheral erythrocytes).

2.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization In a subsequent study performed by this group (78) that was designed to assess the neurotoxic effects of bromomethane in rabbits with longer-term exposures at low concentrations, male New Zealand white rabbits were exposed to 0 (n = 2) or 26.6 ppm (103 mg/m^3, n = 6) 99% pure bromomethane 7.5 h/day, 4 days/week for 8 months (78). Exposure concentrations were monitored every 12 min by an infrared analyzer. Neurobehavioral tests examined the latency rates of the sciatic and ulnar nerves and the amplitude of the eyeblink reflex of the orbicularis oculi muscle. No other parameters, including respiratory effects, were monitored. No exposure-related neurological effects were observed. As part of this study, the animals exposed to 252 mg/m^3 bromomethane for 4 weeks (79) were allowed to recover for 6–8 weeks and the neurological tests were repeated. The animals demonstrated partial, but not complete, recovery within the 6-week period. Therefore rabbits, which are sensitive to the neurotoxic effects of high level exposures to bromomethane, can tolerate long-term low level exposure to bromomethane, and appear to be able to recover from severe neurological effects after cessation of exposure.

2.4.2 Human Experience According to IRIS, the most common signs of acute intoxication with bromomethane in humans are neurotoxic in nature and include headache, dizziness, fainting, apathy, weakness, tiredness, giddiness, delirium, stupor, psychosis, loss of memory, mental confusion, speech impairment, visual effects, limb numbness, tremors, muscle twitching, paralysis, ataxia, seizures, convulsions, and unconsciousness. Several studies have been conducted on the longer-term effects of occupational exposure to bromomethane. None of these studies can serve as the basis for the derivation of an RfC for bromomethane because of concurrent exposures to other chemicals,

inadequate quantification of exposure levels and/or durations, and other deficits in study design.

Possible symptoms include anorexia, nausea, vomiting, corrosion to the skin, severe skin burns, enlarged liver, kidney damage with development of albuminuria, and in fatal cases, cloudy swelling and tubular degeneration. Central nervous system effects include blurred vision, mental confusion, numbness, and tremors. Death following acute poisoning is usually caused by its irritant effect on the lungs. In chronic poisoning, death is due to injury to the central nervous system. Direct skin contact may cause prickling, itching, cold sensation, erythemia, vesication, damage to peripheral nerve tissue, and delayed dermatitis. It may also cause double vision, dizziness, headache, convulsions, muscular tremors, fatal pulmonary edema, and neurological and GI disturbances. It may cause skin irritation. Other symptoms may include mental excitement, acute mania, bronchitis, pneumonia, and severe eye damage. It may cause abdominal pain and death from respiratory or circulatory collapse. It may also cause unconsciousness leading to a prompt “anesthetic” death, malaise, ataxia, myoclonus, exaggerated (or absent) deep reflexes, positive Romberg's sign, paroxysmal abnormalities of the EEG, great agitation, change of personality, coma, and mild euphoria. Exposure to this compound may also cause muscle weakness, loss of coordination and gait, hyperthermia, hepato- and nephrotoxicity, behavioral changes, paralysis of extremities, delirium, epileptiform attacks, and skin lesions. It may cause respiratory tract irritation, organic brain syndrome, psychological depression, seizures, prominent cerebellar and parkinsonian signs, renal failure due to tubula necrosis, jaundice, elevations of liver enzyme activity in serum and abnormal liver function, lassitude, slurring of speech, staggering gait, diplopia, epileptiform convulsions, perhaps with a Jacksonian-type of progression, rapid respirations, cyanosis, pallor and collapse, areflexia, impaired superficial sensation, absent or hypoactive distal-tendon reflexes, and bronchopneumonia after severe pulmonary lesions. It may also cause severe mucous membrane burns. Other symptoms may include DNA mutations and large chromosome alterations and congestion with coughing, chest pain, shortness of breath, confusion, shaking and unconsciousness, severe pulmonary irritation and neurotoxicity, narcosis at high concentrations, vertigo, tremor of the hands, dyspnea, hallucinations, anxiety, inability to concentrate, conjunctivitis and dry, scaling, and itching dermatitis. It may also cause lacrimation from irritation of the eyes, transient dimming of vision and blindness for 12 h, nystagmus on lateral gaze, delirium, apathy, and aphasia, edema of the papilla, and punctiform hemorrhages may be found, as well as optic atrophy. In addition, it causes sleepiness, digestive problems, loss of stability, lack of motor coordination, sensorial problems, and impaired hearing. Somnolence, permanent brain damage, lethargy, and sensory disturbances can occur. It may cause anuria, hyperactivity, blood pressure fall, papilledema, fainting attacks, and bronchospasm. It may also cause retinal and submucous hemorrhages, stomach congestion, and congestion of the brain with multiple hemorrhages associated with degenerative changes, such as necrosis.

2.4.2.1 General Information Reports of a toxic absorption of methyl bromide gas through the skin have been published, but very high exposure concentrations (8000–10000 ppm) were involved and it is possible some leakage around or through respiratory protective devices occurred (99). Obviously skin contact with the liquid and vapor must be minimized in addition to prevention of vapor exposure.

There are difficulties in handling methyl bromide in the drug industry. Repeated splashes on the skin resulted in severe skin lesions. Severe cases showed “vesicles or blebs.” In a less rigorous exposure, severe itching dermatitis was observed. One report by Longley and Jones (100) describes serious systemic effects following gross skin contact with liquid methyl bromide, but inhalation may have been significant despite the absence of lung damage. Methyl bromide may cause difficulty when it is held in contact with skin by clothes. This is a special problem with gloves and shoes. In the case of shoes, it is suspected that a fairly high concentration of vapor near the floor may actually be absorbed into the leather and cause skin irritation. Spills onto or into a shoe may cause a severe burn if allowed to remain in contact with the skin. When methyl bromide is handled, care should be taken to avoid splashes onto the clothing or shoes. When there is a fairly high vapor concentration, as in an accidental spill, care should be taken to prevent seepage into the shoes or on protective clothing, and exposure to the vapor should be minimized.

Liquid methyl bromide can cause severe corneal burns but the vapors do not appear to be painful. Furthermore, a full-face respirator should always be used if vapor concentrations are significant; hence the eyes will be protected from exposure.

Numerous reports attest to the high toxicity of methyl bromide to humans. Many reports indicate failure to use reasonable recommended handling precautions. The symptoms observed in humans from acute exposure have been reported by a number of authors whose reports have been reviewed by von Oettingen (59, pp. 15–30). The early symptoms may be a feeling of illness, headache, nausea, and vomiting. Tremors and even convulsions may be observed, much as they are in animals, as well as lung edema and an associated cyanosis. If the patient survived an acute exposure for the first 2 or 3 days, the probability of complete recovery was very high.

Observations of 10 cases acutely and chronically exposed have been summarized by Hine (101) and electroencephalographic studies on seven cases by Mellerio et al. (102).

2.4.2.2 Clinical Cases Cases of severe methyl bromide poisoning in humans, some of them fatal, were frequently reported. For example, von Oettinger (59) recorded 47 fatal and 174 nonfatal cases of methyl bromide intoxication between 1899 and 1952. Acute poisoning was characterized by lung irritation. The toxicity was manifested as paralysis of extremities, delirium, convulsions, and even typical epileptiform attacks. Some of these symptoms were persistent, and recovery occurred in a matter of months, sometimes incompletely with permanent disability. In all cases, the conditions of exposure are inadequately described, neither the methyl bromide concentration nor the exposure duration are exactly known. However, by retrospective estimate, the methyl bromide concentration could have been as high as 60,000 ppm (103) in some instances.

Severe poisoning with some fatalities resulted from soil disinfection by injection of methyl bromide into greenhouse soil (104). These workers measured methyl bromide levels following application rates ranging from 30–3000 ppm. They found peak values of 200 ppm persisting for a few seconds on initial injection with airborne levels above the soil declining to 4 ppm 5 days posttreatment. Tilling the soil can produce exposures at 15 ppm as long as 9 days after soil treatment (105). Tourangeau and Plamondon (106) reported that tests made in date-processing and date-packing houses, where a number of employees had been stricken, showed concentrations ranging up to 100 ppm in the general workroom air, up to 500 ppm near the walls of ineffectively sealed chambers, and over 1000 ppm at the breathing zone of workers entering the chamber to remove the fumigated fruit. Tourangeau and Plamondon (36, 106) found concentrations up to 390 ppm in a plant where one fatal and one nonfatal case of intoxication occurred. Hine (101) reported concentrations of about 100 ppm in plants where two of his clinical cases were found. Johnstone (107) reported mass poisoning (34 cases) in the date-packing industry. The industrial hygiene survey conducted by the California Department of Health, Division of Industrial Hygiene, indicates that the packers were exposed to less than 50 ppm; however, during the purging of a fumigation chamber, the methyl bromide concentrations in the packing room reached 100 to 500 ppm. Watrous (108) described nausea, vomiting, headache, skin lesions, and symptoms of mild systemic poisoning in workers (90 people) exposed for 2 weeks at concentrations generally below 35 ppm.

Liquid methyl bromide may penetrate through all articles of clothing and may cause superficial burns with much vesication when in contact with skin. Three authors (99, 100, 109) demonstrated the possibility of absorption by the skin of toxic quantities of methyl bromide. Longley and Jones (100) reported severe skin irritation in workers fumigating a medieval castle. Six people were occupationally exposed to ~ 35 g/m^3 (9000 ppm) methyl bromide during a 40-minute fumigation process in spite of adequate airway protection. After a few hours, all fumigators developed sharply demarcated erythema with multiple vesicles and large bullae. Particularly affected were the axillae, groin, and abdomen. Histopathological examination of early skin lesions revealed necrosis of keratinocytes, severe edema of the upper dermis, subepidermal blistering, diffuse infiltration of

neutrophils, and to a lesser extent, eosinophils. Two of the patients developed an urticarial rash about one week post exposure. These late lesions showed the combined features of spongiotic dermatitis and urticaria. No immunopathology was observed. The skin returned to normal in all workers after 4 weeks except for some residual hyperpigmentation. Average plasma bromide levels immediately following exposure (9 mg/L) and 12 h postexposure (6.8 mg/L) strongly suggest dermal absorption of methyl bromide.

2.4.2.2.5 Carcinogenesis Assessment of EPA Classification D (Not classifiable as to human carcinogenicity on the basis of inadequate human and animal data) was based on a single mortality study from which direct exposure associations could not be deduced and studies in several animal species with too few animals, too brief exposure, or observation time for adequate power. A prospective mortality study was reported for a population of 3579 white male chemical workers. The men, employed between 1935 and 1976, were potentially exposed to 1,2-dibromo-3-chloropropane, 2,3-dibromopropyl phosphate, polybrominated biphenyls, DDT, and several brominated organic and inorganic compounds (110). Overall mortality for the cohort, as well as for several subgroups, was less than expected. Of the 665 men exposed to methyl bromides (the only common exposure to organic bromides), two died from testicular cancer, as compared with 0.11 expected. This finding may be noteworthy as testicular cancer is usually associated with a low mortality rate. Therefore, there could be more cancer cases than there appear to be based on mortality. The authors noted that it was difficult to draw definitive conclusions as to causality because of the lack of exposure information and the likelihood that exposure was to many brominated compounds.

2.5 Standards, Regulations, or Guidelines of Exposure

OSHA PEL	In 1989, OSHA established a PEL TWA of 5 ppm, with a skin notation, for methyl bromide. This limit was promulgated to protect workers from the significant risk of incapacitating neurotoxic disease and other systemic effects. As a consequence of the 1992 decision by the U.S. Court of Appeals for the Eleventh Circuit the PELs promulgated under the 1989 rulemaking where vacated; however, it currently has a ceiling limit of 20 ppm, with a skin notation.
NIOSH REL/IDLH	The NIOSH REL for methyl bromide is an exposure to the lowest feasible limit. NIOSH based the REL on its position that methyl bromide be considered a potential occupational carcinogen. NIOSH did not concur with the 1989 PEL and recommended that methyl bromide be addressed in a full section 6(b) rulemaking. NIOSH established an IDLH value of 250 ppm (NIOSH Carcinogen) for this substance.
ACGIH Rationale for TLVs that Differ from the PEL or REL	Methyl bromide remains as a substance suspected of carcinogenic potential. In addition, its capacity for dermal absorption, marked neurotoxicity and significant nasal and dermal irritation warrant a greater degree of caution and a reduction in the previously recommended TLV for occupational exposure. The ACGIH TLV for methyl bromide is 1 ppm.

Carcinogenic classification:

IARC	Group 3, Not classifiable as to its carcinogenicity in humans
MAK	Group IIIB, Justifiably suspected of having carcinogenic potential
NIOSH	Carcinogen, with no further categorization.
TLV	A4, Not classifiable as a human carcinogen.

Other nations: Australia—5 ppm, skin (1990); (Former Federal Republic of) Germany—no MAK value, skin, group IIIB, Justifiably suspected of having carcinogenic potential (1996); Sweden—15 ppm, short-term value 10 ppm, 15 min, skin (1990); United Kingdom—5 ppm, 15-min STEL 15 ppm, skin (1997).

2.6 Studies on Environmental Impact:

NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons
Jon B. Reid, Ph.D., DABT

3.0 Methyl Iodide
3.0.1 CAS Number:
[*74-88-4*]
3.0.2 Synonyms:
Iodomethane; monoiodomethane; methyl iodide; Halon 10001; methyl iodine; methyl iodide (iodomethane).
3.0.3 Trade Names:
Halon 10001
3.0.4 Molecular Weight:
141.95
3.0.5 Molecular Formula:
CH_3I
3.0.6 Molecular Structure:

3.1 Chemical and Physical Properties
3.1.1 General Methyl iodide is a colorless liquid that turns yellow, red, or brown when exposed to light and moisture.

Specific gravity	2.279 (20/4°C)
Melting point	–66.5°C
Boiling point	42.50°C
Vapor pressure	400 torr (25°C)
Refractive index	1.5293 (21.0°C)
Percent in “saturated” air	53 (25°C)
Solubility	1 vol/125 vol water at 15°C; soluble in ethanol, ethyl ether
Flammability	Methyl iodide is nonflammable by standard tests in air
UEL, LEL	Not available (UEL, LEL = upper, lower exposure limits)

3.1.2 Odor and Warning Properties Methyl iodide has a sweet ethereal odor with poor warning properties.
3.2 Production and Use
Methyl iodide has had very limited use as a chemical intermediate (methylations), and in microscopy because of its high refractive index, as imbedding materials for examening diatomes, and in tests for pyridine. It has been proposed as a fire extinguisher and insecticidal fumigant. It is a product of natural biologic processes.
3.3 Exposure Assessment
3.3.1 Air: NA

3.3.2 Background Levels: NA

3.3.3 Workplace Methods NIOSH Method 1014 is recommended for determining workplace exposures to methyl iodide (11).

3.4 Toxic Effects

Little new information (from previous editions) was found. Methyl iodide has not been used extensively; therefore, toxicological investigations and experience have been limited. It is primarily a CNS depressant, but there are also indications of lung irritation and kidney involvement from acute exposures. Because radioactive iodine can be released as methyl iodide, the nuclear industry has investigated its absorption, distribution, and to some extent toxicity when inhaled, ingested, and injected.

3.4.1 Experimental Studies 3.4.1.1 Acute Toxicity Few new data have been published since the last edition.

Buckell (111) determined the LD_{50} for rats dosed either subcutaneously or orally to be 150–200 mg/kg of body weight. This author also reported that it would produce a "vestibular burn" if closely held to the human skin. It was indicated that clothing contaminated with methyl iodide should be removed immediately. Johnson (112) reported that the acute oral LD_{50} for mice was 76 mg/kg, but that repeated doses of 30–50 mg/kg were without effect. Single oral doses of 70 mg/kg were lethal to rabbits, but several oral doses of 50 mg/kg were necessary before they caused death. Penetration of methyl iodide through the skin (species not indicated) was reported by Shugaev and Mazkova (113), who considered absorption to be of more concern than local irritative effects. Von Oettingen (33, pp. 30–32), reported a 15-min exposure at 3800 ppm that was fatal to rats. Buckell (111) reported a LC_{50} for mice at 900 ppm (57-min exposure). A 4 h LC_{50} of 232 ppm was reported by Deichman and Gerarde (114).

Bachem (115) studied the response of mice to methyl iodide. His work is summarized in Table 62.1. Chambers et al. (116) reported the lethal concentration for rats for a 15-min exposure to be 22 mg/L in air (3790 ppm). The rats died within a period of 11 days. They showed lung irritation and pulmonary edema. Buckell (111) reported the LC_{50} for mice to be 5 mg/L in air from a 57-min exposure.

Table 62.1. Acute Effects of Methyl Iodide

Concentration		
mg/L	**ppm**	**Response**
454.4	78,700	Rapid narcosis; death after 10-min exposure
105.1	18,100	Death after 30-min exposure
42.6	7340	After 15–50 min, side position, no complete narcosis, death 1 h after beginning of exposure
21.3–31.6	3670–5370	Death after 2–2.5 h of exposure
0.43–4.26	73–730	Death of all animals within 24 h
0.31	54	Death of all animals within 24 h; no marked toxic

symptoms

3.4.1.2 Chronic and Subchronic Toxicity Blank et al. (117) exposed rats by inhalation for 14 weeks at 30 and 60 ppm. Findings were ocular irritation and depressed body weights but no clinical or microscopic pathologic changes. Mortality occurred in 4 weeks at an exposure of 143 ppm.

The studies by Druckery et al. (118) and Poirier et al. (119) are discussed in Section 3.4.1.5.

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The metabolism of methyl iodide is not yet certain, but there appears to be rapid release of iodide ion and methylation of glutathione in rats dosed orally. The process is enzymatically catalyzed (112). Subcutaneous injection produced similar results (120).

In the available abstract (121), more recent investigators indicate that the addition of reduced, but not oxidized, glutathione inhibited methyl iodide toxicity to rat brain neocortical cultures *in vitro*.

Alveolar absorption of inhaled ^{132}I-methyl iodide by humans resulted in retention of 53–93% depending on the concentration inhaled and the rate of respiration (122).

3.4.1.4 Reproductive and Developmental No data on teratogenesis were found.

3.4.1.5 Carcinogenesis Carcinogenicity classification:

IARC Group 3, Not classifiable as to its carcinogenicity to humans.

MAK Group 2, probably human carcinogen.

NIOSH Carcinogen, with no further classification

NTP has not conducted genetic toxicology or long-term toxicology and carcinogenesis effects studies on methyl iodide.

Druckrey et al. (118) reported local sarcomas following weekly subcutaneous injection in BD-strain rats. Strain A mice (a susceptible strain) that were injected with methyl iodide were reported to have a slight but significant increase in the number of lung tumors per mouse.

3.4.1.6 Genetic and Related Cellular Effects Studies Mutagenic tests on *Salmonella* have been reported by McCann et al. (123) to be weakly positive, but details of the study are lacking. Newer data confirm reported positive results in mutagenic tests in *Salmonella*, mouse lymphoma, Chinese hamster ovary, and mouse lymphoma.

Binding of methyl iodide in male and female rat organs has been reported (124). According to the abstract,

Male and female F344 rats were exposed to ^{14}C-labelled methyl iodide orally or by inhalation in a closed exposure system. DNA adducts were detected in the liver, lung, stomach, and forestomach of the exposed animals. [^{14}C]3-Methyladenine, [^{14}C]7-methylguanine and [^{14}C]O6-methylguanine could be identified by a combination of three different methods of hydrolysing DNA and subsequent HPLC or GC/MS analysis. The highest values of methylated guanines were determined in the stomach and forestomach of the animals following both oral and inhalative exposure. These results demonstrate a systemic genotoxic effect of methyl iodide.

Binding appeared to be due to alkylation rather than metabolic incorporation into DNA.

Methyl iodide was mutagenic for *Salmonella typhimurium* bacterial strains TA1535 and TA100 and also a direct acting mouse lymphoma L5178Y/%K±cells (36).

3.4.2 Human Experience 3.4.2.1 General Information Garland and Camps (125) reported two cases of exposure of humans to the vapors of methyl iodide from industrial operations. The first case was quoted from Jaquet as reported in 1901. This case showed symptoms of vertigo, diplopia, and ataxia, there was evidence of urinary iodine, and the individual developed delirium and serious mental disturbances. The second case was one observed by Garland and Camps. The patient was found to be drowsy and unable to walk, with slurred, incoherent speech. He had iodine in the urine. Death occurred 7–8 days after exposure. Serious CNS involvement was also reported in a chemical worker by Baselga-Monte et al. (122), but the route of exposure was not given. Depression and psychological disturbance persisted for several weeks; complete recovery required 122 days. A report by Appel et al. (126) of a 41-year-old chemist exposed to the vapor of methyl iodide presents similar symptoms. These authors summarize much of the available literature. Skin irritation has been reported even while wearing protective gloves (127).
3.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV TWA is 2 ppm (12 mg/m^3). The OSHA PEL is 5 ppm and the NIOSH REL is 2 ppm.

Other countries (8): Australia—2 ppm, category 3, Suspected human carcinogen, skin, (1990); (Former Federal Republic of) Germany—no MAK, 2, Probably human carcinogen (1998); Sweden—1 ppm, 15-min short-term value 5 ppm, skin, carcinogenic (1991); United Kingdom—5 ppm, 10-min STEL 10 ppm, skin (1991).
3.6 Studies on Environmental Impact:
NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons
Jon B. Reid, Ph.D., DABT

4.0 Methylene Chloride
4.0.1 CAS Number:
[*75-09-2*]
4.0.2 Synonyms:
Dichloromethane; methylene dichloride; methane dichloride; methylene bichloride
4.0.3 Trade Names:
Aeothene MM, DCM, Narkotil, Solaesthin, Solmethine, NCI-C50102, R30, UN 1953; Refrigerant 30; Freon 30; DCM; Plastisolve
4.0.4 Molecular Weight:
84.93
4.0.5 Molecular Formula:
CH_2Cl_2
4.0.6 Molecular Structure:

4.1 Chemical and Physical Properties
Methylene chloride is a clear, colorless, nonflammable, volatile liquid with a penetrating ether-like odor. It is slightly soluble in water, alcohols, phenols, aldehydes, ketones, and organic liquids. Methylene chloride is miscible with chlorinated solvents, diethyl ether, and ethanol. It will form an explosive mixture in an atmosphere with a high oxygen content, or in the presence of liquid oxygen, nitrite, potassium, or sodium. When heated to decomposition, it emits highly toxic fumes of phosgene.

4.1.1 General

Physical state	Colorless liquid
Specific gravity	1.3266 at 20°C
Melting point	–95.1°C
Boiling point	40°C
Vapor pressure	440 torr (25°C)
Refractive index	1.4237 (20°C)
Percent in “saturated” air	55 (25°C)
Solubility	2 g/100 mL water at 25°C; soluble in ethanol, ethyl ether, acetone
Flammability	No flash point or fire point by standard tests in air 15.5–66 vol%
Autoignition temperature	624°C
UEL, LEL	19%, 12%

1 mg/L = 288 ppm and 1 ppm = 3.48 mg/m^3 at 25°C, 760 torr

4.1.2 Odor and Warning Properties Methylene chloride has a “not unpleasant,” sweetish odor at concentrations above 300 ppm, but at about 1000 ppm the odor becomes unpleasant for most people. At 2300 ppm the odor is strong, intensely irritating; there may be dizziness after 5 min exposure. It has a chloroformlike odor.
4.2 Production and Use
Methylene chloide is used principally as a solvent in paint removers. It is also used as an aerosol propellant, processing solvent in the manufacture of steroids, antibiotics, vitamins, and tablet coatings; as a degreasing agent; in electronics manufacturing; and as a urethane foam blowing agent. Methylene chloride is also used in metal cleaning, as a solvent in the production of polycarbonate resins and triacetate fibers, in film processing, in ink formulations, and as an extraction solvent for spice oleoresins, caffeine, and hops. Methylene chloride was once registered for use in the United States as an insecticide for commodity fumigation of strawberries, citrus fruits, and a variety of grains.

Methylene chloride has been used as a blowing agent for foams and as a solvent for many applications, including coating photographic films, pharmaceuticals, aerosol formulations, and to a large extent in paint stripping formulations. It is used as a solvent in a number of extraction processes, where its high volatility is desirable. It has high solvent power for cellulose esters, fats, oils, resins, and rubber, and is more water soluble than most other chlorinated solvents. Formulations for paint stripping may contain other solvents as well as methylene chloride and are frequently found outside the workplace. These formulations often contain other ingredients that retard evaporation and in the process increase the likelihood of skin irritation.
4.3 Exposure Assessment
The exposure characteristics of methylene chloride are discussed in the 1993 ATSDR Toxicological Profile (128). The primary routes of potential human exposure to methylene chloride are inhalation and ingestion. Dermal absorption has been observed, although it occurs more slowly than absorption after ingestion or inhalation. The principal route of exposure for the general population to methylene chloride is inhalation of ambient air. Inhalation exposure may also occur through the use of consumer products containing methylene chloride. USEPA has estimated that over one million workers are currently exposed to methylene chloride. The National Occupational Hazard Survey,

conducted by NIOSH from 1972 to 1974, estimated that 2.5 million workers were potentially exposed to methylene chloride vapors. On the basis of health hazard evaluations of various U.S. companies conducted in 1973 and 1974 by NIOSH, the concentrations of methylene chloride to which workers might be exposed in the following occupations were determined: servicing diesel engines, 11 ppm; spray-painting booths, 1–74 ppm; chemical plant, 0–5520 ppm with an 8-h TWA of 875 ppm; ski manufacture, 0–36 ppm; cleaning foam heads, 3–29 ppm; cleaning nozzles in plastics manufacture, 5–37 ppm; plastic tank construction, several ppm. A 1973 study of occupational exposure to hairspray propellants determined that methylene chloride exposure of beauticians exceeded a daily mean concentration of 1–2 ppm. The use of methylene chloride in hairsprays has been banned by the FDA. An estimated 500 million lb methylene chloride was produced in the United States in 1988. From the data obtained in the EPA Consumer Use and Shelf Survey, the CPSC calculated average individual 45-year risks. They ranged from zero for some of the automotive products to highs of 409 per million for adhesive removers and 95 per million for paint strippers, when the risk was based on malignant tumors in mice in the NTP bioassay; the risks were 924 per million for adhesive removers and 214 per million for paint strippers when the risks were based on malignant plus benign tumors in mice in the NTP bioassay. The Toxic Chemical Release Inventory (EPA) listed 1475 industrial facilities that produced, processed, or otherwise used chloromethane in 1988. In compliance with the Community-Right-to-Know Program, the facilities reported releases of methylene chloride to the environment that were estimated to total 127 million lb. Methylene chloride occurs in surface water, groundwater, finished drinking water, commercially bottled artesian well water, and surface water sites in heavily industrialized river basins. Methylene chloride was the sixth most frequently detected organic contaminant in groundwater from hazardous disposal sites investigated in 1987; it had a frequency detection of 19%.

4.3.2 Background Levels See above (Section 4.3).

4.3.3 Workplace Methods NIOSH Method 1005 is recommended for determining workplace exposures to methylene chloride (11).

4.3.4 Community Methods: NA

4.3.5 Biomonitoring/Biomarkers DiVincenzo et al. (1927) and Stewart et al. (129) discussed biologic monitoring for methylene chloride in expired air. The latter report includes graphs of expired air concentrations following exposures to known concentrations of methylene chloride. Within certain limits these may be useful in determining the exposures of workers. Carboxyhemoglobin levels in blood may also be of some value but interpretations are complicated by other sources of carbon monoxide and because carboxyhemoglobin is not elevated in a linear dose-dependent manner (130).

4.3.5.1 Blood See above (Section 4.3.5).
4.4 Toxic Effects
Methylene chloride is a poison by intravenous route and is moderately toxic by ingestion, subcutaneous, and intraperitoneal routes and mildly toxic by inhalation. It is an experimental carcinogen and tumorigen and an experimental teratogen, and it has experimental reproductive effects. It is severe eye and skin irritant.

Methylene chloride is the least acutely toxic of the four chlorinated methanes. The toxic effect is predominantly narcosis. Methylene chloride and some other dihalomethanes are metabolized to carbon monoxide. The principal problem from use is the “drunkenness” that may cause inept operation, which may result in injury to the employee or other workers in the area. The symptoms of excessive exposure may be dizziness, nausea, tingling or numbness of the extremities, sense of fullness in the head, sense of heat, stupor, or dullness, lethargy, and drunkenness. Exposure to very high concentrations may lead to rapid unconsciousness and death. Prompt removal from exposure prior to death usually results in complete recovery.

Epidemiological data indicate no increase in cancer in workers exposed to methylene chloride.

Positive results have been found in experimental mice (Section 4.4.1.5).

Numerous reviews are available (128, 131, 132), and detailed studies of pharmacokinetics and risk assessments have been published (133–135).

Industrial experience with methylene chloride has resulted in few reports of serious adverse effects. Although dermatitis has been reported due to its common usage in paint remover formulations, only a few anesthetic deaths have occurred, all at very excessive concentrations. Reports of systemic injury are rare, and many are of questionable authenticity. Methylene chloride is known to be metabolized to carbon monoxide, but carboxyhemoglobin levels alone are not a good measure of the toxic effect of methylene chloride. Other sources of carbon monoxide such as automotive exhaust and smoking must be considered in evaluating occupational exposure to methylene chloride.

4.4.1 Experimental Studies 4.4.1.1 Acute Toxicity Methylene chloride has a low to moderate acute oral toxicity in laboratory animals. The acute oral LD_{50} of methylene chloride in rats is about 2000 mg/kg. Slight narcosis occurs at 4000–6100 ppm in several species of animals (136). The lethal concentration for an exposure of 7 h is about 15,000 ppm (33, pp. 35–41; 136, 137).

Instillation of liquid methylene chloride directly into eyes of rabbits produced inflammation of the conjunctiva and eyelid, which persisted for 2 weeks; keratitis and irritis; and a 59% increase in corneal thickness at 6 h, which returned to normal by 9 days (138). Methylene chloride is mildly irritating to the skin of rabbits on repeated contact if allowed to evaporate. Svirbely et al. (137) reported that the LC_{50} for mice was approximately 50 mg/L or 15,000 ppm for an 8-h exposure. Survival of all animals was observed at approximately 11,000 ppm. Lehmann and Schmidt-Kehl (139) reported levels of narcosis in cats; 32 mg/L or 9000 ppm caused “displacement of equilibrium” in 20 min but no narcosis. At 37.5 mg/L or 10,000 ppm, light narcosis occurred in 220 min and deep narcosis at 293 min. They reported that cats and rabbits tolerated 6–7 mg/L for 8–9 h/day for 4 weeks with no significant observable changes. Subsequent studies have confirmed these early data. Plaa and Larson (140) and Gehring (141) investigated the renal and hepatotoxicity of methylene chloride and concluded that the compound had a very low toxicity toward these organs.

4.4.1.2 Chronic and Subchronic Toxicity Heppel and associates (142) reported no pathology or growth depression in dogs, puppies, rats, guinea pigs, or rabbits exposed to 5000 ppm 7 h/day, 5 days/week for 6 months. They did not detect CNS depression by ordinary observation but did not conduct specific tests. At 10,000 ppm they observed light to moderate narcosis. Several animals died, apparently from pulmonary congestion. Heppel and Neal (143) reported experiments with young male rats in an activity cage. At a concentration of 5000 ppm the animals showed definite reduction in activity.

Lifetime exposure of rats and hamsters to 3500, 1500, or 500 ppm 6 h/day for 2 years resulted in “non-life-shortening treatment-related changes, similar to those seen in aging animals, in the livers of male and female rats at all exposure levels.” The details of this study are discussed in Section 4.4.1.5 (144). Hamsters were less affected than rats, with survival of female hamsters much higher than in the control group.

Haun et al. (145) summarized the data from exposure studies in which animals were exposed repeatedly and also described the results of continuous (24 h daily) exposure of rats, mice, monkeys, and dogs for 100 days to either 25 or 100 ppm of methylene chloride vapors. Except for increased carboxyhemoglobin levels, dogs and monkeys were unaffected by this continuous exposure. Mice exposed to 25 ppm were likewise without effect, but the livers of the mice exposed to 100 ppm and rats exposed to both concentrations showed positive fat stains. Cytoplasmic vacuolization was noted in rats, as well as degenerative and regenerative changes in the kidneys. Carboxyhemoglobin was more elevated in the monkeys than in the dogs, which showed no elevation at 25 ppm and about 1.5% elevation at 100 ppm. Levels in monkeys were increased by ~ 1% at 25 ppm and 3–4% at

100 ppm.

In a second continuous exposure study, gerbils appeared to be unusually susceptible to methylene chloride (146). Continuous exposure to 700 ppm resulted in premature termination of the study after 7 weeks and 350 ppm at 10 weeks. Gerbils exposed continuously to 210 ppm were exposed for the intended 3 months. Survivors from the 350- and 210-ppm groups were kept on recovery for 4 months. One female exposed to 210 ppm died, but no control gerbils died. The gerbils exposed to 210 ppm were reported to gain weight normally. Carboxyhemoglobin in the 210-ppm group was 11.5%, versus 10.3% in the 350-ppm group after 3 weeks, which is consistent with other findings of 10 weeks.

An extensive study of neurotoxicologic effects in rats following exposure to 50 ppm (below metabolic saturation), 200 ppm (just below metabolic saturation), and at 2000 ppm (well above metabolic saturation) failed to show deleterious effects (147). Carbon monoxide was similarly studied at 135 ppm in air. Exposure to both substances were 6 h/day, 5 days/week for 13 weeks. Carboxyhemoglobin levels of 10% were attained with the CO as they were with 200 ppm methylene chloride. Postexposure functional tests included an observational battery, hind-limb grip strength, and a battery of evoked potentials (flash, auditory brainstem, somatosensory, caudal nerve). After functional tests were completed, rats from all groups were perfused with fixative and a comprehensive set of nervous tissues from the high exposure group and from controls were examined by light microscopy. The investigators concluded that subchronic exposures as high as 2000 ppm methylene chloride or 135 ppm CO had no deleterious effects on any of the measures of this study.

Methylene chloride is mildly irritating to the skin of rabbits on repeated contact if allowed to evaporate.

Additional studies are discussed in Section 4.4.1.5.

4.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The metabolism of methylene chloride to carbon monoxide and the subsequent production of carboxyhemoglobin (COHb) has been studied in animals and man. In the rat, metabolism appears to be saturable with disproportionately less COHb formed and more unchanged methylene chloride expired as exposure increased (148). Production of carbon monoxide and carboxyhemoglobin has been shown to occur in animals (149) as well as humans.

Von Oettingen et al. (18) studied the absorption and excretion of methylene chloride. They reported that it was rapidly absorbed and largely excreted by the lungs. Although this appears to be partly true, a significant amount is metabolized to carbon dioxide and carbon monoxide.

Figure 62.2 taken from Andersen et al. (133), indicates that CO_2 is produced by either a route involving glutathione *S*-transferase or a route using cytochrome P450 mixed-function oxidase (MFO). Carbon monoxide, however, is produced only in the MFO route. According to Reitz et al. (134), the MFO system plays a protective role, has a higher affinity for methylene chloride, and metabolizes most of the methylene chloride at low concentrations. They conclude that after saturation of the MFO pathway at about 300–500 ppm, the glutathione pathway increases disproportionately.

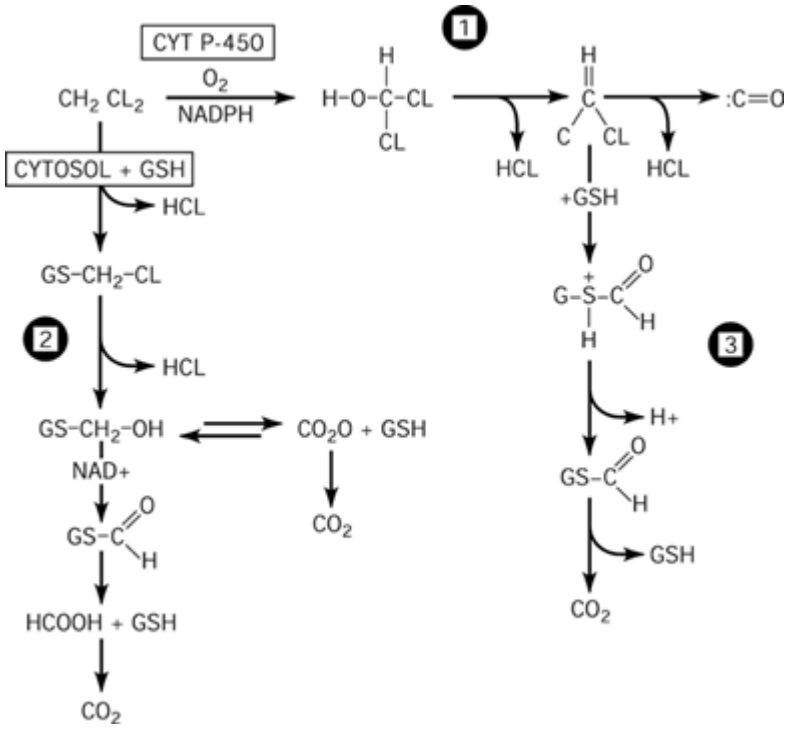


Figure 62.2. Proposed metabolic pathways for methylene chloride metabolism. From Ref. 133.

Different routes of exposure, dosage level/rates of metabolism, respiratory rates, and other factors have been used to develop a physiologically based pharmacokinetic model useful in explaining differences in response in the carcinogenic studies described previously (133). Perhaps the most important result is the calculation that target tissue doses in humans are 140–170-fold lower (by inhalation) or 50–210-fold lower (by drinking water) than would be expected from the customary linear extrapolation and body surface area adjustment used in older risk assessments. However, in 1988 USEPA felt that a nine-fold reduction was more appropriate, despite a report (150) cited in Section 4.4.2 that after a 30-year latency human cancers were not elevated and were well below that predicted by animal studies. *In vitro* data (134) provide support for the Andersen et al. Model.

4.4.1.3.1 Adsorption See above (Section 4.4.1.3).

4.4.1.3.2 Distribution See above (Section 4.4.1.3).

4.4.1.3.3 Excretion See above (Section 4.4.1.3).

4.4.1.4 Reproductive and Developmental Schwetz et al. (151) found no teratogenic effects in rats or mice exposed to 1225 ppm vapor, 7 h/day on days 6–15 of gestation. The young of exposed (4500 ppm) pregnant rats were reported by Bornschein et al. (152) to show retarded behavioral habitation to novel environments. The authors did not attempt to determine whether the effect was due to methylene chloride, carboxyhemoglobin, or the combination of the two. They were also hesitant to extrapolate to possible effects at concentrations of 200–500 ppm. Rats fed up to 4% methylene chloride in their diet showed no teratological effect (153). Neonatal weight was reduced during an 8-week observation period following exposure to 4% in the diet but not after 0.4%.

Wistar rats fed about 2.8 mg/kg of body weight/day in their drinking water (125 ppm) for 91 days were mated or sacrificed at the end of the exposure period; no adverse effects were noted on estrus or reproduction (154).

Nitschke et al. (130) exposed rats and reported the following. Reproductive parameters in Fischer

344 rats were evaluated following inhalation of methylene chloride ($MeCl_2$) for two successive generations. Thirty male and female rats were exposed to 0, 100, 500, or 1500 ppm $MeCl_2$ for 6 h/day, 5 days/week for 14 weeks and then mated to produce F_1 litters. After weaning, 30 randomly selected F_1 pups/sex/group were exposed to $MeCl_2$ for 17 weeks and subsequently mated to produce F_2 litters. Reproductive parameters examined included fertility, litter size and neonatal growth, and survival. All adults and selected weanlings were examined for grossly visible lesions. Tissues from selected weanlings were examined histopathologically. No adverse effects on reproductive parameters, neonatal survival, or neonatal growth were noted in animals exposed to methylene chloride in either F_0 or F_1 generation. Similarly, there were no treatment-related gross pathologic observations in F_0 or F_1 adults or F_1 or F_2 weanlings. Histopathologic examination of tissues from F_1 or F_2 weanlings did not reveal any lesions attributed to methylene chloride. Thus, exposure of rats to concentrations as high as 1500 ppm methylene chloride, which has been shown in a 2-year study to produce treatment-related effects, did not effect any reproductive parameters.

4.4.1.5 Carcinogenesis IARC classifies methylene chloride in group 2B, Probably carcinogenic in humans; MAK, group B, Suspected of having carcinogenic potential; NIOSH, Carcinogen, with no further classification; ACGIH TLV, A3, Confirmed. Animal carcinogen with unknown relevance to humans.

Animal evidence is considered by EPA to be "sufficient" for carcinogenesis. Methylene chloride administered in the drinking water induced a significant increase in combined hepatocellular carcinoma and neoplastic nodules in female F344 rats and a nonsignificant increase in combined hepatocellular carcinoma and neoplastic nodules in male $B6C3F_1$ mice (155, 156). Two inhalation studies with methylene chloride have shown an increased incidence of benign mammary tumors in both sexes of Sprague–Dawley (144) and F344 (157) rats. Male Sprague–Dawley rats had increased salivary gland sarcoma (144) and female F344 rats had increased leukemia incidence (157). Both sexes of $B6C3F_1$ mice developed liver and lung tumors after methylene chloride treatment (157).

In a 2-year study by the National Coffee Association (155, 156), groups of 85 F344 rats/sex/dose received 5, 50, 125, or 250 (mg/kg)/day of methylene chloride in the drinking water. Control groups consisted of 135 rats/sex. In female rats the incidence of combined hepatocellular carcinoma and neoplastic nodules was statistically significantly increased in the 50- and 250-mg/kg dose groups when compared with matched controls (0/134, 1/85, 4/83, 1/85, and 6/85 in the five dose groups 0, 5, 50, 125, and 250 (mg/kg)/day, respectively). The incidence of hepatocellular carcinoma alone was not significantly increased (0/134, 0/85, 2/83, 0/85, 2/85). The combined incidence of hepatocellular carinoma and neoplastic nodules in controls and the four dose groups (472 rats: 4 with carcinoma and 8 with neoplastic nodules) was similar to that for historical controls (419 rats; 5 with carcinoma, 19 with neoplastic nodules). Male rats showed no increase in liver tumors. Also, in this study, $B6C3F_1$ mice received 0, 60, 125, 185, or 250 mg/kg/day of methylene chloride in drinking water. Treatment groups consisted of 50 female mice and 200, 100, 100, and 125 male mice (low to high dose). One hundred females and 125 males served as controls. Male mice had an increased incidence of combined neoplastic nodules and hepatocellular carcinoma (24/125, 51/200, 30/100, 31/99, 35/125). The increase was not dose-related, but the pairwise comparisons for the two middose groups were reported to be statistically significant (132). The hepatocellular carcinoma incidence alone for male mice (which was about 55–65% of the total) was not significantly elevated. Female mice did not have increased liver tumor incidence. The EPA (158) regarded this study as suggestive but not conclusive evidence for carcinogenicity of methylene chloride.

Inhalation exposure of 107–109 Syrian hamsters/sex/dose to 0, 500, 1500, or 3500 ppm of methylene chloride for 6 h/day, 5 days/week for 2 years did not induce neoplasia (144). Sprague–Dawley rats (129/sex/dose) were exposed under the same conditions. Female rats administered the highest dose

experienced significantly reduced survival from 18–24 months. Female rats showed a dose-related increase in the average number of benign mammary tumors per rat (1.7, 2.3, 2.6, 3.0), although the numbers of rats with tumors were not significantly increased. A similar response was observed in male rats, but to a lesser degree. In the male rats there was a statistically significant positive trend in the incidence of sarcomas of the salivary gland (1/93, 0/94, 5/91, 11/88); the incidence was significantly elevated at the high dose. There is a question as to whether these doses reached the MTD, particularly in the hamsters and the male rats.

Groups of 50 each male and female F344/N rats and B6C3F1 mice were exposed to methylene chloride by inhalation, 6 h/day, 5 days/week for 2 years (157). Exposure concentrations were 0, 1000, 2000, or 4000 ppm for rats and 0, 2000, or 4000 ppm for mice. Survival of male rats was low; however, this apparently was not treatment-related. Survival was decreased in a treatment-related fashion for male and female mice and female rats. Mammary adenomas and fibroadenomas were significantly increased in male and female rats after survival adjustment, as were mononuclear cell leukemias in female rats. Among treated mice of both sexes there were significantly increased incidences of hepatocellular adenomas and carcinomas, and of alveolarbronchiolar adenomas and carcinomas, by life-table tests. Adenomas and carcinomas were significantly increased alone as well as in combination. In addition, there were significant dose-related increases in the number of lung tumors per animal multiplicity in both sexes of mice.

4.4.1.6 Genetic and Related Cellular Effects Studies Methylene chloride was mutagenic for *Salmonella typhimurium* with or without the addition of hepatic enzymes (159) and produced mitotic recombination in yeast (160). Results in cultured mammalian cells have generally been negative, but methylene chloride has been shown to transform rat embryo cells and to enhance viral transformation of Syrian hamster embryo cells (161, 162). Although chlorinated solvents have often been suspected of acting through a nongenotoxic mechanism of cell proliferation, Lefevre and Ashby (163) found methylene chloride to be unable to induce hepatocellular division in mice.

Jongen et al. (164) have used methylene chloride in an Ames test with *Salmonella typhimurium* TA98 and TA100. Increased reversions occurred in both strains of bacteria. The activity was only slightly increased by the addition of rat liver homogenate.

4.4.2 Human Experience Symptoms of exposure to this compound may include headache, elevated blood concentrations of carboxyhemoglobin, nausea, and irritation of the skin and eyes. Central nervous system depression, pulmonary edema, hemolysis, chronic intoxication, and paresthesia may also occur. Other symptoms include narcosis, temporary neurobehavioral effects, increase in serum bilirubin, increased urinary formic acid concentrations, and increased risk of spontaneous abortion. In addition, intravascular hemolysis, unconsciousness, lack of response to painful stimuli, rapid followed by slowed respiration, erythema, blistering, toxic encephalopathy, painful joints, swelling of the extremities, mental impairment, diabetes, skin rash, aspiration pneumonia, gross hematuria, reduction of blood pH, GI injury, and narrowing of the intestinal lumen may also occur. Other symptoms may include upper respiratory tract irritation, giddiness, stupor, irritability, numbness, tingling in the limbs, and hallucinations. A dry, scaly and fissured dermatitis, skin burns, coma, and death may also result. Other symptoms may include dizziness, sense of fullness in the head, sense of heat, dullness, lethargy, and drunkenness. In addition, mental confusion, lightheadedness, vomiting, weakness, somnolence, lassitude, anorexia, depression, fatigue, vertigo, liver damage, nose and throat irritation, anesthetic effects, smarting and reddening of the skin, blood dyscrasias, acceleration of the pulse, and congestion in the head may result. Staggering may also occur. Other symptoms of exposure to this compound may include neurasthenic disorders, digestive disturbances, and acoustical and optical delusions. Arrhythmias produced by catecholamines may also result. Additional symptoms include edema, faintness, loss of appetite, and apathy. Hyporeflexia, gross hemoglobinuria, epiglottal edema, metabolic acidosis, gastrointestinal hemorrhage, ulceration of the duodenojejunal junction, and diverticula may also occur. Other symptoms may include kidney damage, lung damage, corneal injury, abdominal pain, and an increase in salivary gland tumors. Cyanosis may also occur. Exposure may also cause altered sleep time, convulsions, euphoria, and a

change in cardiac rate.

4.4.2.1 General Information Experience in use of methylene chloride has generally been favorable, confirming the low toxicity observed in animals. Most commonly, recovery of exposed workers, even from anesthetic concentrations, has been rapid and without sequelae other than carboxyhemoglobin, which appears to persist slightly longer than that resulting from carbon monoxide itself.

Between 1961 and 1980, 33 excessive exposures to methylene chloride were reported to the British Health and Safety Executive (166). Thirteen subjects were unconscious, 9 had headaches, 11 were dizzy, and 13 had GI symptoms, but liver injury was reported only in one subject who also had xylene exposure. One death was reported.

Several laboratory and epidemiologic studies in humans have been reported. An extensive laboratory study of healthy adult test subjects exposed repeatedly 7 h/day to 250 ppm showed no untoward subjective health responses (129). McKenna et al. (148) exposed six healthy male volunteers "to 100 and 350 ppm methylene chloride (CH_2Cl_2) during each of two 6-h exposure periods. Measurement of blood CH_2Cl_2 and carboxyhemoglobin (COHb) levels and CH_2Cl_2 and carbon monoxide (CO) in expired air were performed during exposure and for the first 24 h thereafter. Dose-dependent metabolism of CH_2Cl_2 was evident from both CH_2Cl_2 blood levels and the concentration of CH_2Cl_2 in the expired air when the data from the 100 and 350 ppm exposure experiments were compared. Blood COHb levels and exhaled CO were less than expected following exposure to 350 ppm CH_2Cl_2, indicative of dose-dependent or saturable metabolism of CH_2Cl_2 to CO. The rate of total CH_2Cl_2 metabolism for each subject was calculated from the inspired–expired air concentration and minute ventilation rate obtained at apparent steady-state. The relationship of the rate of CH_2Cl_2 metabolism during exposure to the CH_2Cl_2 exposure concentration followed apparent Michaelis–Menten kinetics." These authors derived a pharmacokinetic model to allow prediction of the extent of methylene chloride metabolism and production of carboxyhemoglobin following exposure to methylene chloride in laboratory animals and humans.

An assessment of the carcinogenic risk to humans has been published in which it is concluded the risk to humans is very low particularly at levels of exposure producing no other adverse effect (135).

4.4.2.2 Clinical Cases See Section 4.4.2.1.

4.4.2.2.1 Acute Toxicity Severe skin burns were observed in a worker found unconscious after about 30 min in a vessel with a high concentration of methylene chloride (165). He was in severe shock and almost pulseless after being taken to the hospital while on oxygen. He was continued on oxygen and 1 h after being rescued still had 12% carboxyhemoglobin despite being on oxygen. When he was discharged 8 days later, the blood protein was reported to be normal, as were liver and renal function tests.

The problem in humans may be accentuated if the chemical is confined to the skin by shoes or tight clothing. The situation may be more severe with paint-remover formulations that form a skin or film to prevent evaporation. Limited absorption through skin occurs, but probably is not of toxicologic significance in industrial situations (167).

4.4.2.2.5 Carcinogenesis An IARC Working Group reported that the data available on methylene chloride were inadequate for an evaluation of its carcinogenicity in humans. The data from a study of 751 occupationally exposed workers also were considered inadequate to assess the carcinogenicity of methylene chloride in humans by later IARC Working Groups.

An epidemiological mortality analysis of a male population exposed to methylene chloride has been reported (168). This study, a follow-up of previously published reports, confirms earlier findings of no increase in cancer.

In a series of five papers the health status and mortality experience of a group of several hundred exposed workers has been described (169). Industrial hygiene measurements indicated exposure of 140 to 475-ppm 8-h time-weighted averages. Cause of death, included ischemic heart disease and cancer, was unaffected. Except for the expected effects of carbon monoxide there were no health affects related to exposure.

4.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV is 50 ppm with an A3 designation. NIOSH considers methylene chloride a carcinogen and recommends the lowest feasible exposure level and an IDLH of 2300 ppm. The OSHA PEL is 25 ppm and a STEL of 125 ppm.

USEPA has published water-quality criteria under CWA and established a reportable quantity (RQ) of 1000 lb for methylene chloride under CERCLA. This chemical is exempted from a tolerance for residues, and is regulated as a toxic inert ingredient of pesticides under FD&CA.

Methylene chloride is a listed hazardous substance under RCRA. USEPA has included methylene chloride on a list of priority hazardous substances under SARA. Further regulatory testing is proceeding under TSCA. FDA regulates methylene chloride as a limited food additive. Specified residues are permitted in spice oleoresins, hops extract, and decaffeinated coffee.

4.6 Studies of Environmental Impact

None found.

Saturated Methyl Halogenated Aliphatic Hydrocarbons

Jon B. Reid, Ph.D., DABT

5.0 Methylene Chlorobromide

5.0.1 CAS Number:

[*74-97-5*]

5.0.2 Synonyms:

Bromochloromethane; bromochloromethane (DOT); chlorobromomethane; chlorobromomethane (ACGIH, OSHA); halon 1011; CB; CBM; monochloromonobromomethane; mil-b-4394-b

5.0.3 Trade Names:

Halon 1011; Methane, bromochloro-; MIL-B-4394-B; Mono-chloromono-bromo-methane; UN1887 (DOT) Bromochloromethane; Chlorobromomethane Monochloromonobromomethane; Monochloromono-bromo-methane methane; Bromochloro-CB; CBM; Halon; 1011; MIL-B-4394-B, UN 1887; CH_2BrCl, CB, BCM

5.0.4 Molecular Weight:

129.39

5.0.5 Molecular Formula:

CH_2ClBr

5.0.6 Molecular Structure:

5.1 Chemical and Physical Properties

Physical state	Colorless liquid
Specific gravity	1.93 at 20°C
Freezing point	–86.5°C
Boiling point	67°C
Vapor pressure	117 torr at 20°C
Refractive index	1.4850 (26°C)
Percent in “saturated” air	21 (25°C)
Solubility	Insoluble in water; soluble in organic solvents
Flammability	No flash or fire points by standard tests in air; it is an effective fire extinguisher

1 mg/L = 189 ppm and 1 ppm = 5.3 mg/m^3 at 25°C, 760 torr

5.1.1 General: NA

5.1.2 Odor and Warning Properties Methylene chlorobromide has a distinctive odor at 400 ppm, and hence has warning properties below any acutely hazardous concentration. Although the odor is distinctive at the acceptable concentration and so gives some warning, it is not disagreeable enough to drive anyone from the area. Employees may tolerate a level well above the acceptable level for chronic exposure.
5.2 Production and Use
This compound is used in fire extinguishers and in organic synthesis.
5.3 Exposure Assessment
5.3.1 Air: NA

5.3.2 Background Levels: NA

5.3.3 Workplace Methods NIOSH Analytical Method: 1003 is recommended (11).
5.4 Toxic Effects
Methylene chlorobromide is one of the least acutely toxic halomethanes. It falls roughly in a class with methylene chloride in acute and short-term toxicity. The primary response to this material is CNS depression. There appears to be very little organic injury following either acute or repeated chronic exposure except possibly lung irritation from acute exposure at high levels. The compound is metabolized to carbon monoxide and produces carboxyhemoglobin as well as inorganic bromide. Few new data were found since the last revised edition. Reviews are available (170, 171).

Methylene chlorobromide is mildly toxic by ingestion and inhalation. This material has a narcotic action of moderate intensity, although of prolonged duration. This compound is corrosive. It is harmful if swallowed, inhaled, or absorbed through the skin. It is extremely destructive to tissue of the mucous membranes, upper respiratory tract, eyes, and skin. It may cause eye, throat, and skin irritation. When heated to decomposition, it emits toxic fumes of carbon monoxide, carbon dioxide, hydrogen chloride gas, and hydrogen bromide gas.

5.4.1 Experimental Studies 5.4.1.1 Acute Toxicity Highman et al. (172) reported that administration of methylene chlorobromide by stomach tube to mice caused no changes at doses of 500 mg/kg. Single doses of 3000 and 4500 mg/kg were followed by fatty degeneration of the liver and kidneys. These same authors observed no liver or kidney injury in animals exposed to the vapors. They commented that the difference in liver injury could be due to a different pathway of absorption from the GI tract than from the lungs.

Svirbely et al. (137) reported the LC_{50} by inhalation for mice exposed for 7 h to be 12.03 mg/L of air

(2273 ppm). Comstock et al. (173) reported that concentrations as low as 3000 ppm produced light narcosis in rats. Transient pulmonary edema was observed at concentrations below 27,000 ppm. At higher concentrations, interstitial pneumonitis resulted in delayed deaths. Delayed deaths were also observed after exposure to 20,000 ppm. Deaths during exposure occurred only from exposures above 27,000 ppm. Matson and Dufour (174) reported limited acute studies on guinea pigs. The principal toxicological observation from the exposure was lung injury. Van Stee et al. (175) exposed dogs to 0.3–1.0% in oxygen to determine the effect on the cardiovascular system. Disturbances in myocardial energy metabolism occurred, including cardiac arrhythmias, but the studies were conducted on anesthetized animals and the industrial significance cannot be ascertained.

5.4.1.2 Chronic and Subchronic Toxicity Repeated exposures by inhalation were reported by Svirbely et al. (137). They exposed animals 7 h/day, 5 days/week for a period of ≤14 weeks to a concentration of 1000 ppm. Rats, rabbits, and dogs survived these exposures and showed no evidence of toxic response. Growth was normal, and there were no histopathological changes.

Torkelson et al. (176) indicate that female rats and dogs survived without significant effect, 370 ppm in air, 7 h/day, 5 days/week for 6 months, but that some liver pathology was observed at 500 ppm. Male rats, male and female guinea pigs, and rabbits showed no effect except for elevated blood bromide at 500 ppm. However, at 1000 ppm several effects were noted, including histopathological changes in the livers and testes in addition to increased blood bromide.

In a similar study, rats and dogs were exposed to methylene chlorobromide vapors 6 h/day for a total of 124 exposures in a 6-month period (177). The exposure levels of 500 and 1000 ppm produced no adverse effect except for an apparent failure of rats to gain as much weight as their controls. The authors suggested that the lower weight might have been related to sedation owing to the elevated levels of bromide ion in the blood. In about 20 days serum bromide levels in both rats and dogs reached an equilibrium of about 150 mg/100 mL in dogs and 140 mg/100 mL in rats exposed to 1000 ppm. Exposures to 500 ppm resulted in equilibrium concentrations of 125 and 100 mg/100 mL in the two species.

5.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Svirbely et al. (137) determined inorganic bromide in blood serum and urine in dogs exposed to 1000 ppm of methylene chlorobromide in air. These animals were exposed 7 h/day, 5 days/week. During the third week, the blood serum inorganic bromide had increased from a normal of 5–10 mg/100 mL to >200 mg. By the 13th and 14th weeks, the concentration was greater than 300 mg of inorganic bromide per 100 mL of blood. The same authors determined the blood concentration of volatile bromide expressed as milligrams of methylene chlorobromide per 100 mL of blood. Taken immediately at the end of the exposure, concentrations between 5 and 9 mg of methylene chlorobromide per 100 mL were observed. At periods of 17–65 h after the end of the last exposure, no volatile bromide was observed in one dog and concentrations of <1 mg in the other. It would appear that methylene chlorobromide as such appears in the blood during exposure to vapors in air, but disappears rapidly on cessation of exposure. Apparently, a significant amount of material is hydrolyzed or metabolized to yield inorganic bromide, which may be useful to determine whether exposures to methylene chlorobromide have occurred.

Female rats exposed to 370 ppm 8 h/day, 5 days/week, had a whole-blood bromide ion concentration of about 70 mg/100 mL; dogs similarly exposed were found to have concentrations of 25–30 mg Br/100 mL whole blood (176).

Although not studied as extensively as methylene chloride, methylene chlorobromide also produces carboxyhemoglobin (178). Intraperitoneal doses of 3 mmol/kg (390 mg/kg) to rats resulted in a maximum carboxyhemoglobin of about 5% at 4 h (methylene chlorobromide) and 8% at 2 h (methylene chloride). Prior administration of phenobarbital, 3-methylcholanthrene, and SKF 525-A did not alter these levels of carboxyhemoglobin. These authors found elevations in carboxyhemoglobin with several dihalomethanes but not with certain other chloromethanes

including carbon tetrachloride, chloroform, and monochloromethane, or with carbon disulfide, methanol, formaldehyde, dimethoxymethane, trichlorofluoromethane, and dichlorodifluoromethane.

5.4.1.4 Reproductive and Developmental No data on teratogenicity or carcinogenicity were found.

5.4.1.5 Carcinogenesis The USEPA classification is D, Not classifiable as to human carcinogenicity. Bromochloromethane is structurally similar to dichloromethane (methylene chloride), which is classified B2, Probable human carcinogen. The classification is based on the lack of data regarding the carcinogenicity of bromochloromethane in humans or animals; however, there are data indicative of genotoxic effects and structural relationships to halogenated methanes classified as B2, Probable human carcinogens.

5.4.1.6 Genetic and Related Cellular Effects Studies When tested in *Salmonella typhimurium* and *Saccharomyces cerevisiae* D3, methylene chlorobromide did not cause a mutagenic response in one study (The Dow Chemical Co., Midland, MI, unpublished data) but was positive in other test systems, including an Ames test and *in vitro* SCE tests with Chinese hamster FAF cells (179).

Mutagenicity tests with bromochloromethane in microorganisms yielded consistently positive results. Osterman-Golkar et al. (180) reported positive responses in reverse mutation assays with *S. typhimurium* TA100 and TA1535 exposed to bromochloromethane in the absence of activation at 20–60 mM and with or without activation in the vapor phase at 10 uL/plate. Similarly, Simmon (94), Simmon et al. (96), and Simmon and Tardiff (93) reported positive results in *S. typhimurium* exposed without activation at 10–50 uL/dessicator. Reverse mutations were observed at the *tyr* locus in *Escherichia coli* WU361089 exposed at 10 uL/plate without activation (180). Prophage induction was also observed in *E. coli* K394 exposed without activation at 10 mL/plate (180).

5.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Methylene chlorobromide, when applied repeatedly to the open skin of rabbits, resulted in some hyperemia and exfoliation. When bandaged on, it produced moderate irritation and hyperemia (181). This material would be expected to have a rather mild effect from ordinary contact, but gross and prolonged contact might cause dermatitis (182).

5.4.2 Human Experience 5.4.2.1 General Information Symptoms of exposure to this compound include disorientation; dizziness; irritation of the skin, eyes and throat; pulmonary edema; headache; anorexia; nausea; vomiting; abdominal pain; weight loss; memory impairment; paralysis; weakness; tremors; convulsions; and narcosis. It may cause coughing, chest pain, and difficulty in breathing. It may also cause transient corneal epithelium damage.

Few reports of adverse effects in humans from exposure to methylene chlorobromide are found in the literature. This is probably because of its low toxicity as well as its limited usage. One report describing exposure was to a mixture of materials, including methyl chloride (183). The neurological effects described fit more closely those expected from methyl chloride than from methylene chlorobromide. A second report by Rotstein (182) describes an incident in which three men were grossly exposed during its use and misuse as a military fire extinguisher. All survived, but two required extensive therapy to prevent anesthetic deaths. The third victim, who was sprayed in the face with the liquid for more than 40 s, did not lose consciousness. All subsequently recovered with no evidence of persistent sequelae. Liver biopsies of the first two victims revealed normal microanatomy, and liver function studies were normal a few days after exposure.

5.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV is 200 ppm (1060 mg/m^3) based on CNS and liver effects. The OSHA PEL and NIOSH REL is also 200 ppm.

International occupational exposure values:

DFG MAK (Germany)

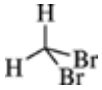
TWA ppm	200
TWA mg/m^3	1100
HSE OES (United Kingdom)	
TWA ppm	200
TWA mg/m^3	1080
STEL/CEIL© ppm	250
STEL/CEIL© mg/m^3	1340
Australia	TWA 200 ppm (1050 mg/m^3); STEL 250 ppm (1300 mg/m^3) January 1993.
Austria	TWA 200 ppm (1050 mg/m^3) January 1993.
Denmark	TWA 200 ppm (1050 mg/m^3) January 1993.
Finland	TWA 200 ppm (1050 mg/m^3); STEL 250 ppm (1315 mg/m^3) January 1993.
France	TWA 200 ppm (1050 mg/m^3) January 1993.
Ireland	TWA 200 ppm (1050 mg/m^3); STEL 250 ppm (1300 mg/m^3) January 1997.
The Netherlands	TWA 200 ppm (1050 mg/m^3) October 1997.
The Philippines	TWA 200 ppm (1050 mg/m^3) January 1993.
Poland	TWA 1000 mg/m^3; STEL 1300 mg/m^3 1998.
Switzerland	TWA 200 ppm (1050 mg/m^3); STEL 400 ppm January 1993.
Turkey	TWA 200 ppm (1050 mg/m^3) January 1993.

5.6 Studies on Environmental Impact:
NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons
Jon B. Reid, Ph.D., DABT

6.0 Methylene Bromide
6.0.1 CAS Number:
[*74-95-3*]
6.0.2 Synonyms:
Bromomethane; methylene dibromide; dibromomethane; methylene bromide (dibromomethane)
6.0.3 Trade Names:
Bercema; Brom-Methan (German); Brom-o-Gas; Brom-o-Gaz; Brom-o-Sol; Bromometano (Italian); Bromomethane; Bromure de Methyle (French); Bromuro di Metile (Italian); Broommethaan (Dutch); Celfume; Curafume; Dawson 100; Detia Gas Ex-M; Dowfume; Dowfume MC-2; Dowfume MC-2 Soil Fumigant; Dowfume MC-33; EDCO; Embafume; Fumigant-1 (obsolete); Halon 1001; Haltox; Iscobrome; Kayafume; MB; MBX; MEBR; Metafume; Methane, Bromo-; Methogas; Methyl Bromide; Methyl Bromide (ACGIH, DOT, OSHA); Methylbromid (German); Metylu Bromek (Polish); Monobromomethane; Pestmaster (obsolete); Profume (obsolete); R 40B1; RCRA Waste Number U029; Rotox; Terabol; Terr-o-Cide II; Terr-o-Gas 100; Terr-o-Gas 67; UN1062 (DOT); Zytox

6.0.4 Molecular Weight:
173.83
6.0.5 Molecular Formula:
CH_2Br_2
6.0.6 Molecular Structure:



6.1 Chemical and Physical Properties

Physical state	Liquid
Specific gravity	2.497 (25/25°C)
Melting point	–53°C
Boiling point	97°C (760 torr)
Vapor pressure	48 torr (25°C)
Refractive index	1.5381 (25°C)
Percent in “saturated” air	6 (25°C)
Solubility	1.18 g/100 mL water at 20°C; soluble in alcohol, ether, acetone
Flammability limits	Not flammable by standard test in air

1 mg/L = 136.7 ppm and 1 ppm = 7.31 mg/m^3 at 25°C, 760 torr
6.2 Production and Use
Methylene bromide has limited use as a solvent and chemical intermediate.
6.3 Exposure Assessment
6.3.1 Air: NA

6.3.2 Background Levels: NA

6.3.3 Workplace Methods: NA

6.3.4 Community Methods: NA

6.3.5 Biomonitoring/Biomarkers Blood bromide and carboxyhemoglobin determinations may be of value in assessing whether exposure to methylene bromide has occurred. However, available data are inadequate to quantify exposure.
6.4 Toxic Effects
Methylene bromide is more acutely toxic than either methylene chloride or methylene chlorobromide. Only limited toxicologic data are available. Carbon dioxide, carbon monoxide, and bromide are among its metabolites. It has the capacity of producing significant liver and kidney injury in animals on repeated exposure. The vapors are anesthetic and are reported to cause cardiac arrhythmias (184). It is apparently produced by marine macroalgae (185). A review is available (186).

6.4.1 Experimental Studies 6.4.1.1 Acute Toxicity Methylene bromide has a low acute oral toxicity; the LD_{50} for rats is > 1000 mg/kg. It is only slightly irritating to the eye and skin of rabbits and does not appear to be absorbed significantly even when applied repeatedly (The Dow Chemical Co., Midland, MI, unpublished data). Although it has been shown by increased blood bromide and increased carboxyhemoglobin that some absorption of the liquid and vapor does occur through rat skin, the investigator concluded that only 5% of the inhaled dose would penetrate the skin during vapor exposure (187). It is sufficiently volatile that inhalation of the vapors can cause anesthesia and

even death. A concentration of 17–20 mg/L (2400–2800 ppm) caused “disorders in the central nervous system” (188). The duration of the exposure and other details were not stated in the available abstract.

When an essentially saturated atmosphere was inhaled by rats, anesthesia occurred in 3 min, with 50% mortality in 18 min (The Dow Chemical Co., Midland, MI, unpublished data).

6.4.1.2 Chronic and Subchronic Toxicity In a very limited study methylene bromide was administered orally to a small group of rabbits at the rate of 300 mg/kg/day (60 doses in 92 days) with no alteration in weight gain, general appearance, or histopathology of the liver. Similar treatment with ≥ 400 mg/kg produced marked anesthesia (The Dow Chemical Co., Midland, MI, unpublished data).

In limited studies in which 10 rats and one rabbit of each sex were exposed to a nominal concentration of 1000 ppm (900–1000 ppm recovered analytically), there was no overt evidence of adverse effect in the rabbits, but liver and kidney degeneration was observed at autopsy following 54 exposures in 73 days (The Dow Chemical Co., Midland, MI, unpublished data). Blood bromide was elevated. Rats were much more affected. Incoordination and staggering were apparent during exposure. Failure to gain weight, possible increased mortality, and histopathological changes in the lungs, liver, and kidneys were observed in rats receiving 30–40 7 h exposures.

In a second equally limited study by this same group, 79 exposures in 114 days to 200 ppm resulted in much less effect, but evidence of stress was still present. The weights of the livers of male rats were elevated when compared to the controls, and histological changes were found in the livers and kidneys of rats and rabbits.

When inhaled 4 h/day for 2 months, 0.25 mg/L (35 ppm) methylene bromide was reported to cause “disorder in the protein-prothrombin and glycogenesis functions of the liver and the filtration capacity of the kidneys.” It was considered less toxic than bromoform (189). The same investigator reported that 2.5 mg/L of the vapor for 10 days (duration of exposure not stated) when inhaled by rabbits produced the same effects with dystrophic changes in these organs. A “threshold” concentration of 0.23 mg/L (32 ppm) was claimed for chronic exposures. When doses of 100–200 mg/kg were injected subcutaneously for 10 days in guinea pigs, pronounced liver and kidney effects were reported. Dykan's report is not consistent with a more extensive study on rats and dogs discussed below.

In another study, 115 male rats, 15 female rats, 4 male and 4 female rabbits, and 3 male beagle dogs were exposed to 0, 25, 75, or 150 ppm methylene bromide vapor 6 h/day, 5 days/week for 13 weeks (190). Male rats received 62 exposures, female rats 63 exposures, and dogs 70 exposures. On the day after their last exposure, 15 male and 15 female rats and the dogs were necropsied. The balance of the male rats were kept for 2 years in a very limited oncological study. Female rats showed a slight increase in liver weight at 75–150 ppm, but other parameters were normal, including mortality, clinical observations, body weight, hematology, clinical chemistry, and gross pathology and histopathology. There was definite evidence of metabolism of methylene bromide; free bromide ion, total bromine, and blood carboxyhemoglobin were increased in a dose-related manner. In the male rats kept for a limited oncological study there were no treatment-related effects grossly or microscopically after 1 year or at the termination of the study except for a possible decrease in body weight beginning on day 121 of the study. Only gross pathological examination of the 2-year animals was conducted and no oncological changes related to exposure were observed at any of the three exposure levels.

6.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Methylene bromide was determined in the plasma of dogs following repeated 6-h exposures to 25, 75, or 150 ppm for 90 days. The plasma clearance was at least biphasic with an ill-defined alpha phase and a terminal phase ($t_{1/2}$ of

103 ± 14 min) at all three concentrations. Blood bromide was elevated markedly in rabbits exposed to ~ 1000 ppm of the vapors, 7 h/day for a month. After 54 exposures in 73 days the blood levels had reached 280–315 mg Br/100 mL of blood. After 79 exposures in 114 days to a vapor concentration of about 200 ppm, blood bromide levels of 85–100 mg Br/100 mL were found in rabbits (190).

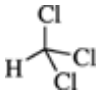
Methylene bromide, like many of the dihalomethanes, is metabolized to produce carbon monoxide (149, 178, 191, 192). Intraperitoneal injection of 520 mg/kg of methylene bromide in corn oil elevated carboxyhemoglobin in rats to 14% 5 h after injection. Repeated daily injection did not result in any significant difference in carboxyhemoglobin concentrations from single injection. *In vitro* studies (178, 193) show that microsomal enzymes in the presence of NADPH and molecular oxygen convert methylene bromide to carbon monoxide and inorganic bromide. There was not significant contribution of glutathione to the overall metabolism of methylene bromide (194). Cytochrome P450 is involved in its metabolism.

6.4.1.4 Reproductive and Developmental No teratological or reproductive data were found, and only the unusual oncological study reported above is available. Methylene bromide has been shown to be mutagenic in certain test systems with bacteria. Methylene bromide has been tested in three strains of *Salmonella typhimurium* activated with liver homogenate and in *Saccharomyces cerevisiae* D3. It was at most weakly mutagenic in *Saccharomyces* and negative in *Salmonella* (The Dow Chemical Co., Midland, MI, unpublished data).

In a study attempting to relate chemical reactivity, glutathione transferase activity, and mutagenicity for a series of dihalomethanes, there was no strong correlation (180). Mixed results were obtained, and methylene bromide was not strongly mutagenic in *E. coli* and *S. typhimurium* systems. Incubation with rat liver microsomes inhanced mutagenic activity (195).
6.5 Standards, Regulations, or Guidelines of Exposure:
NA
6.6 Studies on Environmental Impact:
NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons
Jon B. Reid, Ph.D., DABT

7.0 Chloroform
7.0.1 CAS Number:
[*67-66-3*]
7.0.2 Synonyms:
Trichloromethane, Methenyl chloride, methane trichloride, methyl trichloride, formyl trichloride Methane Trichloride Methane, Trichloro- Methenyl Chloride Methenyl Trichloride Methyl Trichloride, Trichloroform, trichloroform; R 20, r 20 (refrigerant), Refrigerant R20
7.0.3 Trade Names:
Freon 20, R20, R 20 refrigerant, NCI-CO2686, R-20 TCM, UN 1888
7.0.4 Molecular Weight:
119.38
7.0.5 Molecular Formula:
$CHCl_3$
7.0.6 Molecular Structure:



7.1 Chemical and Physical Properties

Physical state	Colorless liquid
Specific gravity	1.49845 (15/4°C) TLV 1.484 at 20°C
Melting point	–63.2°C
Boiling point	–61.3°C
Vapor pressure	200 torr (25°C) 159 torr at 20°C TLV
Solubility	1.0 g/100 mL water at 15°C; soluble in ethanol, ethyl ether, acetone, CS_2
Flammability	Not flammable by standard tests in air
UEL, LEL	Not available

1 mg/L = 206 ppm and 1 ppm = 4.89 mg/m^3 at 25°C, 760 torr

7.1.1 General Chloroform is a colorless, volatile nonflammable liquid with a pleasant, nonirritating odor and slightly sweet taste. It is slightly soluble in water and is miscible with oils, ethanol, ether, and other organic solvents. It is unstable when exposed to air, light, and/or heat, which cause it to break down to phosgene, hydrochloric acid, and chlorine. It is usually stabilized by the addition of 0.6–1% ethanol. When heated to decomposition, chloroform emits toxic fumes of hydrochloric acid and other chlorinated compounds.

7.1.2 Odor and Warning Properties Chloroform has a sweetish odor. Lehmann and Flury (136) indicated that the lowest concentration that could be detected was 200–300 ppm. This might be considered as some warning from exposure to acutely hazardous amounts, but it is by no means low enough to be considered a warning from chronic exposure.

7.2 Production and Use

Chloroform is used primarily in the production of chlorodifluoromethane (hydrochlorofluorocarbon 22 or HCFC-22) used as a refrigerant for home air conditioners or large supermarket freezers and in the production of fluoropolymers. It has also been used as a solvent, a heat-transfer medium in fire extinguishers, and an intermediate in the preparation of dyes and pesticides. Its use as an anesthetic has been discontinued. Chloroform is still used as a local anesthetic and solvent in certain dental endodontic surgery procedures.

Significant commercial production in the United States began in 1992. Since the 1980s, production increased by 20–25% because of a higher demand for HCFC-22. Estimated annual production capacity from the major facilities was 460 million lb. In 1994 it was 565 million lb.

Chloroform has been identified as a hazardous waste by USEPA, and disposal is regulated under RCRA. Ultimate disposal can be accomplished by controlled incineration. Complete combustion must be ensured to prevent phosgene formation and an acid scrubber should be used to remove the haloacids produced.

Miscellaneous uses of chloroform include use as a solvent in the extraction and purification of some antibiotics, alkaloids, vitamins, and flavors; as a solvent for lacquers, floor polishes, artificial silk manufacture, resins, fats, greases, gums, waxes, adhesives, oils, and rubber; as an industrial solvent in photography and dry cleaning; as a heat-transfer medium in fire extinguishers; and as an intermediate in the preparation of dyes and pesticides. At least one grain fumigant mixture had contained chloroform with carbon disulfide. Chloroform formulated with other ingredients is used to control screw worm in animals. Its use as an anesthetic has been largely discontinued.

7.3 Exposure Assessment

An ATSDR Toxicological Profile (Update) for 1998 summarizes relevant material (196). Chloroform is both a synthetic and naturally occurring compound, although anthropogenic sources are responsible for most of the chloroform in the environment. Chloroform is released into the environment as a result of its manufacture and use; its formation in the chlorination of drinking water, municipal and industrial wastewater, and swimming-pool and spa water; and from other water treatment processes involving chlorination. Most of the chloroform released into the environment will eventually enter the atmosphere. In the atmosphere chloroform may be transported long distances before ultimately being degraded by indirect photochemical reactions with such free radicals as hydroxyl. The compound has been detected in ambient air in locations that are remote from anthropogenic sources. Chemical hydrolysis is not a significant removal process. Under aerobic conditions, some bacteria can dehalogenate carbon tetrachloride to release chloroform. While microbial biodegradation of chloroform can take place, such reactions are generally possible only at low concentration levels. Microbial biodegradation may also be inhibited because of high levels of other aromatics, chlorinated hydrocarbons, or heavy metals. Because of its low soil adsorption and slight water solubility, chloroform will readily leach from soil to groundwater. In groundwater, chloroform is expected to persist for a long time.

The general population is probably exposed to chloroform through drinking water and beverages, eating food, inhaling contaminated air, and through dermal contact with water.

The occupations that may involve significant exposure include chemical plants or chlorination process in drinking-water plants, paper-and-pulp plants, and hazardous- and municipal-waste incinerators. A maximum of 3.8×10^{-3} ppm was found in the air in an activated sludge waste-water treatment plant (197).

The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 215,000 workers were potentially exposed to chloroform in the workplace.

A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 95,778 workers in the United States are potentially exposed to chloroform (198).

The NTP database (4) indicates the following. The primary routes of potential human exposure to chloroform are ingestion, inhalation, and dermal contact. Potential human exposure may occur by breathing air contaminated with chloroform, eating food or drinking water that contains chloroform, or absorption of chloroform through the skin. Chloroform has been detected in the atmosphere at concentrations ranging from 0.02 to 13 g/m^3 and in indoor air at 0.07–3.6 g/m^3. Foods such as dairy products, oils/fats, vegetables, bread, and beverages may contain small amounts of chloroform. Drinking-water supplies may contain chloroform as a by-product of chlorination for disinfection purposes. Occupational exposure may occur during the manufacture of chloroform or during one of its uses. Chloroform is used in a number of industries, including building and paperboard industries, iron and steel manufacturing, internal-combustion engine industries, pesticide manufacturing, breweries, dry cleaning, and food processing industries. The Toxic Chemical Release Inventory (USEPA) listed 167 industrial facilities that produced, processed, or otherwise used chloroform in 1988. In compliance with the Community Right-to-Know Program, the facilities reported releases of chloroform to the environment which were estimated to total 23.9 million lb.

7.3.1 Air See above (Section 7.3).

7.3.2 Background Levels Information from 1982 to 1985 reported background level of air over the northern Atlantic Ocean as $2–5 \times 10^{-5}$ ppm (199); in 1976–1979, $4\text{-}4 \times 10^{-5}$ ppm. Typical median indoor air concentrations range from 2×10^{-4} to 4×10^{-3} ppm (200). The air around swimming pools may contain chloroform in the range of 10^{-2} ppm (201). Finished drinking water collected in 1988 from 35 sites across the United States contained median concentrations of chloroform ranging from 9.6 to 15 mg/L (202). Chloroform in sediment samples taken in 1980 from 3 passes of a lake in

Louisiana had concentrations ranging from 1.7 to 18 mg/kg (203). Chloroform has been detected in various foods (196). A maximum of 13.8×10^{-3} ppm was found in the air in an activated-sludge wastewater treatment plant (197). Since chloroform is highly volatile and shows little tendency to bioconcentrate or bioaccumulate in higher lifeforms, it is not ordinarily included in the types of persistent pollutants that are the focus of state fish consumption advisory programs.

7.3.3 Workplace Methods NIOSH Method 1003 is recommended for determining workplace exposures to chloroform (11).

Numerous analytical methods for determining chloroform are presented in the ATSDR Toxicological Profile for 1998 (10). It is essential to take precautions during sampling, storage, and analysis to avoid loss of chloroform. Methods commonly used in air are based on either adsorption onto a sorbent column followed by thermal or solvent desorption with subsequent analysis using GC or directly from a parcel of air (cryogenic). The disadvantages of the sorption tubes are that sorption and desorption efficiencies may not be 100%, and that the background impurities in the sorbent tubes may limit the detection limit for samples at low concentrations. In addition, storage may limit the detection at low concentrations.

7.3.4 Community Methods: NA

7.3.5 Biomonitoring/Biomarkers Analytical sample procedures for biological matrices are given in the ATSDR profile for 1998 (10). Methods exist for analyzing chloroform in biological matrices, including breath, blood, urine and tissues. None of these methods have been standardized by an organization or federal agency, although a blood method by Ashley et al. (204) was developed at the Center for Disease Control and Prevention. Sample preparation methods are based on headspace analysis, purge-and-trap, or solvent extraction. Sample preparation for breath samples typically utilizes an absorbent followed by thermal desorption or direct analysis of an aliquot of breath. These methods all use gas chromatography with various detection methods as analytical techniques. No metabolite has been identified in the blood or urine that can be considered as a useful guide for evaluating occupational exposure to chloroform at concentrations considered acceptable for occupational exposure.

7.4 Toxic Effects

Chloroform is a human poison by ingestion and inhalation, an experimental poison by ingestion and intravenous routes. It is moderately toxic experimentally by intraperitoneal and subcutaneous routes. It is a suspected human carcinogen, an experimental carcinogen, neoplastigen, tumorigen, and teratogen.

Much of our toxicological information has been developed because of the interest in chloroform as an anesthetic. The literature is replete with papers on anesthetic potency or liver and kidney injury as measured by changes in some enzyme level or other parameter. Most of these have limited value to the industrial toxicologist or hygienist.

The most outstanding effect from acute exposure is CNS depression. High concentrations of chloroform result in narcosis, anesthesia, and death. Responses associated with exposure to concentrations below anesthetic or preanesthetic level are typically inebriation and excitation, passing into narcosis. Vomiting and GI upsets may be observed. Exposure to high concentrations may result in cardiac sensitization to adrenalin and similar compounds, as well as liver and kidney injury. In cases of more chronic or repeated exposure to chloroform, liver injury is most typical in humans. This is not unlike the effect of carbon tetrachloride. Although injury to the kidney is not as common as that to the liver, it may be observed from either acute or chronic exposure. The sperm of mice were reported to be affected in one study, but injury has not been observed in many other studies. Teratogenic effects have not been consistently found but retarded fetal development has occurred in some studies.

Chloroform has at most weak mutagenic potency and the positive results found in some carcinogenic studies appear to be the result of a nongenetic response to organ injury.

There appears to be considerable difference in toxic potency between sexes, strains, and species, probably due to differences in the rate of metabolism and other pharmacokinetic parameters.

ATSDR has prepared a Toxicological Profile for Chloroform (10), which provides references to much of the pertinent literature. Extensive effort has been spent developing physiologically based pharmacokinetic models which are described in great detail in the ATSDR update.

Chloroform is considered to be highly fetotoxic, but not teratogenic (205).

7.4.1 Experimental Studies 7.4.1.1 Acute Toxicity When chloroform was administered to rats and mice, the oral LD_{50}s have been reported to range within 444–2000 mg/kg for rats and 118–1400 mg/kg for mice (196). Liver and kidney lesions are found at lower dosages. Deaths at high dosages are probably anesthetic, but organ damages related to metabolism caused delayed death at lower dosages. It has been postulated with some supporting evidence that injury to the organs is due to metabolism in each organ and that species, sex, and strain differences are related to the individual organ's ability to metabolize chloroform to phosgene.

Because of marked differences in response in mice dosed orally with chloroform in water or in corn oil in lifetime carcinogenic studies, Bull et al. (206) conducted a 90-day study using water and corn oil as diluents. Male and female mice were fed 0, 60, 130, or 270 mg/kg/day chloroform either in 2% Emulphor in water or in corn oil. Much greater toxicity was observed in mice fed the corn oil solutions. Decreased body weight, increased liver weight, liver pathology, and blood enzyme changes were all significantly less in water-treated mice than oil-treated. Slight evidence of toxic stress was evident even at the lowest dosage level, 60 mg/kg/day in corn oil. In a similar but shorter study a no-effect level of 50 mg/kg/day was reported for CD1 mice treated for 14 consecutive days with chloroform in an aqueous solution in Emulphor (207). Thompson et al. fed pregnant rats 20 mg/kg/day (10 doses) without effect on the dams; 50 mg/kg appeared to cause fatty changes (208). These data are discussed in more detail in the section on teratology.

Oettel (209) indicated that chloroform was more irritating to the skin and eyes than many other chlorinated solvents. Oettel's conclusions have been confirmed by Torkelson et al. (210). One or two 24 h applications on the skin of rabbits resulted in hyperemia and moderate necrosis. Healing of abraded skin appeared to be delayed by application of a cotton pad soaked in chloroform. Absorption through the intact skin of rabbits occurs as indicated by weight loss and degenerative changes in the kidney tubules, but doses as high as 3980 mg/kg were survived. When the liquid was instilled in the eyes of rabbits, some corneal injury was evident in addition to conjunctivitis. The authors concluded that chloroform was more irritating to rabbit skin and eyes than many common organic solvents tested by the same technique in their laboratory.

7.4.1.2 Chronic and Subchronic Toxicity Major target organs for chloroform are the liver, kidney, and CNS for both humans an animals. Chloroform-induced hepatotoxicity in various animal species has been reported in several studies.

Despite its long usage, few reports of histological examination following repeated exposure of laboratory animals are available. Repeated 7 h exposures 5 days/week for 6 months to either 85, 50, or 25 ppm of the vapor of chloroform resulted in adverse effects in all or some of the species studied, rats, rabbits, guinea pigs, or dogs. The effects of 25 ppm were slight and reversible. Rats exposed 4, 2, or 1 h/day were not adversely affected. Cloudy swelling of the kidneys and centrilobular granular degeneration and necrosis of the liver were the principal adverse effects (210).

The paper by Heywood et al. (211) describes beagle dogs that were administered chloroform in a

toothpaste base [0.5 mL of toothpaste base/kg/day] in gelatin capsules. A control group composed of 16 males and 16 females received the vehicle, and additional control groups of eight animals/sex were administered an alternative toothpaste or were left untreated. Experimental groups of eight male and eight female dogs received 15 or 30 mg chloroform/kg/day for 6 days/week. Treatment was continued for 7.5 years. Fatty cysts, considered to be treatment-related, were observed in livers of some dogs in both treatment groups. Nodules of altered hepatocytes were considered treatment-related but not dose-dependent. A dose-related increase in SGPT levels was noted and a less marked increase in SGOT was noted in the high dose animals. The LOAEL was determined to be 12.9 mg/kg/day, and an RfD was set at 0.01 mg/kg/day.

7.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The metabolism of chloroform is well understood. Approximately 50% of an oral dose of 0.5 g was metabolized to carbon dioxide in humans (212). Metabolism was dose-dependent, decreasing with higher exposure. Approximatly 38% of the dose was converted in the liver, and < 17% was exhaled unchanged from the lungs before reaching the systemic circulation. Metabolism studies indicated that chloroform was, in part, exhaled from the lungs or was converted by oxidative dehydrochlorination of its carbon–hydrogen bond to form phosgene (213). This reaction was mediated by cytochrome P450 and was observed in the liver and kidneys (214). Covalent binding of chloroform to lipids can occur under anaeroic and aerobic conditions, binding to protein occurs only under aerobic conditions (215). Chloroform can induce lipid peroxidation and inactivation of cytochrome P450 in rat liver microsomes under anaerobic conditions (216). Evidence that chloroform is metabolized at its carbon–hydrogen bond is provided by experiments using the deuterated derivative (217).

7.4.1.4 Reproductive and Developmental Several studies indicate that inhalation exposure to chloroform may cause reproductive effects in animals (205). Studies by Bader and Hofmann (218) indicated that exposure to as little as 30 ppm chloroform resulted in increased fetal resorptions. A significant increase in the percentage of abnormal sperm was observed in mice exposed to 400 ppm for 5 days (219).

Chloroform-induced fetotoxicity and teratogenicity were observed in experimental animals (220). The effect of inhaled chloroform on embryonal and fetal development was evaluated in CF1 mice. Pregnant mice were exposed to 0 or 100 ppm of chloroform for 7 h/day on days 6–15, 1–7, or 8–15 of gestation. Exposure to chloroform on days 6–15 or 1–7 produced a significant decrease in the incidence of pregnancy but did not cause significant teratogenicity. In comparison a significant increase in the incidence of cleft palate was observed among the offspring of mice inhaling chloroform on days 8–15 of gestation, but no effect on the incidence of pregnancy was discerned. A significant increase in SGPT activity was observed in mice exposed to chloroform on days 6–15 of gestation; among the mice exposed to chloroform, nonpregnant bred mice had a significantly higher SGPT activity than did pregnant bred mice.

Different results were reported by Dilley et al. (221), who exposed pregnant rats to 20.1 mg/L of chloroform vapor (duration of daily exposure not stated) and produced fetal mortality and decreased fetal weight but no teratological effects. Thompson et al. (208) also failed to produce teratogenic effects in Sprague–Dawley rats by intubation of 0, 30, 50, or 126 mg/kg/day or in Dutch, Belted rabbits given daily doses of 0, 20, 35, or 50 mg/kg. These authors state: “The occurrence of anorexia and weight gain suppression in dams of both species, as well as subclinical nephrosis in the rat and hepatotoxicity in the rabbit, indicated that maximum tolerated doses of chloroform were used. Fetotoxicity in the form of reduced birth weights was observed at the highest dose level in both species. There was no evidence of teratogenicity in either species at any dose tested.” It appears that chloroform has more fetotoxic effect when inhaled than when given by gavage. Thompson et al. (208) speculate that doses given by gavage may result in different blood levels of chloroform, which account for the apparent discrepancy with the effects seen on inhalation. Given the pronounced effect of corn oil on carcinogenic response, it is quite possible that route of exposure might greatly influence reproductive response.

Burkhalter and Balster (222) found no difference in reproductive parameters in control and male and female mice repeatedly gavaged with vehicle (Emulphor-saline) or chloroform. The daily dosage of 31.1 mg/kg was given to both males and females for 21 days prior to mating and throughout mating, and to the dams through gestation and lactation. Pups were dosed beginning on days 7–21. Ruddick et al. (223) treated pregnant rats and rabbits with 200 or 400 mg/kg/day. Fetal weight of only the 400-mg/kg/day rat pups was reduced. Other parameters were unaffected.

7.4.1.5 Carcinogenesis The USEPA classifies chloroform as B2, Probable human carcinogen based on increased incidence of several tumor types in rats and three strains of mice. Chloroform has been tested for carcinogenicity in eight strains of mice, two strains of rats and in beagle dogs.

USEPA derived a $q1^*$ of 8×10^{-2} $[mg/kg/day]^{-1}$ for inhalation exposure to chloroform based on mouse liver tumor data from a chronic gavage study (1976 IRIS). In a gavage bioassay Osborne–Mendel rats and $B6C3F_1$ mice were treated with chloroform in corn oil 5 times/week for 78 weeks. On a daily basis, 50 male rats received 90 or 125 mg/kg; females initially were treated with 125 or 250 mg/kg for 22 weeks and 90 or 180 mg/kg thereafter. Male mice received 100 or 200/mg/kg, raised to 150 or 300 mg/kg at 18 weeks; females were dosed with 200 or 400 mg/kg, raised to 250 or 500 mg/kg. A significant increase in kidney epithelial tumors was observed in male rats and highly significant increases in hepatocellular carcinomas in mice of both sexes. Liver nodular hyperplasia was observed in low dose male mice not developing hepatocellular carcinoma. Hepatomas have also developed in female strain A mice and NLC mice gavaged with chloroform (224, 225).

In 1985 Jorgenson et al. (226) administered chloroform (pesticide quality and distilled) in drinking water to male Osborne–Mendel rats and female $B6C3F_1$ mice at concentrations of 200, 400, 900, and 1800 mg/L for 104 weeks. These concentrations were reported by the author to correspond to daily dosages of 19, 38, 81, and 160 mg/kg for rats and 34, 65, 130, and 263 mg/kg for mice. A significant increase in renal tumors in rats was observed in the highest dose group. The increase was dose-related. The liver tumor incidence in female mice was not significantly increased. This study was specifically designed to measure the effects of low doses of chloroform.

7.4.1.6 Genetic and Related Cellular Effects Studies Very mixed results have resulted from mutagenic studies (227). Chloroform is, at most, a weak mutagen and not likely to be of concern at concentrations considered acceptable for industrial exposure. This conclusion is supported by the low level of binding of chloroform to DNA.

The majority of tests for genotoxicity of chloroform have been negative. These negative findings include covalent binding to DNA, mutation in *Salmonella*, a *Drosophila* sex-linked recessive, tests for DNA damage in a micronucleus test, and transformation of BHK cells. By contrast, one study demonstrated binding of radiolabeled chloroform to calf thymus DNA following metabolism by rat liver microsomes (228). Chloroform caused mitotic recombination in *Saccharomyces* (160) and sister chromatid exchange (SCE) in cultured human lymphocytes and in mouse bone marrow cells exposed *in vivo* (229).

The carcinogenicity of chloroform may be a function of its metabolism to phosgene, which is known to crosslink DNA. A host-mediated assay using mice indicated that chloroform was metabolized *in vivo* to a form mutagenic to *Salmonella* strain TA1537. Likewise, urine extracts from chloroform-treated mice were mutagenic (230). Chloroform administered to mice in drinking water promoted growth and metastasis of Ehrlich ascites cells injected intraperitoneally (IP) (231). Inhalation of 400 ppm chloroform for 5 days increased the percentage of abnormal sperm in mice (219).

7.4.2 Human Experience 7.4.2.1 General Information The NTP DataBase indicates the following: Symptoms of exposure to this compound include nausea, vomiting, eye and skin irritation, unconsciousness, and death. Other symptoms include drowsiness, giddiness, headache, anesthesia, and conjunctivitis. Central nervous system depression may occur. Respiratory failure may also

occur. Exposure may cause lassitude, digestive disturbances, dizziness, and mental dullness. It may also cause coma and an enlarged liver. Other symptoms include hepatotoxicity, nephrotoxicity, reduced cardiac output, cardiac arrhythmias, and abdominal pain. It may also cause cardiac sensitization, GI upset, sensation of fainting, salivation, intracranial pressure, and fatigue. Severe anoxia has been reported. Exposure may lead to chest pain, serious disorientation, hepatomegaly, and, in high concentrations, blepharospasm. It may also lead to ventricular tachycardia, bradycardia, necrosis and hepatomas of the liver, cardiovascular depression, and ventricular fibrillation. Irritation of the upper respiratory tract, nervous system disturbances, and renal or cardiac damage may also occur. Nervous aberrations and profound toxemia may follow exposure. Inhalation may cause hallucinations, distorted perceptions, unspecified gastrointestinal effects, dilation of the pupils, reduced reaction to light, reduced intraocular pressure, feelings of warmth of the face and body, irritation of the mucous membranes, excitation, motor disturbances or loss of reflexes, and loss of sensation. Prolonged inhalation may cause paralysis followed by cardiac respiratory failure. Other symptoms of exposure via inhalation include irritation of the nose and throat, drunkenness, and narcosis. Inhalation of large doses may result in hypotension, respiratory depression, and myocardial depression. Inhalation or ingestion of this compound may cause cardiac irregularities, cardiac arrest, convulsions, reduced blood pressure, and uncontrollable hyperthermia (rare).

Ingestion may cause burning of the throat and mouth. Skin contact may result in smarting and reddening. Prolonged skin contact may result in burns. Prolonged or repeated skin contact may cause dermatitis through defatting of the skin. Eye contact may cause immediate burning pain, tearing, reddening of the conjunctiva, and injury of the corneal epithelium. Chronic exposure may result in jaundice, cirrhosis and damage of the liver, and kidney damage. Alcoholics seem to be affected sooner and more severely.

In humans, chloroform affects the central nervous system, liver, and kidneys. Breathing about 900 ppm in air for a short time causes fatigue, dizziness, and headache. Consuming elevated levels in food can damage liver and kidneys. Large amounts can cause sores on the skin.

Considering the long history of chloroform, there is surprisingly little clinical literature on chronic exposure. There have been almost no quantitative toxicological studies of the response from chronic exposure of humans to chloroform. An attempt to study “causes of death of anesthesiologists from the chloroform era” was limited to too few cases to draw conclusions and certainly did not quantitate exposure (232). Challen et al. (233) studied an industrial operation where chloroform was being used. Groups exposed to concentrations varying between 77 and 237 ppm exhibited definite symptoms. Apparently, there were also some high peak concentrations for very short periods of time. Symptoms were GI distress and depression. Another group with shorter service was exposed to concentrations of 21–71 ppm. They also showed symptoms of comparable nature. Tests of both groups were made to determine possible liver injury, but none were found. It should be remembered, however, that liver function tests are often insensitive to anything except severe liver injury. It is quite possible, as indicated by these authors, that there may have been mild liver injury in these cases. The recommendation of these authors that atmospheric exposure should be kept well below 50 ppm is entirely in order.

Humans are exposed to small amounts of chloroform in drinking water and in beverages made using water that contains chloroform. The amount of chloroform expected to be in air ranges of 0.02–0.05 ppb of air and 2–44 ppb in treated drinking water. The average amount of chloroform that a human may be exposed on a typical day from breathing ranges from 2–5 mg in rural areas to 200 mg in cities to 2200 mg in areas near major sources (10).

7.4.2.2 Clinical Cases See above (Section 7.4.2).

7.4.2.2.1 Acute Toxicity The human lethal dose is 10 mL; the IDLH value is 1000 ppm.

Humans and animals can withstand very high concentrations of chloroform for a short period of

time. Table 62.2, adapted from Lehmann and Flury, gives indications of the response to be expected in humans (136). The response to acute exposures has been indicated in the summary as CNS depression, liver and kidney injury, and possible cardiac sensitization. At the levels of exposure currently considered acceptable for industrial workers, anesthesia and cardiac sensitization are not of practical concern.

Table 62.2. Physiological Response to Various Concentrations of Chloroform in Humans

Concentration		
mg/L	**ppm**	**Response**
70–80	14,336–16,384	Narcotic limiting concentration
20	4096	Vomiting, sensation of fainting
7.2	1475	Dizziness and salivation after a few minutes
5	1024	Dizziness, intracranial pressure, and nausea after 7 min
5	1024	Definite after effects; fatigue and headache still felt later
1.9	389	Endured for 30 min without complaint
1–1.5	205–307	Lowest amount that can be detected by smell

It has been reported that exposures to 40,000 ppm may be lethal unless brief and that surgical anesthesia required 10,000–20,000 ppm. These concentrations and those listed in the table must be used cautiously because the data are old and in many cases involved other drugs during surgery.

7.4.2.2.2 Chronic and Subchronic Toxicity Several studies show kidney toxicity in humans after inhalation exposure. The liver is a primary target of chloroform toxicity in humans.

7.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Chloroform enters the body by skin contact or breathing contaminated air and quickly enters the blood from lungs or intestines. Chloroform usually collects in body fat, but its volatility ensures that it will eventually be removed once the exposure has been removed. Some of the chloroform leaves unchanged and some is broken down.

7.4.2.2.4 Reproductive and Developmental Whether chloroform has caused harmful reproductive effects or birth defects has not been determined.

7.4.2.2.5 Carcinogenesis The USEPA considers the information Inadequate with regard to human carcinogenesis. There are no epidemiological studies of chloroform itself. Chloroform and other trihalomethanes are formed from the interaction of chlorine with organic material found in water. Several ecological and case-control studies of populations consuming chlorinated drinking water in which chloroform was the major chlorinated organic show small significant increases in the risk of rectal, bladder, or colon cancer on an intermittent basis. Many other suspected carcinogens were also present in these water supplies.

There is a possible link between drinking chlorinated water and colon and urinary bladder cancer. However, it is not determined if liver and kidney cancer would develop after long-term exposure in drinking water. The Department of Health and Human Services (DHHS) has determined that

chloroform may reasonably to anticipated to be a carcinogen. IARC has determined that chloroform is possibly carcinogenic to humans (class 2B). The USEPA has determined that chloroform is a probably human carcinogen.

An IARC Working Group considered the evidence for the carcinogenicity of chloroform in humans to be inadequate. Several epidemiological and ecological studies indicate that there is an association between cancer of the large intestine, rectum, and/or urinary bladder and the constituents of chlorinated water. Although data may suggest a possible increased risk of cancer from exposure to chloroform in chlorinated drinking water, the data are insufficient to evaluate the carcinogenic potential of chloroform.

7.4.2.2.6 Genetic and Related Cellular Effects Studies See Section 7.4.2.2.5.

7.4.2.2.7 Other: Neurological, Pulmonary, Skin Sensitization, etc The CNS is a major target for chloroform toxicity in humans and in animals. Once widely used as an anesthetic for humans, levels of 3000–30,000 ppm were reached. A concentration of approx. 40,000 ppm over several minutes can cause death. Dizziness and vertigo were observed in humans after exposure to 920 ppm chloroform for 3 min; headache and slight intoxication occurred at higher concentrations.

7.4.2.3 Epidemiology Studies Most of the data regarding inhalation exposure in humans were obtained from clinical reports describing health effects under anesthesia.

7.4.2.3.1 Acute Toxicity See above (Section 7.4.2.3).

7.4.2.3.2 Chronic and Subchronic Toxicity Chloroform-induced hepatotoxicity is one of the major toxic effects observed in both humans and animals after inhalation exposure.

Workers exposed to 14–400 ppm chloroform for 1–6 months developed toxic hepatitis and other effects, including jaundice, nausea, and vomiting without fever. In contrast, toxic hepatitis was observed in workers exposed to 2-205 ppm.

7.4.2.3.4 Reproductive and Developmental No studies show reproductive effects or developmental effects in humans after inhalation exposure.

7.4.2.3.5 Carcinogenesis No studies were located regarding cancer in humans or animals after inhalation exposure.

Epidemiological studies suggest an association between cancer in humans and the consumption of chlorinated drinking water, but the results are not conclusive at this time. Many confounding effects in these studies are still unaccounted for. The studies dif-fered regarding the type of cancer associated with consumption of chlorinated water. Confounding factors include the presence of other trihalomethanes, haloacetic acids, halo-acetonitriles, halogenated aldehydes, ketones and furanones, and chlorine. Overall, the human data are insufficient to support a conclusion regarding carcinogenicity in humans.

7.4.2.3.6 Genetic and Related Cellular Effects Studies No studies indicated genotoxic effects in humans after inhalation studies.

7.4.2.3.7 Other: Neurological, Pulmonary, Skin Sensitization, etc Epidemiological studies indicate that chloroform can cause cardiac effects in patients under anesthesia.

7.5 Standards, Regulations, or Guidelines of Exposure

NIOSH recognizes chloroform as a carcinogen, and recommends a STEL of 2 ppm; ACGIH, TLV TWA is 10 ppm, with an A3 designation. OSHA has a ceiling limit of 50 ppm.

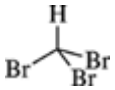
WHO has a drinking water guideline of 30 mg/L.

IARC classifies chloroform as a group 2B (possibly carcinogenic to humans, and EPA as a B2, probable human carcinogen

The NTP database gives the following information. EPA regulates chloroform under the Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Food, Drug, and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Chloroform is a toxic pollutant of air and water. EPA has established water-quality criteria for chloroform, effluent guidelines, rules for regulating hazardous spills, general threshold amounts, and requirements for handling and disposal of chloroform wastes. A reportable quantity (RQ) of 10 lb has been established for chloroform under CERCLA and CWA. Chloroform is exempted under FD&CA from tolerances for pesticide chemicals. Chloroform is recognized as an inert ingredient of toxicological concern under FD&CA. A rebuttable presumption against registration of chloroform-containing pesticides has been issued under FIFRA. Chloroform is regulated as a hazardous constituent of waste under RCRA. USEPA requires removal of chloroform from drinking water and establishes a maximum contaminant level (MCL) of 100 mg/L under SDWA. Under EPCRA, EPA identifies chloroform as an extremely hazardous substance and established a threshold planning quantity (TPQ) of 10,000 lb for chloroform. FDA regulates chloroform as an indirect food additive for adhesive components in food packaging materials and as a component of materials that come into contact with food. The use of chloroform in food, drugs (for both humans and animals), and cosmetics for use in cough preparations, liniments, cosmetics, and toothache drops is banned under the Federal Food, Drug, and Cosmetic Act
7.6 Studies on Environmental Impact:
NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons
Jon B. Reid, Ph.D., DABT

8.0 Bromoform
8.0.1 CAS Number:
[*75-25-2*]
8.0.2 Synonyms:
Methenyl tribromide, tribromomethane; methyl tribromide
8.0.3 Trade Names:
NCI-C55130, RCRA Waste Number U225, UN 2515
8.0.4 Molecular Weight:
252.73
8.0.5 Molecular Formula:
$CHBr_3$
8.0.6 Molecular Structure:



8.1 Chemical and Physical Properties
8.1.1 General Bromoform is a colorless, nonflammable, heavy liquid, similar to chloroform in odor

and taste.

Physical state	Colorless liquid
Specific gravity	2.890 (20/4°C)
Melting point	9°C
Boiling point	149.5°C
Vapor pressure	5 torr at 20°C
Refractive index	1.5980 (19°C)
Percent in “saturated” air	0.7 (25°C)
Solubility	0.3 g/100 mL water at 30°C; soluble in ethanol, ethyl ether, benzene
Flammability	Not flammable by standard tests in air

1 mg/L = 97 ppm and 1 ppm = 10.34 mg/m^3 at 25°C, 760 torr

8.1.2 Odor and Warning Properties Bromoform has a sweetish, chloroformlike odor but odor should not be considered as a warning property.

8.2 Production and Use

Bromoform has quite limited use as a chemical intermediate. It was formerly used as an antiseptic and sedative. It is formed during the chlorination of certain water supplies and sewage. It is also used to make high density liquids for geologic analysis and in the shipbuilding and aircraft industries.

8.3 Exposure Assessment

Bromoform may be absorbed through the lungs, from the GI tract, and, to a certain extent, through the skin. The brain contains higher concentrations of bromoform than blood and liver following inhalation (234). After oral administration, bromoform is rapidly absorbed. Gastrointestinal absorption following oral exposure has been estimated to be 60–90% complete following a single gavage dose; this percentage of the administered dose was recovered in the expired air, in urine, or in the tissues (235). Tribromomethane has been identified as a drinking-water contaminant resulting from water chlorination.

8.3.3 Workplace Methods NIOSH Analytical Method 1003 is recommended for determining workplace exposures to bromoform (11).

8.3.4 Community Methods: NA

8.3.5 Biomonitoring/Biomarkers Blood bromide might be useful in monitoring exposure to bromoform, but at this time data are inadequate to quantitate exposure.

8.4 Toxic Effects

This compound is a lacrimator. It can damage the liver to a serious degree and cause death. It is an irritant of the skin, eyes and respiratory tract and has narcotic effects. When heated to decomposition it emits toxic fumes of bromine. It may be absorbed through the skin. Bromoform causes anesthesia and sedation in animals that may take days for recovery following treatment.

The health effects of exposure to tribromomethane have been reviewed (236).

In the early 1900s, tribromomethane was administered as a sedative to children suffering from whooping cough, and several deaths resulted from accidental overdoses (59, pp. 65–67). The most obvious clinical sign in these fatal cases was profound CNS depression that was manifested as unconsciousness, stupor, and loss of reflexes. Death was usually the result of respiratory failure. These case reports are of limited value because doses were not quantified; however, the doses were likely in the range of 20–40 drops (150–300 mg/kg) daily.

Very limited industrial experience is reported for bromoform. Data from studies in animals indicate pronounced CNS effects, moderate acute and chronic liver and kidney toxicity, and a probably carcinogenic response in rats but not mice. An ATSDR review is available (237).

8.4.1 Experimental Studies The principal cause of death in laboratory animals following acute oral exposure to tribromomethane is CNS depression (238). Moody and Smuckler (239) exposed Sprague–Dawley rats ($n = 3$) to single-gavage doses of 1000 mg/kg tribromomethane and observed significant reductions in the liver microsomal cytochrome P450 content and aminolevulinic acid–dehydratase activity and increases in porphyrin and glutathione content. These effects suggest disturbances in hepatic heme metabolism, because porphyrins are major intermediates in heme synthesis. Chu et al. (240) reported that female rats were more sensitive than male rats to lethal doses of tribromomethane based on LD_{50} values of 1388 and 1147 for males and females, respectively.

8.4.1.1 Acute Toxicity Dogs were exposed to an atmosphere of bromoform at ≥ 7000 ppm. The dogs were deeply anesthetized after 8 min and died after a 1 h exposure (241). An inhalation LC_{Lo} of 4500 mg/m^3 for the rat from a 4 h exposure to bromoform has been reported (242). Results of subcutaneous administration have been reported. An LD_{50} of 1820 mg/kg for the mouse was reported by Kutob and Plaa. (243). Narcosis and hepatotoxic effects were observed. Undiluted bromoform was moderately irritating to rabbit eyes, but healing was complete in 1–2 days. Repeated skin contact caused moderate irritation to rabbit skin (244).

8.4.1.2 Chronic and Subchronic Toxicity The results of 2-year gavage study are discussed in the section on carcinogenicity (245).

Low-level inhalation exposure of humans to tribromomethane results in irritation, lacrimation, and reddening of the face, suggesting the potential for portal-of-entry effects. The information available on inhalation exposure in laboratory animals comes primarily from older studies that employed high concentrations for short durations. In these studies, the CNS, liver, and kidney are major target organs following acute inhalation exposures. Exposure to tribromomethane vapors may also cause irritation to the respiratory tract and lacrimation (59, pp. 65–67).

In another study, 10 F344/N rats/sex were gavaged with 0, 12, 25, 50, 100, or 200 mg/kg bromoform and 10 B6C3F$_1$ mice/sex were gavaged with 0, 25, 50, 100, 200, or 400 mg/kg bromoform 5 days/week for 13 weeks. Complete histology was conducted on high dose and vehicle control groups of both species. Liver histology was conducted on all rats and on male mice receiving doses of > 100 mg/kg. Females of both species did not show any chemically-related effects. A decrease in body weight of both sexes of mice was reported, but was not dose-related. The male mice showed fatty metamorphosis of the liver at doses of 200 and 400 mg/kg. The only effect reported for male rats was a dose-related increase in clear cell foci of the liver. A Fisher Exact Test showed that the incidence of the clear cell foci at doses of ≥ 50 mg/kg (the LOAEL) or above was statistically elevated relative to the vehicle control ($p = .035$); therefore, 25 mg/kg is the NOEL for F344/N rats (246).

The health effects data for bromoform (tribromomethane) were reviewed by the USEPA RfD/RfC Work Group (5) and determined to be inadequate for the derivation of an inhalation RfC. The verification status for this chemical is currently “Not verifiable.”

The only studies of subchronic-duration inhalation exposure are reported in abstracts that do not provide sufficient detail for critical evaluation. Tribromomethane had a narcotic effect on rabbits administered single inhalation exposures of 1064–1741 ppm tribromomethane (188). Rats administered 240 ppm tribromomethane vapor for 10 days developed CNS effects and dystrophic and vascular alterations of the liver and kidney (188). Vapor concentrations of 24 ppm for 2 months also induced hepatic disorders, characterized by decreased blood clotting and impaired glycogenesis, and altered renal filtration capacity (189). A concentration of 4.8 ppm tribromomethane in rats did not elicit any adverse effects in rats after 2 months of exposure (188). These reports provide no details regarding exposure generation or characterization, specific effect measures, or results and are

inadequate for derivation of an RfC.

Studies of 14–90 days' duration in rats and mice exposed by gavage have reported liver, kidney, and thyroid effects, as well as transient lethargy at high concentrations (207, 246). In the NTP (246) study, the incidences of hepatocyte vacuolization in male rats were 3/10, 6/10, 5/10, 8/10, 8/10, and 10/10 for the control, 12, 25, 50, 100, and 200 mg/kg groups, respectively. In mice, 5/10 male mice that received 200 mg/kg and 8/10 male mice that received 400 mg/kg tribromomethane developed cytoplasmic vacuolization. This dose-related, minimal-to-moderate change involved only a few cells or was diffuse. Behavioral effects (decreased response rate in an operant-conditioning test) were also reported in mice treated by gavage with 100 or 400 mg/kg daily for 60 days (247).

A 2-year chronic gavage bioassay was conducted in F344/N rats and B6C3F1 mice (50/sex/group), in which doses of 0, 100, or 200 mg/kg (rats and female mice) or 0, 50, or 100 mg/kg (male mice) dibromomethane were administered 5 days/week for 103 weeks (246). In the high dose rats (both sexes), mean body weights were significantly (10–28%) lower than controls throughout the second year of the study. Survival of the male rats administered 200 mg/kg was significantly reduced ($p < .001$) after week 91. Dose-related lethargy was observed in male and female rats. Non-neoplastic changes, including fatty change and scattered minimal necrosis (males) and mixed-cell foci (females), occurred in the liver of treated rats. The incidence of focal or diffuse fatty change in both sexes was increased (males—23/50, 49/50, and 50/50; females—19/50, 39/50, and 46/50). The lowest daily dose tested in this bioassay (100 mg/kg) induced effects on the liver, salivary gland, prostate gland, lungs, and forestomach, and thus is considered a LOAEL for rats. High dose female mice developed an increased incidence of follicular cell hyperplasia of the thyroid gland (5/49, 4/49, and 19/47). Female mice in both groups exhibited increased incidences of minimal-to-mild fatty change of the liver consisting of scattered hepatocyte foci with vacuolated cytoplasm (1/49, 9/50, and 24/50). Thus, 100 mg/kg also is considered a LOAEL for liver changes in female mice.

The database for tribromomethane is inadequate for the derivation of an RfC. No chronic or subchronic inhalation studies on tribromomethane, and no reproductive or developmental studies that employed an inhalation exposure regimen were found. The toxicokinetic data for the inhalation route are insufficient for route-to-route extrapolation from oral data, and the potential for portal-of-entry respiratory tract toxicity has not been adequately characterized.

8.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The metabolism of tribromomethane is similar to the metabolism of other trihalomethanes (248, 249). Protein synthesis and lipid peroxidation were evaluated in rat liver slices in the presence of oxidants and protein synthesis inhibitors (2, 3). The ability of carbon tetrabromide (and several other halogenated compounds) to inhibit protein synthesis was correlated with its ability to induce lipid peroxidation and was also correlated with their toxicity as indicated by the LD_{50}.

8.4.1.4 Reproductive and Developmental Developmental effects were monitored following gavage administration of 50, 100, or 200 mg/kg/day tribromomethane to pregnant Sprague–Dawley rats (15/group) from days 6–15 of gestation (223). Slight increases in several skeletal anomalies were observed in treated animals and, to a lesser extent, in controls. No other significant maternal toxicity, fetotoxicity, or teratogenicity was observed.

In a reproductive study, effects of tribromomethane were assessed in Swiss CD1 mice ($n = 17–20$/group) exposed by gavage to 0, 50, 100, or 200 mg/kg/day (250). Postnatal survival was significantly decreased in the 200-mg/kg/day group. No other reproductive effects were seen in the F1 or F2 generations.

The reproductive toxicology has recently been reviewed in *Environmental Health Perspectives* (251).

8.4.1.5 Carcinogenesis The USEPA classification is B2, Probable human carcinogen on the basis of inadequate human data and sufficient evidence of carcinogenicity in animals, (*viz.*, an increased incidence of tumors after oral administration of bromoform in rats and IP administration in mice). Bromoform is genotoxic in several assay systems. Also, bromoform is structurally related to other trihalomethanes (*e.g.*, chloroform, bromodichloromethane, dibromochloromethane) that have been verified as either probable or possible carcinogens.

The USEPA considers the animal information "sufficient." Bromoform has been tested for carcinogenicity in two species, rat and mouse (245), by oral or intraperitoneal administration (252).

In a gavage study (245), F344/N rats (50/sex/group) and $B6C3F_1$ mice (50/sex/group) were administered bromoform in corn oil by gavage 5 days/week for 2 years at 0, 100, or 200 mg/kg (rats and female mice) or 0, 50, or 100 mg/kg (male mice). Decreased body weight and survival in rats and female mice suggest that the MTD was reached. In male rats, mean body weight was decreased in the high and low dose groups by 12–28% and 5–14%, respectively. Survival was significantly lower in the high-dose males after week 91. In female rats, body weight was decreased in the high dose group by 10–25%. In male mice, body weight and survival were comparable to controls. In female mice, however, body weight was decreased in the high and low dose groups by 5–16% and 6–11%, respectively; survival was significantly lower in both dose groups after week 77. Neoplastic lesions (adenomatous polyps or adenocarcinomas) were observed in the large intestine (colon or rectum) of male rats (0/50, 0/50, 3/50) and female rats (0/50, 1/50, 8/50). Adenocarcinomas alone were not significantly increased compared with controls. The reduced survival of male rats in the high dose group may account for the lower incidence of lesions in this group. No treatment-related tumors were observed in mice at either dose level. Under the conditions of this study, the NTP judged that there was clear evidence of carcinogenicity for female rats, some evidence of carcinogenicity for male rats, and no evidence of carcinogenicity for male and female mice.

Theiss et al. (252) administered bromoform by IP injection to male A/St mice (20/group). Doses of 100, 48, and 4 mg/kg were given 3 times/week for a total of 24, 23, or 18 injections, respectively. Mice in the control group received 24 IP injections of the vehicle, tricaprylin. Animals were sacrificed 24 weeks after the first injection and the lungs were examined for surface adenomas. Some surface nodules were examined histologically to confirm the morphological appearance of adenomas. The number of lung tumors/mouse for the control, low, mid, and high dose groups were 0.27, 0.53, 1.13, and 0.67, respectively. Only the ratio of the middose group was statistically significantly elevated over that of controls.

In a feeding study with microencapsulated bromoform, Kurokawa (253) observed no evidence of carcinogenicity in male or female Wistar rats exposed for 24 months at concentrations of 400, 1600, or 6500 ppm.

8.4.1.6 Genetic and Related Cellular Effects Studies Bromoform is not strongly mutagenic but positive results have been observed.

Pereira et al. (254, 255) determined that bromoform did not induce GGTase-positive foci in the rat liver at 1 mM (253 mg/kg) or 0.8 mM (202 mg/kg) following a 2/3 hepatectomy and promotion with phenobarbital. However, Pereira found that bromoform is a potent inducer of ornithine decarboxylase, which is an indication of tumor promotion activity in the skin and liver.

Bromoform has been shown to produce mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535 with and without rat hepatic homogenates (245). Bromoform also produces mutations at the TK locus in mouse cells (245); SCE induction in Chinese hamster ovary cells, human lymphocytes (*in vitro*) and mouse bone marrow cells (*in vivo*) (245); chromosomal aberrations in Chinese hamster ovary (CHO) cells (256); cell cycle delay in human lymphocytes (229); and an increased incidence of micronuclei in bone marrow erythrocytes from mice given

bromoform IP (245).

8.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization The undiluted liquid was moderately irritating to rabbit eyes, but healing appeared complete in 1–2 days. It was only moderately irritating to rabbit skin even on repeated contact. Single doses of 2000 mg/kg under a cuff on the intact skin of rabbits were survived by two rabbits treated with undiluted bromoform. Lethargy and slight weight loss were noted from these 24 h applications.

8.4.2 Human Experience Exposure to bromoform vapor is reported to have caused irritation of the respiratory tract, pharynx, and larynx, as well as lacrimation and salivation. Accidental ingestion of the liquid has produced CNS depression with coma and loss of reflexes; smaller doses have led to listlessness, headache, and vertigo (59, pp. 65–67).

8.4.2.1 General Information Symptoms of exposure to this compound may include irritation of the eyes, skin, and respiratory tract. Ingestion may cause respiratory difficulties, tremors, and unconsciousness. Dizziness, disorientation, slurred speech, and death may also result from ingestion. Inhalation may be fatal as a result of spasm, inflammation, and edema of the larynx and bronchi; chemical pneumonitis; and pulmonary edema. Other symptoms may include liver and kidney damage and CNS depression. Inhalation may cause irritation of the respiratory tract, pharynx, and larynx, producing lacrimation and salivation. It can also cause skin and eye irritation. Repeated or prolonged contact may cause dermatitis.

Much of the experience in poisoning cases in humans has been from the oral administration of the material. This was summarized by von Oettingen in 1955 (59, pp. 65–67) and ATSDR in 1990 (237). Anesthesia including respiratory failure has been reported. It has been speculated that an oral dose of 250–500 mg/kg may be lethal to a child, with death be due to CNS depression.

8.4.2.2.5 Carcinogenesis The USEPA considers the information with regard to human carcinogenicity as “inadequate.” Cantor et al. (257) suggest a positive correlation between levels of trihalomethane in drinking water and the incidence of several human cancers. Additional geographic studies of bromoform indicate that there may be an association between the levels of trihalomethanes in drinking water and the incidence of bladder, colon, rectal, or pancreatic cancer in humans. However, the information from these studies is considered incomplete and preliminary because their designs do not permit consideration of several possible variables that may be involved (e.g., personal habits, information on residential histories, and previous exposures) (245).

8.5 Standards, Regulations, or Guidelines of Exposure

Bromoform exposure limits (TWAs) are as follows: NIOSH/OSHA 0.5 ppm; NIOSH IDLH 850 ppm.

The ACGIH recommendation (8) is as follows. Because of its irritant qualities and reported skin absorption, in addition to its potential to cause liver damage and by analogy to related bromine compounds, a TLV TWA of 0.5 ppm, with a skin notation, is recommended for bromoform. At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on excursion limits in the “Introduction to the Chemical Substances” of the current TLV/BEI booklet for guidance and control of excursions above the TLV TWA, even when the 8-h TWA is within the recommended limits. In light of the recent reports on the genotoxicity and carcinogenicity of bromoform, this substance is under review by the TLV Committee.

8.6 Studies on Environmental Impact:

NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons
Jon B. Reid, Ph.D., DABT

9.0 Iodoform
9.0.1 CAS Number:
[*75-47-8*]
9.0.2 Synonyms:
Triiodomethane jodoform (Czech); methane, triiodo-; NCI-C04568; triiodomethane; trijodmethane (Czech)
9.0.3 Trade Names:
NA
9.0.4 Molecular Weight:
393.78
9.0.5 Molecular Formula:
CHI_3
9.0.6 Molecular Structure:

9.1 Chemical and Physical Properties
Iodoform is a yellow or greenish-yellow powder or crystalline solid that is volatile with steam and contains 96.69% iodine. It has a very characteristic pungent odor. An odor threshold of 0.005 ppm has been reported.

9.1.1 General

Physical state	Yellow solid
Specific gravity	4.008 (20.4°C)
Melting point	119°C
Flammability	Not flammable by standard tests in air
Boiling point	210°C, sublimates, explodes
Refractive index	1.800 (20°C)
Solubility	0.01 g/100 mL water at 25°C
UEL, LEL	Not available

1 mg/L = 62.1 ppm and 1 ppm = 16.1 mg/m^3 at 25°C, 760 torr
9.2 Production and Use
Iodoform has limited use as a chemical intermediate and for medicinal purposes as disinfectant and antiseptic. It may still be used in veterinary medicine.
9.3 Exposure Assessment
9.3.1 Air: NA

9.3.2 Background Levels: NA

9.3.3 Workplace Methods: NA

9.3.4 Community Methods: NA

9.3.5 Biomonitoring/Biomarkers Increased iodine and carboxyhemoglobin levels may occur in the blood but data are inadequate to evaluate their usefulness in monitoring occupational exposure.
9.4 Toxic Effects

Little additional information was found.

This material is irritating to the skin, eyes, and mucous membranes. It may be absorbed through the skin. When heated to decomposition this compound emits toxic fumes of carbon dioxide, carbon monoxide, and hydrogen iodide. Decomposition becomes violent at 204°C (400°F).

Most of the problems associated with iodoform have been related to its topical application as an antiseptic material and to oral administration. Absorption of significant amounts of this material may result in CNS depression and injury to the heart, liver, and kidneys. Serious injury to the eyes has been reported following early use of iodoform as a topical and intravitreal antiseptic.

9.4.1 Experimental Studies 9.4.1.1 Acute Toxicity According to the available information, iodoform has oral LD_{50}s of 355, 810, and 487 mg/kg for rats, mice, and guinea pigs, respectively (258). Drowsiness and low activity were first observed without loss of motor activity, but bloody nasal exudate, breathing disturbances, tonic–clonic convulsions, and paralysis of the extremities preceded death. Daily oral administration of 35.5 mg/kg (carrier not described) caused liver and kidney injury. The report also described changes in the brain and thyroid. This report does not appear to be consistent with the NCI report discussed in the section on carcinogenesis.

Administration of iodoform to rats has produced an acute hepatic necrosis, not unlike that observed following exposure to carbon tetrachloride (259).

No reports on testing of iodoform in the eyes of animals were found. Old medical literature describes serious injury to the eyes following treatment of humans with iodoform as an antiseptic.

According to Grant (260), iodoform formerly was employed as a topical and intravitreal antiseptic. Systemic intoxication and visual disturbances resulted from absorption of excessive amounts applied to wounds or abscesses, or from ingestion of large quantities, but not from application to the eye. Numerous cases of visual disturbance were reported early in the twentieth century. Most characteristically vision was impaired by retrobulbar neuritis with accompanying central scotoma. In rare instances transitory complete blindness occurred. In some cases the bulbar portion of the optic nerve was involved, with neuroretinitis and occasional retinal hemorrhages. As a rule, recovery was slow, requiring many months. In most cases vision was completely or partially recovered, but residual pallor of the temporal part of the optic nervehead was common. Exceptionally the whole nervehead became atrophic and white and little vision was recovered.

A percutaneous LD_{50} of 1184 mg/kg was determined in rabbits for a 70% ointment of iodoform (258). Some veterinary reports indicate toxicity from use on the skin of dogs and cats, but it is not clear whether the material was absorbed dermally or ingested.

Rats were exposed once or 7 times to iodoform vapors (261). A 7 h LC_{50} of 183 ppm was determined for the single exposure of rats. Seven 7 h exposures were given to 0, 1, or 14 ppm (verified analytically). There were no changes in rats' appearance, food or water intake, urine and feces output, or SMR (standardized mortality rate) 12/60 blood value for any group. The only histological manifestation was mineralized deposits in medullary renal tubules of some rats exposed to 14 ppm.

Kutob and Plaa (243) administered iodoform subcutaneously to mice in an investigation of hepatotoxicity of a series of halogenated methanes. The LD_{50} by this route was 1.6 mmol/kg (630 mg/kg) compared to 27.5 mmol/kg for chloroform and 7.2 mmol/kg for bromoform. The doses causing changes in a phenobarbital sleeping time study were 0.59, 1.7, and 2.3 mmol/kg for iodoform, chloroform, and bromoform, respectively. Histological damage to the liver was noted at 1.28 mmol/kg (504 mg/kg) but not at 0.32 mmol/kg.

9.4.1.2 Chronic and Subchronic Toxicity No adequate study to determine the chronic toxicity of iodoform exists. Although survival and body weight were affected in the NCI bioassay reported in Section 9.4.1.1 (262), the doses fed were so high as to be improbable as vapor concentrations. They would indicate a low order of systemic toxicity.

9.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The limited data that are available indicate iodoform exposure results in increased carboxyhemoglobin levels in rats. A rat liver microsomal fraction requiring both NADPH and molecular oxygen produced the carbon monoxide (248, 263). A mixed-function oxidase has been reported to be involved.

9.4.1.5 Carcinogenesis Iodoform has been included in the NCI daily bioassay program (262). According to their summary: the high and low time-weighted average daily dosages of iodoform were, respectively, 142 and 71 mg/kg for male rats, 55 and 27 mg/kg for female rats, and 93 and 47 mg/kg for male and female mice. A significant positive association between dosage and mortality was observed in male rats but not in female rats or in mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. No statistical significance could be attributed to the incidences of any neoplasms in rats or mice of either sex when compared to their respective controls. Under the conditions of this bioassay, no convincing evidence was provided for the carcinogenicity of iodoform in Osborne–Mendel rats or $B6C3F_1$ mice.

9.4.1.6 Genetic and Related Cellular Effects Studies Limited data indicate some mutagenic potency, but the data appear inadequate to draw a conclusion toward industrial significance.

9.4.2 Human Experience The 1980s–1990s literature deals mainly with the veterinary uses of the compound. Used as an antiseptic, iodoform produces acute depression of the central nervous system, systemic toxicity, vomiting, coma, and kidney, liver, and heart damage (264). Only one instance of delirium and hallucination has been reported (265).

9.4.2.1 General Information Symptoms of exposure to this compound may include dermatitis, vomiting, varying degrees of cerebral depression or excitation (including delirium, hallucinations, coma, and death), very rapid pulse, possible slight fever, CNS depression, collapse, frequent liquid stools, abdominal pain, thirst, metallic taste, shock, anuria, stupor, esophageal stricture, diarrhea, vesiculation and oozing of skin, intense itching, burning pain, tenderness, nausea, uremia, respiratory distress, and circulatory collapse. Exposure may also result in injury to the heart, liver, and kidneys.

No reports in the literature were found for industrial use of iodoform.

9.4.2.2 Clinical Cases There are several reports of iodoform toxicity caused by medical uses. Authors warn that iodoform toxicity is not as rare as thought and has been underdiagnosed. A case of iodoform toxicity caused by use of 5% iodoformed bandages in occlusive surgical dressings caused signs and symptoms of iodoform toxicity syndrome (266). In another paper (267), where three cases of iodoform toxicity were described following dressings with 10% iodoform gauze on extended wounds, the author indicated that 5, 10, and 16 days after beginning of dressings, the patients became confused, hallucinated, and one of them was subsequently comatose. Within a few days (3–8) after the iodoform dressings were discontinued, the signs of iodoform toxicity disappeared. The author suggests that the toxicity of iodoform is probably unrecognized if the rarity of the observations published and the amount of iodoform gauzes annually sold are compared.

9.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV TWA is 0.6 ppm (10 mg/m^3). The NIOSH REL is also 0.6 ppm.

HSE OES (United Kingdom) 0.6 TWA ppm

TWA mg/m^3	
STEL/CEIL© ppm	1
STEL/CEIL© mg/m^3	16

The ACGIH (8) reports are as follows. Toxicologic data on inhaled iodoform are very limited. Depression of the CNS and damage to the kidneys, liver, and heart following topical application of high, local concentrations to damaged skin have occurred in humans. Accordingly, a TLV TWA of 0.6 ppm is recommended for iodoform. This value is slightly greater than that for bromoform, but on a molar basis, it is considerably higher. Both limits should be used with caution, as there are only scant data and little pertinent use experience with inhaled iodoform. The iodoform TLV approximates that of methyl iodide on an iodine basis. At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be.

International occupational exposure values:

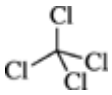
Australia	TWA 0.6 ppm (10 mg/m^3) January 1993.
Belgium	TWA 0.6 ppm (10 mg/m^3) January 1993.
Denmark	TWA 0.2 ppm (3 mg/m^3) January 1993.
Finland	TWA 0.2 ppm (3 mg/m^3); STEL 0.6 ppm (10 mg/m^3); Skin January 1993.
France	TWA 0.6 ppm (10 mg/m^3) January 1993.
Ireland	TWA 0.6 ppm (10 mg/m^3); STEL 1 ppm (20 mg/m^3) January 1997.
The Netherlands	TWA 0.2 ppm (3 mg/m^3) October 1997.
Switzerland	TWA 0.6 ppm (10 mg/m^3) January 1993.

9.6 Studies on Environmental Impact:
NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons
Jon B. Reid, Ph.D., DABT

10.0 Carbon Tetrachloride
10.0.1 CAS Number:
[*56-23-5*]
10.0.2 Synonyms:
Tetrachloromethane; methane tetrachloride; perchloromethane; tetrachlorocarbon; tetrachloromethane; carbon tet; R10, r 10 (refrigerant), Refrigerant R 10; necatorina; benzinoform, carbon chloride; carbona; flukoids; necatorine; tetrafinol; tetraform; tetrasol; univerm; vermoestricid
10.0.3 Trade Names:
Benzinoform, Carbona, ENT 4,705, ENT 27164, Fasciolin, Flukoids, Necatorina, Necatorine, R 10, Tetrachlorormetaan, Tetrafinol, Tetraform, Tetrasol, Un 1846, univerm, vermoestricid, R10 (Refrigerant)
10.0.4 Molecular Weight:
153.84
10.0.5 Molecular Formula:
CCl_4

10.0.6 Molecular Structure:



10.1 Chemical and Physical Properties
Carbon tetrachloride is a colorless, highly volatile liquid with a strong ethereal odor similar to chloroform. It mixes sparingly with water. When heated to decomposition, it emits highly toxic fumes of phosgene.

10.1.1 General

Physical state	Colorless liquid
Specific gravity	1.589 at 25°C
Freezing point	–23°C
Boiling point	76.5°C
Vapor pressure	115.2 torr at 25°C
Refractive index	1.46305 (15°C)
Percent in “saturated” air	15 (25°C)
Solubility	0.08 g/100 g water at 20°C; miscible with alcohol, ethyl ether, benzene
Flammability	Not flammable by standard tests in air; will not support combustion
UEL, LEL	Not available

1 mg/L = 159 ppm and 1 ppm = 6.29 mg/m^3 at 25°C, 760 torr

10.1.2 Odor and Warning Properties Carbon tetrachloride has a sweetish odor. It is not considered particularly disagreeable by most people, although some people may be nauseated by small amounts. The odor is one to which the average individual becomes readily adapted. The odor would certainly not be considered a satisfactory warning of excessive exposure. According to one reference, the threshold of detection of the odor of carbon tetrachloride is approximately 79 ppm and the odor is strong at 176 ppm (268). Another reference states that 100% of a small panel of test subjects recognized 21 ppm of carbon tetrachloride produced from carbon disulfide and 100 ppm of carbon tetrachloride produced by chlorination of methane (269).
10.2 Production and Use
Our understanding of the industrial hygiene measures necessary to handle carbon tetrachloride has changed little since Irish prepared his chapter in Patty's Toxicology for the second revised edition of Volume 2. Awareness of its hepato- and renal toxicity and the availability of less hazardous solvents have resulted in virtually no use as a solvent; most of current production is consumed in the production of fluorocarbons. Use of carbon tetrachloride in fire extinguishers has essentially disappeared, as has use in fumigant mixtures.

Carbon tetrachloride is used primarily as a chemical intermediate in the production of the refrigerants Freon 11 and 12. Freon 11 and 12 are also used as solvents, in plastic and resin production, and as foam blowing agents, and previously as aerosol propellants. Carbon tetrachloride also is used as a general solvent in industrial degreasing operations. Its use as a grain fumigant was banned by USEPA in 1985.

Chemical and Engineering News reported that 271 million lb of carbon tetrachloride was produced domestically in 1990. U.S. imports of carbon tetrachloride have tended to increase, and exports have tended to decrease. Carbon tetrachloride imports exceeded 111 million lb in 1987. Imports increased to over 57 million lb in 1985 from 7 million lb in 1983. Exports decreased from 86 million lb in 1980 to 36 million lb in 1985.

10.3 Exposure Assessment

The primary routes of potential human exposure to carbon tetrachloride are inhalation, ingestion, and dermal contact. The greatest risk of occupational exposure to carbon tetrachloride occurred most likely during fumigation processes before this use was banned in 1985. NIOSH estimated that workers exposed to carbon tetrachloride are primarily those at blast furnaces and steel mills, in the air transportation industry, and in motor vehicle and telephone and telegraph equipment manufacturing.

About 4500 workers are possibly exposed during production processes, and 52,000 during industrial use of the chemical. OSHA estimated that 3.4 million workers may possibly be exposed to carbon tetrachloride directly or indirectly.

Exposure to carbon tetrachloride used to occur in dry-cleaning establishments, where ambient-air concentrations have been determined to average between 20 and 70 ppm. Average exposures of 206 and 338 ppm with excursions of 1252 and 7100 ppm have been reported during dry-cleaning machine operations. Occupational exposure is also possible during its use in the manufacture of Freon 11 and 12. Exposure during fluorocarbon production is most likely to be experienced by tank farm and process operators, who may be exposed to emissions arising from storage tank vents or resulting from transfer of the chemical or process equipment leaks or spills. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 160,000 workers were exposed to carbon tetrachloride in the workplace, including 25,000 workers exposed during grain fumigation. The National Occupational Exposure Survey (1981–1983) estimated that 77,315 workers, including 12,605 women, potentially were exposed to carbon tetrachloride. ACGIH has noted the potential contribution to overall exposure by the cutaneous route, including mucous membranes and eyes, either by airborne, or more particularly, by direct contact with the substance.

The Toxic Chemical Release Inventory (EPA) (4) listed 95 industrial facilities that produced, processed, or otherwise used carbon tetrachloride in 1988. In compliance with the Community Right-to-Know Program, the facilities reported releases of carbon tetrachloride to the environment which were estimated to total 3.9 million lb. These releases indicate that a large proportion of the general population is possibly exposed to the chemical. EPA estimated that 8 million people living within 12.5 m of manufacturing sites are possibly exposed to average levels of 0.5 g/m^3, with peaks of 1580 g/m^3. Carbon tetrachloride is readily volatile at ambient temperature and is a stable chemical that is degraded very slowly, so there has been a gradual accumulation of carbon tetrachloride in the environment (270). It is broken down, by chemical reactions in air, but this occurs so slowly that elimination of 50% of the carbon tetrachloride takes between 30 and 100 years. Carbon tetrachloride is formed in the troposphere by solar-induced photochemical reactions of chlorinated alkenes. Concentrations of 0.1 ppb in air are common worldwide with somewhat higher values (0.2–0.6 ppb) in cities (270). Of 113 public water systems surveyed, 10% had mean concentrations of carbon tetrachloride ranging from 2.4 to 6.4 g/L. Investigators also found the chemical in 45% of surface-water supplies and in 25% of groundwater samples, at concentrations of 0.001–0.40 mg/L. Estimates indicate that 19 million people may potentially be exposed to carbon tetrachloride through ambient air, 20 million possibly through contaminated drinking water, and 2 million possibly through contaminated soil or landfills. Assuming inhalation of 20 m^3/day by a 70-kg adult and 40% absorption of carbon tetrachloride across the lung, typical levels of carbon tetrachloride in ambient air (~ 1 g/m^3) yield daily exposure levels of ~ 0.1 g/kg per day (270). Somewhat higher exposures could occur near point sources of carbon tetrachloride. For water, consumption of 2 L/day by a 70-kg adult at a typical carbon tetrachloride concentration of 0.5 g/L yields a typical intake by this route of ~ 0.01 g/kg per day. Carbon tetrachloride may possibly have been ingested as a contaminant of foods that were treated with the chemical prior to its banning as a grain fumigant in 1985. When carbon tetrachloride was used as a fumigant on stored grain, residue concentrations of the chemical ranged from 3.0 to 72 mg/kg. Carbon tetrachloride may possibly be ingested in water contaminated with the chemical (reported concentrations range 0.2–18 ppm). Also, the chemical possibly may be ingested as a contaminant of drinking water treated with chlorine. Investigators have found carbon

tetrachloride in human tissues in concentrations of 1–13 ppm.

10.3.1 Air See above (Section 10.3).

10.3.2 Background Levels See above (Section 10.3).

10.3.3 Workplace Methods NIOSH Method 1003, for halogenated hydrocarbons, is recommended for determining workplace exposures to carbon tetrachloride (11).

10.3.4 Community Methods: NA

10.3.5 Biomonitoring/Biomarkers Unchanged carbon tetrachloride can be measured in the expired air following exposures. Stewart et al. (271) have shown the relationship of exposure concentration and time to exhaled concentration, and it would appear that at the low levels of exposure considered safe for chronic exposure, breath samples are of very limited value. Expired air may be of value in definitive diagnosis of acute exposure and possibly in semiquantitation of the magnitude of exposure.

At present, metabolites in blood or urine appear to be of limited value in monitoring exposure at levels recognized as acceptable for industrial exposure because exposure to 5 ppm vapor permits daily intake of only 4.5 mg/kg (272).

10.4 Toxic Effects

Carbon tetrachloride is a human poison by ingestion and possibly other routes and a poison by subcutaneous and intravenous routes. It is mildly toxic by inhalation; an experimental carcinogen, neoplastigen, tumorigen, teratogen and suspected human carcinogen; and an eye and skin irritant. Individual susceptibility varies widely. It has a narcotic action resembling that of chloroform, although not as strong. The aftereffects following recovery from narcosis are more serious than those of delayed chloroform poisoning, usually taking the form of damage to the kidneys, liver, and lungs. When recovery takes place, there may be no permanent disability. Marked variation in individual susceptibility to this compound exists; some persons appear to be unaffected by exposures that seriously poison their fellow workers. Concentrations on the order of 1000–1500 ppm are sufficient to cause symptoms if exposure continues for several hours. Repeated daily exposure to such concentrations may result in poisoning. Exposure to high concentrations of carbon tetrachloride results in depression of the central nervous system and possibly cardiac sensitization. If the concentration is not high enough to lead to rapid loss of consciousness, other indications of CNS effects such as dizziness, vertigo, headache, depression, mental confusion, and incoordination are observed. Many individuals also show GI responses such as nausea, vomiting, abdominal pain, and diarrhea. This may be a conditioned reflex or a direct CNS effect. Functional and destructive injury of the liver and kidney may occur from a single acute exposure, but it is much more likely to occur from repeated exposures. In a case of long-term chronic exposure to low concentrations, kidney and liver injury dominate the picture. The milder the exposure, the greater the tendency for the injury to be predominantly in the liver. At threshold concentrations, the injury of the liver appears mostly as malfunction and/or enlargement. Many enlarged livers are observed in animals at the threshold of response and enlargement appears reversible. The detection of an enlarged liver in humans should be considered important, although enlargement may occur from a great many other causes. It has been recognized that the concurrent or past intake of significant amounts of alcohol with exposure to carbon tetrachloride may greatly increase the probability of injury. Other chemicals such as isopropyl alcohol, acetone, chlorinated insecticides, phenobarbital, and many other mixed-function oxidase inducers may also be involved. Diabetes and certain nutritional deficiencies have been implicated in enhanced toxic effects from carbon tetrachloride (273).

Because metabolism of carbon tetrachloride is required for most of its toxic effects, there are many examples of species and strain differences in toxicity. Carcinogenic effects ascribed to carbon tetrachloride appear likely to be due to organ injury.

An ATSDR profile (270) exists for carbon tetrachloride, and numerous other reviews are available. Excellent reviews of metabolism, mode of toxic action, and detailed discussion of biochemical effects are presented in two standard reference books (272, 274). Much of our understanding of metabolism by the liver and toxic effects on that organ by other chemicals has come from the numerous studies on carbon tetrachloride.

10.4.1 Experimental Studies 10.4.1.1 Acute Toxicity This compound is toxic by ingestion, inhalation, or skin absorption. It is an irritant of the skin, eyes, mucous membranes, and respiratory tract. It is readily absorbed through the skin. It may cause lacrimation. It is narcotic. When heated to decomposition it emits irritating fumes and toxic fumes of chlorine, carbon monoxide, carbon dioxide, hydrogen chloride, and phosgene. It may also emit other hydrocarbon products (273).

The former availability of carbon tetrachloride in odd containers around the home and shop made ingestion a serious problem. The LD_{50} for rats is reported by McCollister et al. as 2920 mg/kg (275). The Registry of Toxic Effects of Chemical Substances (1983/84 Supplement) lists LD_{50}s of 2800 mg/kg for the rat, 12,800 mg/kg for the mouse, 6380 mg/kg for the rabbit; and 3680 mg/kg for the hamster (276). Numerous values for other routes of exposure are also cited. Liver injury occurs in animals at levels well below those causing death. The therapeutic dose previously used in humans for treatment of ascariasis ranged from 32 mg/kg for infants to 90–100 mg/kg for adults. Consumption of alcohol caused serious complications in some cases.

Because carbon tetrachloride is a good lipid solvent, it removes the fats from the skin and, in so doing, causes a dry disagreeable feeling and may facilitate secondary infection. Contact with the eyes may cause a transient disagreeable irritation but does not lead to serious injury.

10.4.1.2 Chronic and Subchronic Toxicity The IRIS database indicates the study by Bruckner et al. (277) as the basis for subchronic toxicity of the compound. Male Sprague–Dawley rats were given 1, 10, or 33 mg carbon tetrachloride/kg per day by corn oil gavage, 5 days/week for 12 weeks. Liver lesions, as evidenced by mild centrilobular vacuolization and statistically significant increases in serum sorbitol dehydrogenase activity, were observed at the 10- and 33-mg/kg/day doses in a doses-related manner. Therefore, the LOAEL was established at 10 mg/kg/day [converted to 7.1 mg/kg/day] and the NOAEL was 1 mg/kg/day) [converted to 0.71 mg/kg/day].

Adams et al. (278) reported the response of laboratory animals to a single exposure to various concentrations of carbon tetrachloride. The maximum time-concentrations in air survived by rats were as follows: 12000 ppm for 15 min, 7300 ppm for 1.5 h, 4600 ppm for 5 h, and 3000 ppm for 8 h. The maximum time-concentrations in air having no adverse effects in male rats were as follows: 3000 ppm for 6 min, 800 ppm for 30 min, and 50 ppm for 7 h. Similar data were reported for rabbits by Lehmann. The data from these two sources indicated that rabbits and guinea pigs show a somewhat greater tolerance for carbon tetrachloride than rats do. In any case, the acute data given for the different animals are in the same range.

The responses observed in animals and humans are reasonably comparable. There seems to be a higher probability of significant kidney response in humans than is observed in animals. Qualitatively, such injury is observed in both animals and humans. Histopathological and biochemical studies of acutely injured animals show marked hepatic injury, as has been demonstrated by increased plasma prothrombin clotting time, an increase of serum phosphatase, an increase in liver weight, an increase of total lipid content of the liver, and central fatty degeneration of the liver. Renal injury was not apparent in the acute exposure of rats in the studies of Adams (278). Quite significant kidney injury has been reported, however, from what were thought to be single exposures in humans.

Although responses referable to the nervous system or GI tract may still be observed in chronic exposure, they are much less important factors. These effects may not be noticed at all following a

long period of chronic exposure to low concentrations; the organic and functional injury of the internal organs becomes predominant, particularly of the liver and the kidney. It is noticeable in the literature that carbon tetrachloride has become a classic agent for producing liver injury for laboratory investigations.

One comprehensive toxicologic investigation in animals is that of Adams et al. (278). These investigators studied rats, guinea pigs, rabbits, and monkeys, which were given repeated 7 h daily exposures 5 days/week. At a concentration of 400 ppm (2.52 mg/L), rats and guinea pigs suffered severe intoxication. Less than half of them lived for 127 exposures during a period of 173 days. There was an increase in liver weight up to twice that of the controls and a moderate increase in kidney weight. Histological examination of the tissues showed central fatty degeneration with cirrhosis of the liver and slight parenchymatous degeneration of the tubular epithelium of the kidneys. Animals examined after 2 weeks of exposure demonstrated advanced liver and kidney changes by that time. At a concentration of 200 ppm (1.26 mg/L), rats and guinea pigs still showed a definite response and high mortality. Biochemical and histological studies were comparable but less severe than in the 400-ppm exposure. At a concentration of 100 ppm (0.63 mg/L), rats, rabbits, guinea pigs, and monkeys tolerated 146–163 exposures without evidence of adverse effect on gross appearance, behavior, growth, and other parameters. They all showed histopathological changes. The changes were equivocal in the monkey.

A continuous exposure at 61 mg/m^3 (10 ppm) resulted in the deaths of three guinea pigs, as well as growth depression and liver damage in the survivors of all species. A second continuous exposure at 6.1 mg/m^3 (1 ppm) did not cause deaths or visible toxic signs in any species. All species except the rat exhibited slight growth depression but no hematological or histopathological evidence of toxicity, at 6.1 mg/m^3.

Alumot et al. (279) fed rats diets containing carbon tetrachloride for 2 years. On the basis of growth, fertility, reproduction, biochemical tests, and apparently limited histological examination, primarily of the liver, the authors concluded that they had fed a no-effect level of 200 ppm. On the basis of food consumption, this was calculated to be 10–18 mg CCl_4/kg body weight per day. They also reported fatty livers occurred in rats after 5–6 weeks on a diet containing 275 ppm CCL_4, ~ 40 mg/kg/day, and decreased weight gain in male rats fed 520 ppm. Total lipid and triglycerides were significantly higher at 275 and 520 ppm but not 150 ppm after 5–6 weeks.

10.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Early studies to measure absorption and excretion of carbon tetrachloride were handicapped by analytic difficulties. Studies were made only at very high concentrations. McCollister et al. (280) were among the first who studied the absorption, distribution, and elimination of carbon tetrachloride by using radioactive carbon. This allowed them to study these factors at concentrations that were physiologically significant from a chronic exposure point of view. They exposed monkeys to concentrations of 46 ppm (0.290 mg/L) of carbon tetrachloride that was ^{14}C labeled. Approximately 30% was absorbed. The equivalent of at least 51% of the radioactivity due to carbon tetrachloride absorbed during an inhalation period was estimated to have been eliminated in the expired air within 75 days. The remainder was excreted largely in the urine and feces. Approximately 4.4% was eliminated as carbon dioxide. Some 94.3% of the radioactivity in the urine was a nonvolatile, unidentified intermediate. Small amounts occurred as urea and carbonate. Numerous subsequent references to the metabolism of carbon tetrachloride have been published. The review by ATSDR (270) summarized in a diagram the metabolism of carbon tetrachloride as adapted from Shah et al. (281). Metabolism is primarily in the liver but many other organs have also been shown to metabolize it. The identified products underlined in Figure 62.3 support a NADP H-dependent cytochrome P450 isoenzyme reductive dehalogenation, formation of a trichloromethyl free radical, binding to microsomal lipids and proteins, and a number of other reactions to form products such as carbon dioxide, carbon monoxide, hexachloroethane, chloroform, and phosgene. Metabolism is thought to be dose-dependent and saturable, and to involve destruction

of the cytochrome P450 during the metabolism process.

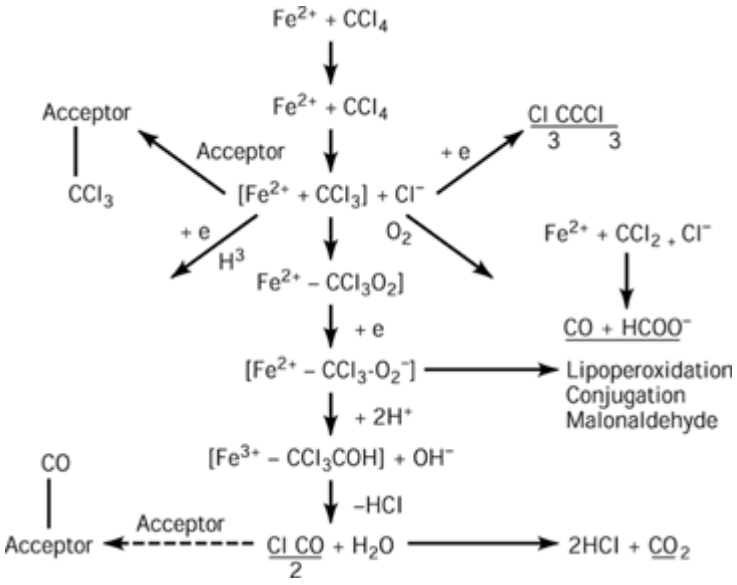


Figure 62.3. Pathways of CCl_4 metabolism. Products identified as carbon tetrachloride metabolites are underlined. [Adapted from Ref. 281.]

Dose–response ratio, time course, and pharmacokinetics following single oral gavage doses of ^{14}C-labeled CCl_4 to rats were studied extensively (282). Carbon dioxide was identified as a major metabolite, with 20–30 times less bound to liver macromolecules. An intermediate amount was excreted in the liver and feces. Metabolism changed extensively as doses were increased. Chloroform, for example, was the least abundant metabolite at low doses, but the second most abundant at high doses. Metabolism by the pathways leading to CO_2 and $CHCl_3$ were more associated with concurrent liver injury as measured by increased transaminase activity than it was to pathways leading to metabolites bound to liver or excreted in urine. Metabolism of CCl_4 clearly impaired the pathway to CO_2 after 2 h of exposure. A significant first-pass effect through the liver is apparent after gavage; unfortunately, few data on metabolism after inhalation are available.

The fatty changes that are characteristic of carbon tetrachloride toxic effect on the liver are due to accumulation of triglycerides, but the mechanism is not yet clear (283). The mechanism is not the same as that producing liver necrosis, another characteristic effect of carbon tetrachloride. Metabolism of carbon tetrachloride is certainly required and lipid peroxidation may play a key role.

10.4.1.3.1 Adsorption Absorption through the skin of monkeys from the vapor phase was studied by McCollister et al. (280). By using radioactive carbon tetrachloride, they were able to detect small amounts in the blood after exposure of the skin to vapor concentrations of 485 and 1150 ppm. Although traces were absorbed through the skin under these conditions, their conclusions were that "absorption through the intact skin would appear to be of no practical significance in considering the hazard to the health of industrial workers exposed to concentrations of at least as high as 1150 ppm in the air."

Stewart and Dodd (167) considered absorption of the liquid through the skin to present a potential problem based on a limited study on human subjects. In view of the high potential hepatotoxicity of carbon tetrachloride, contact of the skin with the liquid should be prevented, particularly if it could lead to repeated exposure.

10.4.1.3.2 Distribution See Section 10.4.1.3.1.

10.4.1.3.3 Excretion See Section 10.4.1.3.1.

10.4.1.4 Reproductive and Developmental Schwetz et al. (283) exposed pregnant rats 7 h/day to either 330 or 1000 ppm carbon tetrachloride vapors from days 6–15 of pregnancy. These exposures had no effect on fetal resorptions but

At both concentrations fetal body weight and crown-rump length were significantly less than that of controls. No anomalies were seen upon gross examination of the fetuses. A significant incidence of subcutaneous edema was observed at 300 ppm but not at 1000 ppm. The incidence of sternal abnormalities was significantly increased in the fetuses of rats exposed to 1000 ppm CCl_4.

Considerable hepatotoxicity was observed in the dams at both concentrations. The authors concluded that carbon tetrachloride is not teratogenic, but is embryo toxic at these concentrations, and that these are not related to hepatotoxicity in the mothers. Smyth et al. (284) observed three generations of rats exposed to 50–400 ppm vapor. In these studies no evidence of reduced fertility or embryonic or fetal abnormalities were observed.

Alumot et al. (279) fed rats diets fumigated with carbon tetrachloride for ≤ 2 years. Storage of diets was in hematically sealed containers and diets were assayed at 80 ± 5 and 200 ± 20 ppm CCl_4. The females were rebred at 2-month intervals for a total of seven matings. From this somewhat unusual experimental design, they concluded that exposure of both male and female rats to diets containing 80–200 ppm had no effect on male fertility, female fertility, or reproductive parameters. On the basis of food consumption during the 2-year period, this amounted to 10–18 mg/kg/day.

After 6 months of repeated 7-h exposure to 200 ppm vapor, the testicular germinal epithelium of rats was adversely affected, perhaps as a secondary effect (278).

10.4.1.5 Carcinogenesis The USEPA (5) classifies carbon tetrachloride as B2 (Animal carcinogenicity data is sufficient); probable human carcinogen on the basis of carcinogenicity in rats, mice, and hamsters. Carbon tetrachloride has produced hepatocellular carcinomas in rats, mice, and hamsters, the species evaluated to date.

Hepatocellular carcinomas developed in Osborne–Mendel, Japanese, and Wistar rats, but not Sprague–Dawley or black rats, following subcutaneous (SC) injection of carbon tetrachloride. Hyperplastic nodules were noted in Buffalo rats treated SC (285–287). Sensitivity varied among strains, and trends in incidence appeared inversely related to severity of cirrhosis. Fifty Osborne–Mendel rats/sex were administered carbon tetrachloride by corn oil gavage at 47 and 94 mg/kg/injection for males and 80 and 159 mg/kg for females 5 times/week for 78 weeks. At 110 weeks, only 7/50 high-dose males and 14/50 high-dose females survived; 14/50 low-dose males and 20/50 low-dose females survived. The incidence of hepatocellular carcinomas was increased in animals exposed to carbon tetrachloride as compared with pooled colony controls. The apparent decrease in the incidence of hepatocellular carcinomas in high dose female rats compared with the low dose females (1/14 *vs.* 4/20, respectively) was attributed by the authors to increased lethality before tumors could be expressed (288–290). In this same study, using the same dosing schedule, male and female $B6C3F_1$ mice received 1250 or 2500 mg/kg carbon tetrachloride. The incidences of hepatocellular carcinomas in males were 5/77, 49/49, and 47/48 in the control, low and high dose groups, respectively, and 1/80, 40/40, and 43/45 in the control, low, and high dose groups, respectively.

Carbon tetrachloride administered by gavage has also been shown to produce neoplastic changes in livers of five additional strains of mice (C3H, A, Y, C, and L). In the last study, 56 male and 19 female L mice, which have a low incidence of spontaneous hepatomas, were treated with 0.1 mL of

40% carbon tetrachloride 2 or 3 times/week over 4 months, for a total of 46 treatments. Animals were killed 3–3.5 months after the last treatment. The combined hepatoma incidence of treated male mice was 47% (7/15 *vs.* 2/71 in the untreated male controls); treated females showed an incidence of 38% (3/8 *vs.* 0/81 in the untreated female controls).

As part of a large study of liver carcinogens, Della Porta et al. (290a) treated Syrian golden hamsters (10/sex/dose) with carbon tetrachloride by gavage, weekly for 30 weeks. For the first 7 weeks, 0.25 mL of 0.05% carbon tetrachloride in corn oil was administered; this dose was halved for the remainder of the exposure period. All animals were observed for an additional 25 weeks. All of the 10 hamsters that were killed or died between weeks 43 and 55 had liver cell carcinomas, compared with none in controls.

IARC (294, 295) states that there is sufficient evidence for the carcinogenicity of carbon tetrachloride in experimental animals. When administered by gavage, carbon tetrachloride increased the incidences of hepatomas and hepatocellular carcinomas in mice of both sexes. By the same route of administration, the compound increased the incidence of neoplastic nodules of the liver in rats of both sexes. When administered by subcutaneous injection, carbon tetrachloride induced hepatocellular carcinomas in male rats and mammary adenocarcinomas and fibroadenomas in female rats. When administered by inhalation, carbon tetrachloride induced liver carcinomas in rats. When administered intrarectally, the compound induced nodular hyperplasia of the liver in male mice.

10.4.1.6 Genetic and Related Cellular Effects Studies Carbon tetrachloride was not mutagenic to either *S. typhimurium* or *E. coli*. At low concentrations, carbon tetrachloride did not produce chromatid or chromosomal aberrations in an epithelial cell line derived from rat liver (291). *In vivo* unscheduled DNA synthesis assays have likewise been negative in male Fischer 344 rats (292). Carbon tetrachloride produced mitotic recombination and gene conversion in *Saccharomyces cerevisiae*, but only at concentrations that reduced viability to 10% (160). Carbon tetrachloride may be metabolized to reactive intermediates capable of binding to cellular nucleophilic macromolecules. Negative responses in bacterial mutagenicity assays may have been due to inadequate metabolic activation in the test systems.

10.4.2 Human Experience 10.4.2.1 General Information Symptoms of exposure to this compound may include headache, mental confusion, CNS depression, fatigue, anorexia, nausea, vomiting, coma, abdominal cramps, dizziness, unconsciousness, weakness, amnesia, paresthesia, tremors, jaundice, and liver and kidney damage. It may also cause depression, loss of appetite, bronchitis, internal irritation, stupor, and damage to the heart and nervous system. Skin contact may remove the natural lipid cover of the skin and it may also lead to a dry, scaly, fissured dermatitis. Other symptoms include GI disturbances, abdominal pain, diarrhea, enlarged and tender liver, toxic hepatitis, diminished urinary volume, red and white blood cells in the urine, and albuminuria. It may also cause narcosis, lung damage, acute nephrosis of the kidney, polyneuritis, narrowing of visual fields and other neurological changes, cirrhosis of the liver, lacrimation, burning of the eyes, malaise, dark urine, renal casts, uremia, epigastric distress, visual disturbances (such as blind spots, spots before the eyes, visual “haze” and restriction of the visual fields), and death. Exposure to this compound depresses and injures almost all cells of the body, including the CNS, liver, kidney, and blood vessels. Depression of the heart muscle may result in ventricular arrhythmias. Damage to the kidneys may result in marked edema and fatty degeneration of the tubules. Other symptoms include slowed respiration, slowed or irregular pulse, fall of blood pressure, sudden weight gain, azotemia, anemia, blurred vision, and loss of peripheral color vision. It may also cause drowsiness, giddiness, oliguria, cellular necrosis of the liver, acute nephritis, and aplastic anemia. Eye and skin irritation, dyspnea, hematemesis, hematuria, proteinuria, weight loss, cyanosis, and miosis have also been reported. Ingestion of this compound with alcohol will intensify the effects of the chemical. Other symptoms include hepatomegaly, optic atrophy, optic neuritis, and pulmonary edema. It may also cause a permanent reduction in vision, deafness, and retrobulbar neuritis. Mucous membrane irritation and anesthesia have also been reported. Hepatic nodular hyperplasia may also occur. Other symptoms include sleepiness, increased peristalsis, erythema, gastroenteritis, and death from

ventricular fibrillation. It may cause disorientation. Alveolitis has occurred. It may cause irritation of the nose and throat, a sense of fullness in the head, convulsions, hepatic steatosis, hypertension, acidosis, and sudden death from depression of vital medullary centers. Other symptoms include flatulence, fatty liver, elevated SGOT, and elevated serum bilirubin. It may also cause incoordination, vertigo, and increased nitrogen retention. Other symptoms are pupillary constriction, unspecified respiratory system and GI system effects, somnolence, severe GI upset, and liver enlargement (273).

Numerous reports of injury and death following acute and repeated exposure of humans to carbon tetrachloride can be found. Few, if any, epidemiological, studies have been completed on an occupationally exposed population, nor have there been laboratory studies of long duration.

Stewart and Dodd (167) and Stewart et al. (271) have conducted experimental human exposure studies with volunteer subjects. These reports indicate that absorption of the liquid through the skin may be significant, particularly in chronic exposure. They have also determined the concentration of carbon tetrachloride in expired air following exposure to the vapor.

10.4.2.2.5 Carcinogenesis An IARC Working Group (294, 295) reported that there were no adequate data to evaluate the carcinogenicity of carbon tetrachloride in humans. Three case reports described liver tumors associated with cirrhosis in humans exposed to carbon tetrachloride. A mortality study of laundry and dry cleaning workers exposed to a variety of solvents suggested an excess of respiratory cancers, liver tumors, and leukemia.

The EPA considers the human data re: carcinogenesis as “inadequate.” There have been three case reports of liver tumors developing after carbon tetrachloride exposure. Several studies of workers (293) who may have used carbon tetrachloride have suggested that these workers may have an excess risk of cancer.

The International Agency for Research on Cancer (IARC) reviewed the available carcinogenicity data in 1972 (294) and again in 1979 (295). Carbon tetrachloride is grouped with 18 chemicals considered “probably carcinogenic for humans” and, according to IARC, is to be regarded “as if it presented a carcinogenic risk to humans.” The EPA reached a similar conclusion in 1988 (296). In a study by the NCI bioassay program, hepatocellular carcinomas developed in mice that received gavaged daily doses of 2500 or 1250 mg/kg for 78 weeks (297). These massive doses also resulted in adrenal tumors. The amount of noncancerous pathology in the liver was not discussed, but may have been significant. Rats were fed doses of 100 (male) or 150 (female) mg/kg, 5 days/week for 78 weeks and then kept for 32 additional weeks. Half of these doses were fed to second groups of rats. According to Weisburger (297), in rats “carbon tetrachloride caused neoplastic nodules and a few carcinomas of the liver. However, the incidence was lower than anticipated.”

Considering the low mutagenic activity and the failure to alkylate DNA, a relationship of liver injury to causation of liver tumors seems plausible.

There appear to be no data on tumors resulting from inhalation of carbon tetrachloride.

10.5 Standards, Regulations, or Guidelines of Exposure

Exposure limits: NIOSH carcinogen, lowest feasible concentration, with a STEL of 2 ppm and an IDLH of 200 ppm. OSHA PEL is 10 ppm, ceiling is 25 ppm and 5-min peak in any 4 hrs is 200 ppm. The ACGIH TLV TWA is 5 ppm and the STEL/C is 10 ppm with an A2 notation.

CPSC banned the use of carbon tetrachloride under the authority of the Federal Hazardous Substances Act (FHSA), as well as mixtures containing the chemical, except for unavoidable manufacturing residues of carbon tetrachloride in other chemicals that do not, during use, result in an air concentration greater than 10 ppm. EPA regulates carbon tetrachloride under the Clean Air Act (CAA), Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Food, Drug,

and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Carbon tetrachloride is designated as a hazardous air pollutant under CAA, hazardous waste under RCRA, and a hazardous substance under CWA. Under CAA, EPA has set emission standards for carbon tetrachloride for point-source categories and any stationary source for which the standards apply. Effluent discharge guidelines have been set under CWA. Carbon tetrachloride is subject to reporting rules under CWA, CERCLA, RCRA, and SARA. Under CERCLA, EPA has lowered the reportable quantity (RQ) of 5000 lb established under CWA to 10 lb (SARA final RQ). EPA has banned the use of carbon tetrachloride as a grain fumigant under FIFRA. Under FD&CA, EPA published data collection and labeling requirements for pesticides containing carbon tetrachloride as an inert ingredient. Carbon tetrachloride is regulated as a hazardous constituent of waste under RCRA (hazardous-waste number, U211; regulatory level, 0.5 mg/L). Under SDWA, EPA set a maximum contaminant level goal (MCLG; 0 mg/L) and a maximum contaminant level (MCL; 0.005 mg/L) for carbon tetrachloride. The World Health Organization (WHO) recommends that no detectable residues (limit: 0.01 ppm) of carbon tetrachloride be allowed on food or feed, but permits 50 mg/kg on cooked cereals. FDA regulates, under FD&CA, the amount of carbon tetrachloride in bottled water and indirect food additives.

10.6 Studies on Environmental Impact:

NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons

Jon B. Reid, Ph.D., DABT

11.0 Carbon Tetrabromide

11.0.1 CAS Number:

[*558-13-4*]

11.0.2 Synonyms:

Tetrabromomethane

11.0.3 Trade Names:

Bromid uhlicity (Czech); Carbon bromide

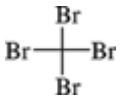
11.0.4 Molecular Weight:

331.63

11.0.5 Molecular Formula:

CBr_4

11.0.6 Molecular Structure:



11.1 Chemical and Physical Properties

11.1.1 General

Physical state	Colorless solid when pure; often yellow to brown
Specific gravity	3.42 (20°C)
Melting point	(*a*) 48.4°C; (*b*) 90.1°C (slight decomposition on melting)
Boiling point	189.5°C (slight decomposition)
Refractive index	1.59998 (99.5°C)
Solubility	0.24 g/100 mL water at 30°C; soluble in ethanol, ethyl ether, chloroform

Flammability Not flammable by standard tests in air

1 mg/L = 74 ppm and 1 ppm = 13.58 mg/m^3 at 25°C, 760 torr

11.1.2 Odor and Warning Properties Carbon tetrabromide has significant lacrimatory effect on the eye at low concentrations. This may be reasonably good warning of acute exposure, but may not be adequate to prevent excessive repeated exposure.

11.2 Production and Use

Carbon tetrabromide is used to a limited extent as a chemical intermediate. It has been isolated from red algae, *Asparagopsis toxiformis*, found in the ocean near Hawaii.

11.3 Exposure Assessment:

NA

11.4 Toxic Effects

Carbon tetrabromide is a highly toxic material, based on the limited amount of toxicologic data available. Little new information is available since the previous edition.

11.4.1 Experimental Studies 11.4.1.1 Acute Toxicity Acute exposure to high concentrations causes upper respiratory irritation and injury to the lungs, liver, and kidneys. The response to chronic exposure at very low concentrations is primarily liver injury. The material is a lacrimator, even at low levels.

The LD_{50} by oral administration was found to be 1800 mg/kg body weight in the rat.

In the eyes of rabbits, the undiluted material caused severe irritation and permanent corneal damage. When the material was promptly washed from the eyes, pain and irritation were noted but the corneal damage was temporary.

Skin contact causes relatively slight irritation in rabbits. If the material is confined tightly to the skin, it may cause hyperemia and a moderate edema. From observations made when the material was repeatedly bandaged onto the skin, there was no indication of toxic absorption, but no attempt was made to quantify the dosage.

The hepatotoxic and nephrotoxic effects of carbon tetrabromide were studied in male Sprague–Dawley rats following a single IP administration in a dose range of 25–125 mL/kg. Carbon tetrabromide did not cause hepatotoxic effects when given alone or in combination wth prior exposure to chlorodecone. It caused renal dysfunction, but these effects were abolished by dietary chlordecone pretreatment. *In vitro* incubation of renal cortical slices obtained from treated animals revealed a significant depression of organic anion transport.

11.4.1.2 Chronic and Subchronic Toxicity Exposure of rats to carbon tetrabromide “fumes” (0.01–1 mg/L) (0.07–74 ppm), 4 h/day for 4 months was reported to cause irritation of the eyes and respiratory tract.

In another (unpublished) study, repeated exposures of rats 7 h/day, 5 days/week for 6 months to the vapors of carbon tetrabromide were studied. When the concentration in air was determined by combustion of air samples and determination of halogen, the concentration without effect was found to be 0.1 ppm by volume. When the concentration in air was determined by a polarographic method, the concentration was 0.3–0.5 ppm by volume. Higher concentrations than this caused poor growth and fatty and degenerative changes in the liver.

11.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The small amount of data that is available suggests that either hydrolysis or metabolism produces some bromide ion. Carbon tetrabromide would not be expected to produce physiologically significant quantities of bromide ion in the blood at levels of exposure considered acceptable by inhalation. Carbon tetrabromide is metabolized *in vitro* to produce carbon monoxide, but the *in vivo* significance has not been established.

Like classic lipid peroxidation chemicals such as carbon tetrachloride, carbon tetrabromide show similar activity. Protein synthesis and lipid peroxidation were evaluated in rat liver slices in the presence of oxidants and protein synthesis inhibitors (2, 3). The ability of carbon tetrabromide (and several other halogenated compounds) to inhibit protein synthesis was correlated with its ability to induce lipid peroxidation and was also correlated with their toxicity as indicated by the LD_{50}. The authors suggest that oxidant-induced lipid peroxidation and protein synthesis damage occurs concurrently, and that protein synthesis inhibition may be involved in cell injury or death mediated by free radicals.

Carbon tetrabromide (as well as some other brominated and chlorinated methanes) undergoes oxidate metabolism to electrophilic halogens by liver microsomes.

11.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV TWA is 0.1 ppm and the STEL/C is 0.3 ppm.

The NIOSH REL is 0.1 ppm with an STEL of 0.3 ppm. OSHA currently does not have a PEL.

International occupational exposure values:

Australia	TWA 0.1 ppm (1.4 mg/m^3); STEL 0.3 ppm (4 mg/m^3) January 1993.
Belgium	TWA 0.1 ppm (1.4 mg/m^3); STEL 0.3 ppm (4.1 mg/m^3) January 1993.
Denmark	TWA 0.1 ppm (1.4 mg/m^3) January 1993.
Finland	TWA 0.1 ppm (1.4 mg/m^3); STEL 0.4 ppm; “skin” notation January 1993.
France	TWA 0.1 ppm (1.4 mg/m^3) January 1993.
Ireland	TWA 0.1 ppm (1.4 mg/m^3); STEL 0.3 ppm (4 mg/m^3) January 1997.
The Netherlands	TWA 0.1 ppm (1.4 mg/m^3) October 1997.
Switzerland	TWA 0.1 ppm (1.4 mg/m^3) January 1993.
United Kingdom	TWA 0.1 ppm (1.4 mg/m^3) STEL/C: 0.3 ppm.

11.6 Studies on Environmental Impact:

NA

Saturated Methyl Halogenated Aliphatic Hydrocarbons

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Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Ethyl Chloride
1.0.1 CAS Number:
[*75-00-3*]
1.0.2 Synonyms:
Chloroethane, hydrochloric ether, monochloroethane, and muriatic ether
1.0.3 Trade Names:
Aethylos chloridium, Anodynon, Chelen, Chlorene, Chloretilo, Chloroethyl, Chloryl, Chloryl anesthetic, Dublofix, Ether chloratus, Hydrochloric ether, Kelene, Monochloroethane, Moriatic ether, Narcotile, and NCI-C06224
1.0.4 Molecular Weight:
64.52
1.0.5 Molecular Formula:
CH_3CH_2Cl
1.0.6 Molecular Structure:

1.1 Chemical and Physical Properties
Ethyl chloride is a colorless gas with an ethereal, somewhat pungent odor and burning taste. It is highly flammable, even at ordinary temperature and pressure, and a severe fire and explosion risk. Under increased pressure and lower temperatures, it is a very volatile liquid.

Physical	Colorless gas
Specific gravity	0.8917 (25/25°C)0.897 at 20°C
Melting Point	–138.7
Boiling Point	12.3
Vapor pressure	1200 torr (25°C) 1000 torr at 20°C
Solubility	0.57g/100 mL water at 20°C, 48 g/100 mL ethanol at 21°C 0.6% in H_2O
Flammability limits	3.8–15.4% by volume in air
Autoignition temperature	519°C
Flash point	–50°C (closed cup); –43°C (open cup)

1.1.1 General The principal problem in industrial use of ethyl chloride is that typical of an anesthetic material where “drunkenness” and incoordination may lead to inept operation and therefore the possibility of an injury. Cardiac arrhythmia are possible, but high concentrations are required (6). The older data were summarized by von Oettingen (7), and an ATSDR profile (update) has been published by the U.S. Public Health Service in December, 1998 (8).

1.1.2 Odor and Warning Properties Ethyl chloride has an ethereal, somewhat pungent odor recognizable at concentrations of 100–600 ppm (9). High concentrations are necessary for potentially serious physiological effects, which may be considered a possible warning property for acute effects. According to AD Little (9), in humans, 50% of the subjects detected the odor of ethyl chloride at 140 ppm and 100% detected 680 ppm. An odor threshold of 4.2 ppm has been reported by Amoore (10).

1.2 Production and Use

Ethyl chloride is used in the manufacture of tetraethyl lead, ethylcellulose, dyes, drugs, and perfumes. It is also used as an alkylating and analytical agent, in organic syntheses, and as a solvent for fats, oils, waxes, phosphorus, acetylene, and many resins. It is also used as a propellant, an anesthetic, in refrigeration, and in the formulation of insecticides. Ethyl chloride has been used as a chemical intermediate, as a topical anesthetic, and to a limited degree as a refrigerant. The most serious problems have been with its use as an anesthetic. The major problems encountered in industry has been fire and explosion.

1.3 Exposure Assessment

According to the ATSDR toxicity profile (8), humans can be exposed to chloroethane from environmental, occupational, and consumer sources. In the 1970s and 1980s, chloroethane was found in outdoor air at levels of 41–140 ppt, but current levels are expected to be lower because of decreased production. Extremely low levels of chloroethane are present in drinking water, which may form during chlorination. There are no data on chloroethane in food. Exposure can result from contact with consumer products such as paints and refrigerants via skin. Occupational exposure may result from inhalation or skin contact. According to a NIOSH survey between 1981 and 1983, an estimated 49,212 workers in the United States were exposed to chloroethane in the workplace at that time.

1.3.1 Air See the preceding.

1.3.2 Background Levels See the preceding.

1.3.3 Workplace Methods NIOSH Method 2519 is recommended for determining workplace exposures to ethyl chloride.

1.3.4 Community Methods Environmental methods are given in the ATSDR profile (8). These address: ambient air, air from a contaminated site, air from a landfill, raw/treated water, finished drinking/ raw source water, water, wastewater, groundwater, soil and sediment, solid and liquid

waste.

1.3.5 Biomonitoring/Biomarkers Biological monitoring of expired air would appear to be of little value owing to the physical properties of ethyl chloride, which suggest rapid excretion.

The ATSDR profile (8) gives a table of methods for biological samples, including exhaled air, human milk, blood and urine, urine and adipose tissue, and also for fish and marine biota. The purge and trap method is used for both environmental and biological samples.

1.3.5.1 Blood The ATSDR profile (8) offers a method for blood and urine: The sample is mixed with water and antifoaming agent, purged at 50°C, trapped in Tenax, and thermal desorption, followed by Cryofocus—using high-resolution gas chromatography, flame ionization chromatography, and mass spectrometry. The detection limit is 3 mg/L of blood and 3 mg/L of urine with >80% recovery.

1.3.5.2 Urine See the preceding.

1.4 Toxic Effects

According to Sax (1) ethyl chloride has moderate toxicity via oral and inhalation routes. It is an irritant of skin, eyes, and mucous membranes. The liquid is harmful to the eyes and can cause smoke irritation. In the case of guinea pigs, symptoms attending exposure are similar to those caused by methyl chloride, except that the signs of lung irritation are not as pronounced. It gives some warning of its presence because it is irritating, but it is possible to tolerate an exposure until one becomes unconscious. It is the least toxic of all the chlorinated hydrocarbons, but at high concentrations ethyl chloride can cause narcosis, anesthesia, and even death on single exposure. It can cause narcosis, although the effects are usually transient. Animal experiments show some evidence of kidney irritation and accumulation of fat due to this material in the kidneys, cardiac mucles, and liver. It is also readily absorbed through the skin. It is a highly dangerous fire hazard and forms phosgene on combustion. When heated to decomposition, ethyl chloride may emit toxic fumes of HCl and may also release fumes of CO.

1.4.1 Experimental Studies 1.4.1.1 Acute Toxicity A single reference reports allergic eczematous eruption in two subjects after ethyl chloride was sprayed on the skin in an allergy-testing procedure (11). The wide use of ethyl chloride as a local anesthetic suggests that these must have been rare subjects.

Rats were anesthetized for 2 h with ethyl chloride (12). Complete disappearance of glycogen in the liver, a decrease in acid phosphatase levels, and increases in alkaline phosphatase and succinic dehydrogenase levels were reported.

A 2 h LC_{50} of 152 mg/L (57,600 ppm) has been reported (13). Deaths were anesthetic in nature but hyperemia, edema, and hemorrhages were reported in the internal organs, brain, and lungs. Repeated 2 h exposures for 60 d to 14 mg/L (5300 ppm) were alleged to cause a decrease in the phagocytic activity of the leukocytes, lowered hippuric acid formation in the liver, and histological or pathological changes in the liver, brain, and lungs. However, Troshina's results are not consistent with newer data. In the limited study on rats and dogs, exposures to 0, 1600, 4000, or 10,000 ppm were given 6 h/d, 5 d/wk for 2 wk (14) there were no adverse effects on any of the extensive number of toxicological parameters studied except for a slight increase in liver to body weight ratios in rats exposed to 4000 and 10,000 ppm. Nonprotein sulfhydryl was decreased in rats and mice.

In a 11 d study in which mice were exposed 23 h/d to 0, 250, 1250, or 5000 ppm the only effect was a slight liver weight increase and hepatocellular vacuolization at 5000 ppm (17). In a teratological study at 0, 500, 1500, or 5000 ppm reported in a subsequent section, no toxicologic effects were noted in pregnant mice after 10 consecutive 6 h daily exposures to 500, 1500, or 5000 ppm (18). As part of a lifetime carcinogenic study also reported in a subsequent section, rats and mice were exposed 1, 10, or 65 times (19). Then 6 h exposures 5 d/wk for 14 d to 19,000 ppm also produced no

evidence of toxicity in male and female rats.

Ethyl chloride has been demonstrated to be a cardiac sensitizer (31) in dogs at or near concentrations producing anesthesia, 30,000–45,000 ppm (32). In this condition, cardiac tissue is hypersensitized to the effects of stimulatory endogenous catecholamines, which can result in arrhythmias and cardiac arrest.

1.4.1.2 Chronic and Subchronic Toxicity In a 13 wk study, rats were exposed 6 h/d, 5 d/w (65 exposures) to 0, 2500, 5000, 10,000 or 19,000 ppm. The only effect was a slight liver weight increase at 19,000 ppm as well as slightly lowered body weights in both sexes. Based on the effects seen with similar compounds, and limited data on dogs, sensitization of the heart to adrenaline could be a hazard at very high (anesthetic) concentrations (20, 21). It is not possible to determine whether deaths that occurred during the short period of time it was used as a general anesthetic were due to anesthesia and/or cardiac toxicity or to some other conditions related to surgery.

In an NTP study (19), groups of F344 rats and $B6C3F_1$ mice (50/group/sex) were exposed to either 0 (air) or 15,000 ppm of 99.5% ethyl chloride (39.6 g/m^3) 5 d/wk, 6 h/d for 102 wk (rats) or 100 wk (mice). The duration-adjusted concentration becomes 7.1 g/m^3. The exposure level was set at this limit because of safety considerations for explosions. A single level of exposure was chosen as no exposure-related changes were seen in the 90-d study at a slightly higher concentration (19,000 ppm). Survival of female mice after week 82 was significantly lower than controls, apparently due to an increase in deaths from carcinomas of the uterus; there were no other statistically significant differences in survival between control and treated animals of either species. Mean body weights were decreased in both male and female rats. In females, the maximum difference in body wieghts between exposed and control animals was 13% and occurred at 59 wk of exposure when 49 of 50 test animals were still alive. Although some fluctuations towards normalcy were observed from this time forward, terminal body weights of 23 surviving treated animals were still 10% less than their corresponding controls. In male rats, mean body weights were also decreased when compared with controls, although the decrease achieved a miximum differential of only 8%. The mean body weights of mice were not affected by exposure. Based on the mild decrease in mean body weight gain, 15,000 ppm is judged as a free-standing NOAEL. The NOAEL (HEC) = 7.1 g/m^3.

Groups of F344 rats and $B6C3F_1$ mice (10/group) were exposed to either 0 (air), 2500 ppm (6.6 g/m^3), 5000 ppm (13.2 g/m^3), 10,000 ppm (26.4 g/m^3), or 19,000 ppm (50.1 g/m^3) of 99.5% ethyl chloride 5 d/wk, 6 h/d for 13 wk (19). The duration-adjusted concentrations are 0, 1.2, 2.4, 4.7, or 9.0 g/m^3, respectively. Monitoring for toxicological effects was by daily observation, body weights, and a complete necropsy and histologic examination including tissues of the entire respiratory tract and brian.

No exposure-related clinical signs or gross or histopathological effects were observed in either species. Relative liver weights were slightly increased in the male rats (14%) and female mice (18%) exposed to 19,000 ppm. Slight decreases in mean body weights were noted in the rats (8% in the males, 4% in the females) exposed to 19,000 ppm; no dose-related tendency could be discerned from the data. As no toxicity was apparent, 19,000 ppm is considered as a free-standing NOAEL in this study. The NOAEL(HEC)= 9.0 $g/m.^3$

The results obtained in the two studies of Troshina (13, 22) are not consistent with those of NTP (19) or Landy et al. (14, 17). Deficiencies preclude consideration of these studies as a reliable source of information about the toxic effects of this chemical.

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Conjugation with glutathione has been shown to occur at a much higher rate in mice than rats (25). These data suggest that this conjugation,

which is species specific and dose dependent, may be extremely important in understanding the development of toxicity and tumors in female mice. A nongenetic (hormonal) mechanism of uterine tumors induction has been suggested.

1.4.1.4 Reproductive and Developmental In a developmental study conducted in groups of 30 CF-1 mice, Scortichini et al. (18) exposed animals to mean time-weighted averages of 0 (air), 491 ± 37 ppm (1.3 g/m^3), 1504 ± 84 ppm (4000 mg/m^3), and 4946 ± 159 ppm (13,000 mg/m^3) 99.9% ethyl chloride for 6 h/d on days 6 through 15 of gestation. The animals were sacrificed on the eighteenth day of gestation. (These values are not duration adjusted.) This study shows that exposure to ethyl chloride results in fetotoxicity. The exposure concentration of 1504 ppm is the NOAEL of this study NOAEL(HEC) = 4000 mg/m^3 based on foramina of the skull bones. The highest concentration used in this study, 4946 ppm, is a LOAEL, (HEC) = 13,000 mg/m^3.

According to Hanley et al. (23), the reproductive organs were not affected following subchronic inhalation exposures to ethyl chloride. Exposures to mice at concentrations of 500, 1500, or 5000 ppm during organogenesis produced no teratogenic effects. The presence of a few small unossified areas in the skull bones at 5000 ppm suggest very slight fetotoxicity.

Experiments conducted by Breslin et al. (24) suggest that exposure to ethyl chloride may disrupt the estrus cycle of mice. Two groups (10/group) of female B6C3F$_1$ mice were acclimated in exposure chambers over a 2 wk period or until the estrus cycles of most mice was a 4–6 d interval (as judged by a vaginal lavage technique). Males were included in each chamber to synchronize and promote regular estrus cyclicity. Following acclimatization one group was exposed to 15,000 ppm (39.6 g/m^3 ethyl chloride 6 h/d for a minimum of 14 consecutive days (through 3 estrus cycles). No effects on behavior, gross, or histopathology were observed in the group undergoing exposure, although the mean body weights in the exposed group were significantly increased rather than decreased. The mean length of the estrus cycle in exposed mice was 5.6 d, significantly longer in duration than the pre-exposure duration for the same group (5.0 d) and for the corresponding controls (4.5 d). The protraction of the period could not be attributed to an increase in any particular phase of the estrus cycle and is therefore suggestive of a general stress response. A direct exposure-related effect of ethyl chloride on neuroendocrine function cannot be excluded. As this effect is regarded as a systemic effect, the exposure is duration adjusted to establish a free-standing LOAEL of 6.6 g/m^3. The LOAEL(HEC) = 6.6 g/m^3.

1.4.1.5 Carcinogenesis The EPA (IRIS) has not made a carcinogenicity assessment at this time.

Increased cancer of the uterus of female mice has been produced by exposure to 15,000 ppm, but lower concentrations have not been studied. Rats and mice were exposed to 0 or 15,000 ppm of ethyl chloride in an NTP 2-year study with mixed results (19). Results in male rats were considered equivocal based on a combined total of five skin tumors versus none in the control male rats. Likewise female rats results were considered equivocal because three astrocytomas were found versus none in the female control rats. The male mouse group had such poor survival that it was deemed an inadequate study although combined alveolar/bronchiolar adenomas and carcinomas were reported (10/48 versus 5/50 in the control male rats). Female mice exposed to 15,000 ppm had clear evidence of an effect, for 43/50 mice had endometrial uterine carcinomas versus 0/49 in the female control mice. In addition, there was a suggestion of an increase in combined hepatocellular adenomas and carcinomas in the female mice (8/48 exposed versus 3/49 control).

1.4.1.6 Genetic and Related Cellular Effects Studies According to the NTP report of carcinogenic studies, ethyl chloride was found to be mutagenic in *Salmonella* both with and without S-9 activation. The report considers the effect to be consistent with alkylating activity in base substitution strains TA100 and TA1535. Studies of chromosomal aberration in the bone marrow of mice exposed for 2 years were negative (19), as were all transformation studies in mouse BALB/c-

3T3 cells (26).

1.4.2 Human Experience Exposure to ethyl chloride can cause irritation of the eyes. It can also be iritating to the nose, throat, and respiratory tract. At concentrations of approximately 2% (molar), it can cause an anesthetic or narcotic effect. This can result in headache and nausea and also dizziness. At higher concentrations, exposure can cause unconsciousness. It may also produce central nervous system depression. This depression is usually brief and reversible. Due to its rapid rate of evaporation, it can cause tissue freezing or frostbite on dermal contact. Other symptoms include drowsiness, noisy talkativeness, and sensitizing effects on the myocardium. It may also cause irregular heart beat. It may cause liver and kidney damage, incoordination, and abdominal cramps. It may cause slight symptoms of inebriation. Exposure may also cause lung irritation, damage to internal organs, excitement, and paralysis of respiration. It may cause lung damage. Ethyl chloride may irritate the kidneys and cause fat accumulation in the kidneys, cardiac muscles, and liver. It is absorbed readily through the lungs, and rapidly given off through the lungs. Other symptoms reported include cardiac arrhythmias at high concentrations; rare allergic eczematous eruptions when sprayed on skin; and hyperemia, edema, and hemorrhages in the internal organs, brain, and lungs. It may also cause weak analgesia. It may cause stupor. The most serious problem from severe acute exposure, other than the anesthetic effect, is the possibility of the potentiation of adrenalin, and the resultant cardiac problems (27, p. 247). Exposure to this compound may cause death due to respiratory or cardiac arrest. Deaths are anesthetic in nature.

Although used as a surgical anesthetic, ethyl chloride has a narrow margin of safety for this purpose as anesthesia occurs at 20–30 mg % and respiratory failure at 40 mg % (28). Ethyl chloride is explosive at 4% (40,000 ppm, 106 g/m^3) in air, overlapping the concentrations required to produce anesthesia (3–4.5%) Neurological symptoms have been observed in human case studies in instances of ethyl chloride abuse. Hes et al. (29) noted cerebellar-related symptoms including ataxia, tremors, dysarthria (speech difficulties), slowed reflexes, nystagmus (involuntary movement of the eyeball), and hallucinations in a 28-year old female who sniffed 200–300 mL of ethyl chloride off her coat sleeve daily for 4 mo. Examination revealed that her liver was enlarged (3 cm) and slightly tender and was accompanied by a mild and transient disturbance (not clinically described) of liver function. All symptoms were resolved by the end of 4 wks. Similar neurological symptoms were noted in a 52-year-old male who had a 30-year history of intermittent ethyl chloride (as well as alcohol and barbiturate) abuse (30). Questioning upon hospitalization revealed that he had been inhaling at least 100 mL of ethyl chloride daily for the previous 4 mo. No liver effects were reported, and the patient fully recovered from the neurological symptoms by 6 wk after admission.

Ethyl chloride has been used experimentally and clinically as a topical and inhalation anesthetic in human subjects; reviews are available (6, 7).

In a study by Davidson (33) ethyl chloride was administered to humans. Intoxication started at 1.3%, memory loss at 1.9%, incoordination at 2.5%, and at 3.36%, incoordination was followed by cyanosis, nausea, and vomiting.

1.4.2.1 General Information The acute toxicity for animals was reported by Sayers et al. (15) (see Table 63.1) and the narcotic concentrations for humans were reported by Lehann and Flury (16) (see Table 63.2). More recent data have not changed their conclusion significantly.

Table 63.1. Response of Guinea Pigs to Ethyl Chloride Vapor in Air (15)

Concentration (%)	Exposure time (min)	Response
23–24	5–10	Unconscious, some deaths

15.3	40	Some deaths in 30 min; some survived 40 min
9.1	30	Survived; histopathological changes in lungs, liver, etc.
5	40	Survived; lungs congested
4	122	Survived; returned to normal
	270	Survived; histopathological changes in lungs, liver, and kidneys
	540	Some deaths
2	270	Survived; returned to normal
	540	Survived; histopathological changes in liver and kidneys
1	810	Survived; returned to normal

Table 63.2. Narcotic Ethyl Chloride Concentrations in Humans
Concentrations in Humans

Concentration		
mg/L	**ppm**	**Response**
105.6	40,000	After 2 inhalations, stupor, irritation of eyes, and stomach cramps
88.7	33,000	After 30 sec, quickly increased toxic effect
66.0	25,000	Lack of coordination
52.8	20,000	After 4 inhalations, dizziness and slight abdominal cramps
50.4	19,000	Weak analgesia after 12 min
34.3	13,000	Slight symptoms of poisoning

1.4.2.2.4 Reproductive and Developmental Early and late pregnancy toxemias have been observed in women occupationally exposed to ethyl chloride and other chemicals such as ethyl bromide and butanol (34).

Women who were exposed occupationally to unknown concentrations of ethyl chloride along with ethylenediamine, ammonia, polyethylene polyamines, vinyl chloride, and hot summer temperatures had genital disorders that included inflammatory diseases of the cervix and uterus and vaginitis (35).

1.4.2.2.5 Carcinogenesis The EPA (IRIS) has not made a carcinogenicity assessment at this time (36).
1.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV TWA is 100 ppm with an A3 designation (confirmed animal carcinogen with

unknown relevance to humans). The NIOSH considers that ethyl chloride be treated in the workplace with caution because if its structural similarity to chloroethanes shown to be carcinogenic in animals. The OSHA PEL is 1000 ppm.

Other Nations:

Australia: 1000 ppm (1993); Federal Republic of Germany: no MAK, Group B carcinogen, justifiably suspected of having carcinogenic potential (1995); Sweden: 500 ppm, short-term value 700 ppm, 15 min (1993); United Kingdom: 1000 ppm, 15 min STEL 1250 ppm (1995).
1.6 Studies of Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

1,1-Dichloroethane
2.0.1 CAS Number:
[*75-34-3*]
2.0.2 Synonyms:
Ethylidene chloride, ethylidene dichloride
2.0.3 Trade Names:
Chlorinated hydrochloric Ether, HSDB 64
2.0.4 Molecular Weight:
98.97
2.0.5 Molecular Formula:
CH_3CHCl_2
2.0.6 Molecular Structure:

2.1 Chemical and Physical Properties
Dichloroethane-1,1 is a colorless, oily liquid with a chloroformlike odor.

Physical state	Colorless liquid
Specific gravity	1.175 (20°C)
Melting point	–96.98°C
Boiling point	57.3°C
Vapor pressure	234 torr (25°C)
Refractive index	1.41655 (20°C)
Percent in “saturated;”air	30.8(25°C)
Solubility	0.5 g/100 MI water at 20°C; soluble in (5500 mg/L) ethanol, ethyl ether
Flash point	14°C (open cup); –8.33°C (closed cup)
Flammability limits	5.6–11.4% by volume in air
Ignition temperature	493°C

2.1.1 General

2.1.2 Odor and Warning Properties 1,1-Dichloroethane has been stated to have a “chloroformlike” odor, but the level at which this odor is detectable has not been determined.
2.2 Producton and Use
1,1-Dichloroethane is flammable and has limited use as a solvent. Its major use is as a chemical intermediate. Formerly used as an anesthetic, it is of no importance in this field today. It appears to be an environmental breakdown product of some commonly used chlorinated solvents. An ATSDR toxicology profile is available (3).
2.3 Exposure Assessment
Exposure routes are inhalation, ingestion, skin, and/or eye contat. The substance can be absorbed into the body by inhalation and by ingestion. A harmful concentration in the air can be reached rather quickly on evaporation of this substance at 20°C. The vapor is heavier than air and may travel along the ground; distant ignition possible.

2.3.3 Workplace Methods NIOSH Method 1003 for halogenated hydrocarbons is recommended for determining workplace exposures to 1,1-dichloroethane.

2.3.5 Biomonitoring/Biomarkers Although biologic monitoring for expired 1,1-dichloroethane in air might be useful for determining recent exposure, inadequate data are available to quantify exposure. Urinary metabolites (dichloroacetic acid and monochloroacetic acid) would be expected only in low concentrations if present at all.
2.4 Toxic Effects
1,1-Dichloroethane may be harmful by inhalation, ingestion, or skin absorption. Vapor or mist is irritating to the eyes, mucous membranes, skin, and upper respiratory tract. When heated to decomposition, it emits toxic fumes of carbon monoxide, carbon dioxide, hydrogen chloride gas, and phosgene. It is narcotic in high concentrations. It may also have anesthetic effects at high concentrations. It is a lacrimator.

Much less has been published on the toxicity of 1,1-dichloroethane than on its more toxic isomer 1,2-dichloroethane (ethylene dichloride). 1,1-Dichloroethane is rather low in toxicity. It is capable of causing anesthesia, but has a relatively low capacity to cause liver or kidney injury even on repeated exposure. Massive doses by gavage in oil were questionably carcinogenic in rats and mice, but when fed in drinking water, no increase in liver cancer occurred in a limited study in male mice.

2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity Although the 1985 NIOSH Registry of Toxic Effects of Chemical Substances (42) lists an oral. LD_{50} of 725 mg/kg for rats based on a 1967 article, this must be an error, because repeated daily doses higher than this were given by gavage for 78 wk (43). No original reference is given for a report of an oral LD_{50} of 14.1 g/kg for rats.

In a study by Muralidhara et al. (44), adult male Sprague–Dawley rats were given single doses of 0, 0.5, 1.0, 2.0, 4.0, and 8.0 g/kg in corn oil. There was significant mortality only at 8 g/kg and no evidence of treatment-related effects on serum or urinary enzyme levels, organ weights, or tissue morphology. Rats received repeated oral doses of 0, 0.5, 1.0, 2.0, or 4.0 g/kg 5 d/wk for 12 wk. There was marked CNS depression and high mortality only in the 4-g/kg group but little evidence of toxicity other than transient CNS depression at lower levels.

Inhalation Acute: In 1956, Smyth (45) found that rats survived an 8 h exposure to 4000 ppm but were killed by 16,000 ppm. Deaths were probably due to anesthesia.

Schwetz et al. (46) showed that pregnant and nonpregnant rats survived 10 repeated 7 h exposures to 6000 ppm with no effect except for a slight liver weight increases in nonpregnant rats.

Intraperitoneal: Plaa and Larson (47) found little liver and kidney toxicity following intraperitoneal

injection. Doses of 1000 mg/kg produced no renal necrosis in mice but some evidence of tubular swelling was reported. Urinary protein was increased after injection of 2000 mg/kg and urinary glucose increased after 4000 mg/kg.

Klinkead and Leahy (48) report on a 4 h male, rat, inhalation exposure which gave a LC_{50} of ca. 13,000 ppm. In the same paper the authors reported no toxic effects in rabbits dermally exposed to an upper limit of 2 mL/kg body weight for 24 h for 14 d.

Mueller (49) observed anesthetic effects in mice that inhaled 8,000–10,000 ppm for 2 h with a minimum lethal dose of 17,300 ppm.

2.4.1.2 Chronic and Subchronic Toxicity In two studies by Muralindhara and Ramanthan (44), rats were given a single oral bolus of 0, 500, 1000, 2000, or 4000 mg 1,1-dichloroethane/kg body weight for 5 or 10 consecutive days. Glutathione showed a dose-dependent increase in the kidney after 5 and 10 d of exposure, but liver GSH and other indices were not different from controls. Reported in the same paper was a subchronic study where rats were given single oral doses of 0, 500, 1000, 2000, or 4000 mg/kg body weight 5 d/wk for up to 12 wk. CNS depression, marked and high mortality occurred in the 4000 mg/kg group, but little signs of toxicity were seen at lower dosage levels.

Hofmann et al. (50) reported that rats guinea pigs, rabbits, and cats tolerated 6 h daily exposures to 500 ppm 5 d/wk for 13 wk with no adverse effects. Rats, guinea pigs, and rabbits also tolerated an additional 13 wk at 1000 ppm, but cats showed histological evidence of kidney injury and increased blood urea.

In a study by Schwetz et al. (46) pregnant female rats were exposed on days 6 to 15 of gestation to 3800 or 6000 ppm 1,1-dichloroethane vapors. Exposures were for 7h/d. Essentially no effect occurred in either the dams or fetuses except for slight but statistically significant decreases in food consumption and weight gain by the dams and delayed ossification in the fetuses. No teratological effects were related to exposures. Liver weights of a group of nonpregnant rats were increased by similar exposure, but no histological changes were apparent grossly or microscopically.

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms In a study by McCall et al. (51) the authors proposed that 1,1-dichloroethane is metabolized by hepatic microsomal cytochrome P-450 *in vitro*, and this metabolism is important in the toxicity of the compound.

Mitoma et al. (52) studied the metabolism of 1,1-dichloroethane after chronic oral dosing of adult mice and rats at maximum tolerated doses. The results are presented in Table 63.3. The maximum tolerated dose was 700 mg/kg for rats and 1800 mg/kg for mice. Animals were treated 5 d/wk for 4 wk with unlabeled 1,1-dichloroethane prior to a single gavage dose of labeled material in corn oil. The animals were placed in metabolism cages for 2 d following treatment. Rats excreted 86% as unchanged 1,1-dichloroethane and mice 70%. Total metabolism (primarily CO_2) was 7.5 and 29%, respectively, and the metabolic products were similar in the two species. Although the investigators report radioactivity as “bound” the “binding” may have been due to incorporation as metabolites rather than due to alkylation.

Table 63.3. Metabolic Disposition of Chlorinated Hydrocarbons in Rats and Mice

	Percentage of the Administered Dose Average (S.D.)

Species	Dose (mmol/kg)	Expired Air	CO_2 (*a*)	Excrete (*b*)	Carcass (*c*)	Recovery	Metabolized *a* + *b* + *c* Expired Air
1,1-Dichloroethane							
Rat	7.07	86.13 (8.53)	5.12 (0.43)	0.92 (0.35)	1.41 (0.19)	93.46 (8.45)	7.45
Mouse	18.19	70.42 (5.50)	25.23 (5.37)	1.64 (0.29)	2.43 (1.04)	99.74 (2.81)	29.3
1,2-Dichloroethane							
Rat	1.01	11.48 (7.19)	8.20 (3.93)	69.51 (5.11)	7.05 (1.48)	96.26 (14.07)	84.76
Mouse	1.51	7.65 (7.27)	18.21 (3.22)	81.88 (6.92)	2.37 (0.23)	110.12 (1.85)	102.46
1,1,1-Trichloroethane							
Rat	22.48	83.13 (3.25)	0.87 (0.14)	2.05 (0.46)	1.20 (0.28)	89.26 (3.95)	4.12
Mouse	29.98	92.94 (2.89)	2.01 (0.07)	3.36 (0.35)	0.72 (0.03)	99.04 (3.15)	6.09
1,1,2-Trichloroethane							
Rat	0.52	9.49 (2.64)	5.08 (1.45)	72.10 (11.94)	3.85 (0.54)	90.53 (8.77)	81.03
Mouse	2.24	6.81 (2.10)	3.09 (0.90)	75.92 (1.97)	2.29 (0.29)	88.11 (2.48)	81.3
Trichloroethylene							
Rat	9.89	57.41 (2.97)	1.80 (1.18)	21.64 (2.47)	6.67 (0.92)	87.54 (5.16)	30.11
Mouse	15.22	18.18 (3.59)	3.89 (0.86)	66.65 (4.06)	11.08 (1.78)	99.81 (7.20)	81.62
1,1,2,2-Tetrachloroethane							
Rat	0.59	7.03 (1.01)	1.98 (0.25)	46.01 (0.85)	30.75 (2.10)	85.77 (1.59)	78.74
Mouse	1.19	9.69 (1.13)	10.14 (2.95)	30.29 (0.21)	27.44 (0.74)	77.57 (3.41)	67.87
1,1,1,2-Tetrachloroethane							
Rat	1.19	34.14 (6.91)	1.47 (0.84)	60.09 (5.27)	3.20 (0.80)	98.90 (2.66)	64.76
Mouse	2.38	5.89 (0.08)	2.08 (0.60)	77.21 (3.51)	5.04 (0.58)	90.22 (5.28)	84.33
Tetrachloroethylene							
Rat	6.03	79.19 (8.99)	1.94 (0.69)	2.39 (0.12)	0.77 (0.17)	84.30 (9.17)	5.1
Mouse	5.42	57.46 (9.79)	2.45 (0.48)	14.35 (1.85)	5.40 (1.24)	79.65 (9.13)	22.2
Hexachloroethane							
Rat	2.11	64.55 (6.67)	2.37 (0.76)	6.33 (2.39)	20.02 (3.70)	93.28 (6.23)	28.72

Mouse	4.22	71.51 (5.09)	1.84 (0.94)	16.21 (3.76)	5.90 (1.60)	95.47 (9.59)	23.95

Thompson et al. (53) reported *in vitro* studies that confirmed that little 1,1- dichloroethane is metabolized. Cytochrome P450 appears to play a major role in metabolism and the addition of substances that increase P450 increase metabolism of 1,1-di-chloroethane. Addition of glutathione had a protective effect.

2.4.1.4 Reproductive and Developmental See the study by Schwetz et al. (46) reported in the subchronic/chronic section.

2.4.1.5 Carcinogenesis The EPA (IRIS) (2) classifies 1,1-dichloroethane as C; possible human carcinogen based on no human data and limited evidence of carcinogenicity in two animal species (rats and mice) as shown by an increased incidence of mammary gland adenocarcinomas and hemangiosarcomas in female rats and an increased incidence of hepatocellular carcinomas and benign uterine polyps in mice. The EPA offers no estimate of carcinogenic risk from inhalation or oral exposure. The EPA states (IRIS) that because of similarities in structure and target organs, the carcinogenic evidence for 1,2-dichloroethane is considered to be supportive of the classification of 1,1-dichloroethane in group C, a possible human carcinogen.

The EPA considers the animal carcinogenicity "limited." The NCI bioassay (43), provides limited evidence for the carcinogenicity of 1,1-dichloroethane in Osborne–Mendel rats and $B6C3F_1$ mice. This is based on significant dose-related increases in the incidence of hemangiosarcomas at various sites and mammary carcinomas in female rats and statistically significant increases in the incidence of liver carcinomas in male mice and benign uterine polyps in female mice. The study is limited by high mortality in many groups. The low survival rates precluded the appearance of possible late-developing tumors and decreased the statistical power of this bioassay. Technical-grade 1,1-dichloroethane in corn oil was administered by gavage 5 d/wk for 78 wk to groups of 50 Osborne–Mendel rats/sex/dose. All surviving animals were necropsied following a 33 wk observation period. Due to toxicity, dosing was not continuous (3 wk on, then 1 wk off), making the TWAs for 5 d/wk 382 and 764 mg/kg/d for low- and high-dose males and 475 and 950 mg/kg/d for low- and high-dose females, respectively. Both a vehicle and an untreated (not intubated) control group (20 rats/sex/group) were included in the study. A high incidence of pneumonia (approximately 80%) in all 4 groups of each sex was considered to be the cause for the low survival at termination of the study. Survival at 111 wk was 30, 5, 4, and 8% in the untreated control, the vehicle control, the low-dose, and the high-dose male rat groups, respectively. Survival at termination for the female rat groups was 40, 20, 16, and 18% for the untreated control, vehicle control, low- and high-dose groups, respectively. In female rats there was a statistically significant positive dose-related trend in incidence of hemangiosarcomas (0/19 for matched vehicle controls, 0/50 for the low-dose group, and 4/50 for the high-dose group). The incidence of mammary gland adenocarcinomas (1/20 for the untreated group, 0/19 for the vehicle control group, 1/50 for low-dose, and 5/50 for high-dose groups) showed a statistically significant dose-related positive trend in those female rats surviving at least 52 wk; tumor incidence was 0/16, 1/28, and 5/31 for vehicle control, low- and high-dose groups, respectively. (Tumor incidence at termination for the untreated control females surviving at least 52 wk was not reported.) This bioassay was conducted before the life table tests were implemented; so results adjusted for mortality are not available. No mammary gland adenomas or hemangiosarcomas were observed in the dosed-male rats.

In the same NCI (43) study, groups of 50 $B6C3F_1$ mice/sex/group were administered technical-grade 1,1-dichloroethane in corn oil by gavage 5 d/wk for 70 wk. As in the rat study, the dosage pattern was 3 wk on and 1 wk off; the surviving animals were necropsied 13 wk after the termination of dosing. The TWAs for 5 d/wk for the low- and high-dose groups were 1442 and 2885 mg/kg/d for

male and 1665 and 3331 mg/kg/d for female mice.

Control groups, indentical to those in the rat study and consisting of 20 mice/sex/group, were also used. Survival at termination was 80, 80, 80, and 50% for the untreated control group, the vehicle control group, the low- and high-dose females, respectively. In male mice survival was 35, 55, 62, and 32% in the untreated control group, the vehicle control group, the low- and high-dose groups, respectively. An increased incidence of hepatocellular carcinoma in male mice was not statistically significant by either pairwise or trend test (2/17 in the untreated control group, 1/19 in the vehicle control group, 8/49 in the low-dose, and 8/47 in the high-dose groups). The incidence of hepatocellular carcinoma in male mice surviving at least 52 wk was 1/19, 6/72, 8/48, and 8/32 in the matched vehicle control group, a pooled vehicle control group consisting of mice from this and identical controls from other concurrent experiments, and the low- and high-dose groups, respectively; this positive trend was statistically significant. In female mice, liver carcinomas were reported in only the vehicle control (1/19) and the low-dose groups (1/47), no liver tumors were seen in the untreated controls or in the high-dose group. A statistically significant increase in benign uterine endometrial stromal polyps (4/46) was observed in high-dose females; these were not observed in any other group. A preliminary report of the NCI (43) study was published by Weisburger (54).

To determine if 1,1-dichloroethane in drinking water could act as a tumor promoter or a complete carcinogen, Klaunig et al. (55) exposed groups of 35 male B6C3Fl mice to 1,1-dichloroethane in drinking water at 0, 835, or 2500 mg/L for up to 52 wk following a 4-wk treatment with either drinking water containing 10 mg/L diethyl nitrosamine (DENA-initiated groups) or with deionized water (noninitiated groups). The investigators estimated that the approximate weekly dose of 1,1-dichloroethane was 3.8 mg/g/wk (corresponding to 543 mg/kg/d) for the groups exposed to 2500 mg/L. Upon sacrifice at the end of either 24 wk (10 mice/group) or 52 wk (25 mice/group) of promotion, all tissues were examined for gross pathologic lesions and histologic sections of the liver, kidneys, and lungs were examined. Neither the initiated nor the noninitiated 1,1-dichloroethane-treated groups showed a significant increase in the incidence of liver or lung tumors compared with initiated or noninitiated controls, respectively. The authors concluded that 1,1-dichloroethane was not carcinogenic to mice and did not act as a tumor promotor following initiation with DENA. These conclusions may not be entirely justified, since the duration of the study may have been inadequate for the development of tumors in noninitiated 1,1-dichloroethane-treated animals. In addition, the incidence of liver tumors in DENA-initiated controls was 70% at 24 wk and 100% at 52 wk, and the number of tumors/mouse in DENA-initiated controls at these times was 3.00 and 29.30, respectively. Hence, an increase in tumors or decrease in latency in 1,1-dichloroethane-treated DENA-initiated animals would have to be marked in order to be detectable.

Carcinogenicity Classifications:

EPA	Group C, Possible Human Carcinogen
ACGIH TLV	A4, Not classifiable as a Human carcinogen

2.4.1.6 Genetic and Related Cellular Effects Studies As reported in the ATSDR Toxicological profile (56) 1,1-dichloroethane has been shown to be weakly mutagenic in some but not all test systems primarily with metabolic activation and without glutathione, which appears to play a detoxification role. Addition of glutathione reduces the extent of metabolic covalent binding to macromolecules, raising the question of the suitability of bacterial test systems that are low in glutathione in evaluating mammalian toxicity.

2.4.2 Human Experience Symptoms of exposure to this compound may include liver and kidney damage, skin and eye irritation, dermatitis, and skin burns. It may cause unconsciousness, central nervous system depression, and drowsiness. It may also cause nausea, vomiting, faintness, irritation of the respiratory tract, salivation, sneezing, coughing, dizziness, lacrimation, reddening of the

conjunctiva, cyanosis, circulatory failure, and slight smarting of the eyes and respiratory system. It is narcotic in high concentrations.

No reports of human experiments or experience were found.

A published report by Hamilton and Hardy (57) indicated that 1,1-dichloroethane is irritating to the eyes and respiratory tract, produces salivation, sneezing, and coughing, is associated with dizziness, nausea, and vomiting. Hepatic and renal injury were present in severe and fatal cases.

2.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV for 1,1-dichloroethane is 100 ppm with an A4 designation, not classifiable as a human carcinogen. The NIOSH REL is 100 ppm with an IDLH of 3000 ppm. The OSHA PEL is also 100 ppm.

Other Occupational Exposure Values: Australia: 200 ppm, STEL 250 ppm, substance under review (1993); Federal Republic of Germany: 100 ppm, short-term level 200 ppm, 30 min, 4 times per shift, pregnancy group D, insufficient evidence for a final evaluation (1997); United Kingdom: 200 ppm, 15-min STEL 400 ppm (1995).

2.6 Studies of Environmental Impact

None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons

Jon B. Reid, Ph.D., DABT

Ethylene Dichloride

3.0.1 CAS Number:

[*107-06-2*]

3.0.2 Synonyms:

1,2-Dichloroethane, sym-dichloroethane, 1,2-bichloroethane, 1,2-ethylene dichloride, alpha, beta-dichloroethane, glycoldichloride

3.0.3 Trade Names:

Borer sol, Brocide, Destruxol Borer-sol, Dichloremulsion, Dutch oil, Di-chlor-mulsion, Dutch liquid, Freon 150, Dichlor-ulsion, Dichloremulsion

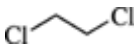
3.0.4 Molecular Weight:

98.960

3.0.5 Molecular Formula:

$C_2H_4Cl_2$ or $ClCH_2CH_2Cl$

3.0.6 Molecular Structure:



3.1 Chemical and Physical Properties

Ethylene dichloride is a colorless liquid with an odor typical of chlorinated hydrocarbons. An odor threshold of 88 ppm has been reported (10). Chemical and physical properties include (58):

Physical state	Colorless liquid
Specific gravity	1.2569 at 20°C (20/4°C)
Melting point	–35.5°C
Boiling point	83.5°C

Vapor pressure	87 torr (25°C)
Refractive index	1.44432 (20°C)
Percent in “saturated”air	11.5 (25°C)
Solubility	0.9 g/100 ML water at 20°C; soluble in ethanol, ethyl ether
Flash point	18.3°C (open cup); 13°C (Closed cup)
Explosive limits	6.2–15.9% by volume in air
Ignition temperature	415°C

3.1.1 General An ATSDR Toxicological Profile for this material is available.

3.1.2 Odor and Warning Properties Ethylene dichloride has a sweetish, not particularly disagreeable odor. The odor is barely detectable at 50 ppm in air and is definite but not unpleasant at 100 ppm. Although it is pronounced at 200 ppm, it still would not be considered unpleasant. Even though the odor may be definite enough to act as a warning of acutely hazardous concentrations, it is probably not sufficiently striking to be considered a significant warning of hazardous chronic exposure. This is particularly true because one can adapt to the odor at low concentrations.

3.2 Production and Use

In the United States almost all the current production of ethylene dichloride is used as the starting material for preparation of vinyl chloride monomer. Other applications are much smaller. It was formerly used in antiknock fluids for gasoline, in fumigant mixtures, and as a solvent. Because of its toxicity and flammability, usage as a solvent has decreased considerably as less hazardous replacements have become available.

3.3.3 Workplace Methods NIOSH Method 1003, for halogenated hydrocarbons, is recommended for determining workplace exposures to 1,2-dichloroethane (10a).

3.3.5 Biomonitoring/Biomarkers No references were found that would indicate biologic monitoring to be satisfactory for industrial hygiene control at acceptable levels of exposure.

3.4 Toxic Effects

1,2-Dichloroethane is toxic by ingestion, inhalation, and skin contact. It can be absorbed through the skin. It is an irritant of the skin, eyes, and respiratory tract. The vapor is heavier than air and may travel a considerable distance to a source of ignition and flash back. When heated to decomposition, it emits toxic fumes of carbon monoxide, carbon dioxide, hydrogen chloride gas, and phosgene.

The toxicity of ethylene dichloride has been extensively investigated both in animals and humans. It has been reviewed by several authors (7, 59–62). At very high concentrations, ethylene dichloride is irritating to the eyes, nose, and throat. Other symptoms are largely related to CNS depression or gastrointestinal upset, that is, mental confusion, dizziness, nausea, and vomiting. Cardiac sensitization appears to be less important. At subacute levels, similar symptoms of CNS depression and gastrointestinal upset are observed. Definite liver, kidney, and adrenal injury may occur at these levels. From chronic exposure to lower concentrations, some indications of CNS depression are still observed. Nausea and vomiting are quite common in humans. The sympton of nausea and vomiting for ethylene dichloride is quite striking and similar to that often observed from carbon tetrachloride. The pathological picture from repeated exposure is injury of the liver, kidneys, and adrenals. This general pattern has been consistent in animal investigative work and in experience from human exposure.

Ethylene dichloride does not appear to be teratogenic or to have significant reproductive effects, but current animal data suggest it may have mutagenic, and possibly carcinogenic, potential. There is also a question of its immunologic suppression that remains unanswered. Human studies have not supported the carcinogenic or immunologic effects seen in animal studies, but as is often the case in epidemiology, the study populations have been small.

3.4.1 Experimental Studies 3.4.1.1 Acute Toxicity Animal studies show liver and kidney injury. Smyth et al. (63) calculated an oral LD_{50} in rats of 770 mg/kg. Opacity of the cornea was reported in dogs and foxes following administration of ethylene dichloride (7, p.144).

3.4.1.2 Chronic and Subchronic Toxicity The results of lifetime oral studies are discussed in the carcinogenesis section.

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The metabolism of ethylene dichloride has been recently reviewed (62). Figure 63.1 has a proposed metabolic map taken from Loew et al. (64). It is readily absorbed via the lungs and gastrointestinal tract and to a lesser degree through the skin. Although steady-state blood concentrations in the rat were achieved in 2–3 h at 150 ppm, the equilibrium concentration in blood at 6 h was exponentially related to the inhaled concentration. Blood levels of 1.4, 8.3, and 31.3 mg/mL were found after exposure to 50, 150, and 250 ppm in air for 6 h. About 70% of the inhaled ethylene dichloride was absorbed in a 6 h exposure to 150 ppm, and clearance from the blood was rapid. Elimination following oral doses was also rapid, resulting in both cases in nonlinear kinetics. Approximately 85% of radioactivity was excreted in the urine as thiodiacetic acid and thiodiacetic sulfoxide with some exhalation of unchanged [^{14}C]1,2-dichloroethane. The parent compound, as well as 2-chloroethanol, monochloroacetic acid, and 2-chloroacetadehyde, has been found in the organs of cadavers following acute poisoning (65). Two paths of metabolism involve microsomal cytochrome P450 or cytosolic glutathione transferase. The cytosolic pathway was considered responsible for the mutagenicity and covalent DNA binding (66), but other investigators found no evidence of covalent binding from the cytosol route (67). A physiologically based pharmacokinetic model has been developed that described glutathione depletion and resynthesis in rats and mice (68).

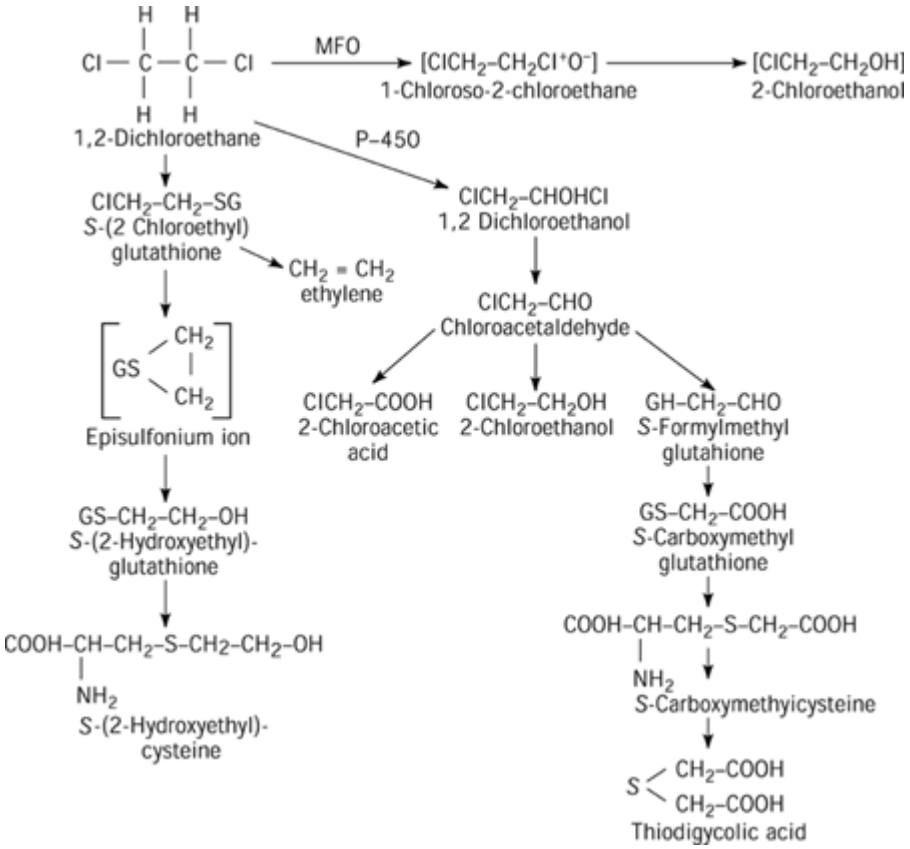


Figure 63.1. Proposed metabolism of 1,2-dichloreothane (from Ref. 64).

3.4.1.4 Reproductive and Developmental In the available abstract, Vozovaya (69) states he produced

decreased fertility and other adverse effects in pregnant female rats and the progeny of the first generation, but not of the second, by giving them repeated 4 h/d exposures to 57 mg/m^3 (14 ppm). However, an attempt to confirm this report failed to do so, even though the rats were exposed to 100 ppm 7 h/d for several months (70). Furthermore, pregnant Sprague–Dawley rats and New Zealand white rabbits were exposed to 0, 100, or 300 ppm of ethylene dichloride on days 6 through 15 (rats) and 6 through 18 (rabbits) of gestation. Severe maternal toxicity was observed among rats exposed to 300 ppm of ethylene dichloride; two-thirds of the dams died during the exposure period. No signs of toxicity were observed among rats at the 100-ppm dose level. Maternal toxicity was noted in rabbits as evidenced by maternal deaths at both dose levels. No adverse effects on embryonal or fetal development were observed among litters from the exposed rats at 100 ppm or among those from exposed rabbits. Owing to the severe maternal toxicity observed, no conclusions could be drawn concerning the teratogenic potential of inhaled ethylene dichloride in the rat at 300 ppm; ethylene dichloride was not embryotoxic or teratogenic in rats inhaling either 100 ppm or in rabbits inhaling 100 or 300 ppm of the compound during gestation (70).

Pregnant CD mice were fed water containing a mixture of potential water contaminants including ethylene dichloride with no effects on the usually teratological parameters (71).

The reproduction and developmental effects of ethylene dichloride were studied in a multigeneration study (72). Male and female ICR Swiss mice received 0, 5.14, 15.4, or 49.7 mg/kg/d. There appeared to be no dose-dependent effects on fertility, gestation, viability, or lactation indices. Pup survival and weight gain were not adversely affected. Gross necropsy of male and female F0 generation mice treated with 1,2-DCE or 1,1,1-TCE failed to reveal compound or dose-related effects.

3.4.1.5 Carcinogenesis The EPA classifies ethylene dichloride as B2; probable human carcinogen on the basis of the induction of several tumor types in rats and mice treated by gavage and lung papillomas in mice after topical application. There are no human carcinogenicity data. An NCI study in 1978 (73) is the basis for the conclusion.

The International Agency for Research on Cancer (74, p. 62) classified ethylene dichloride in group 2B, possibly carcinogenic to humans, based on sufficient evidence for carcinogenicity in animals and no adequate data for humans.

In the NCI (75) study, 1,2-dichloroethane in corn oil was administered by gavage to groups of 50 each male and female Osborne–Mendel rats and B6C3F1 mice. Treatment was for 78 wk followed by an additional observation period of 12–13 weeks for mice or 32 wk for low-dose rats. TWA dosages were 47 and 95 mg/kg/d for rats, 97 and 195 mg/kg/d for male mice, and 149 and 299 mg/kg/d for female mice. All high-dose male rats died after 23 wk of observation; the last high-dose female died after 15 wk. Male rats had significantly increased incidence of forestomach squamous-cell carcinomas and circulatory system hemangiosarcomas. Female rats and mice were observed to have significant increases in mammary adenocarcinoma incidence. Mice of both sexes developed alveolar/bronchiolar adenomas, females developed endometrial stromal polyps and sarcomas, and males developed hepatocellular carcinomas.

In the studies by Spencer et al. (76) and Maltoni et al. (77) inhalation exposure of Wistar, Sprague–Dawley rats, and Swiss mice did not result in increased tumor incidence.

An elevation that was not statistically significant in lung adenomas was seen in A/st mice treated IP with 1,2-dichloroethane in tricaprylin (78).

ICR/Ha Swiss mice treated topically had a significant increase in benign lung papillomas, but not skin carcinomas (79).

Carcinogenicity Classification:

EPA	Group B2, Probable human carcinogen; sufficient evidence from animal studies; inadequate evidence or no data from epdemiologic studies.
IARC	Group 2B, Possibly carcinogenic in humans.
MAK	Group 2, Probable human carcinogen.
NIOSH	Carcinogen, with no further categorization.
NTP	Reasonably anticipated to be a human carcinogen (RAHC).
ACGIH TLV	A4, Not Classifiable as a Human Carcinogen.

3.4.1.6 Genetic and Related Cellular Effects Studies 1,2-Dichloroethane was mutagenic for *Salmonella* in assays wherein excessive evaporation was prevented; exogenous metabolism by mammalian systems enhanced the response (80–82). Both somatic cell mutations and sex-linked recessives were induced in *Drosophila* (83–86).

Metabolites of 1,2-chloroethane have been shown to form adducts with DNA after *in vitro* or *in vivo* exposures.

3.4.2 Human Experience Symptoms of exposure to this compound may include irritation of the skin, eyes, and respiratory tract, corneal clouding, and dermatitis. It may cause conjunctivitis, corneal ulceration, headache, mental confusion, depression, fatigue, albuminuria, central nervous system depression, convulsions, diarrhea, hepatomegaly, hypoglycemia, jaundice, narcosis, and pulmonary edema. It may also cause flaccid paralysis without anesthesia, somnolence, cough, nausea, vomiting, hypermotility, ulceration, fatty liver degeneration, change in cardiac rate, cyanosis, coma, edema of the lungs, and toxic effects on the kidneys. It may cause feelings of drunkeness or drowsiness, unconsciousness, and death from respiratory and cardiac failure, defatting of the skin, swelling of the skin, and chemical pneumonia. Other symptoms may include mental confusion, abdominal pains, and liver and kidney damage. It can also cause watery stool, weak and rapid pulse, and internal bleeding. It may cause corneal opacity. Other symptoms may include edema of the brain, vascular congestion in the lungs, heart, and spleen, weight loss, and oliguria. It may also cause dizziness, narcosis, intestinal hemorrhages, weakness, trembling, and severe shock. Chronic exposure may result in loss of appetite, epigastric distress, tremors, nystagmus, leukocytosis, and low blood sugar levels.

3.4.2.2 Clinical Cases There have been clinical cases of acute exposure to ethylene dichloride reported in the literature that confirm the picture observed in the animals. Menschick (87) reported four acute cases showing a “hepato-renal syndrome.” The author also lists 27 cases of poisoning by inhalation collected from the literature.

Ethylene dichloride does present a problem from oral ingestion. There are a significant number of the poisoning cases reported in the literature by this route. The response is CNS depression, gastrointestinal upset, and injury to the liver, kidneys, and the lungs, and delayed deaths.

The Criteria Document (88) cited papers that indicate fatalities from inhalation in concentrations insufficient to cause anesthesia.

Two epidemiologic studies, one positive and one negative, have been reported, but the results are not conclusive owing to mixed exposures or small sample size (89, 90).

3.4.2.3 Epidemiology Studies Two epidemiologic studies, one positive and one negative, have been reported, but the results are not conclusive owing to mixed exposures or small sample size (89, 90).

3.5 Standards, Regulations, or Guidelines of Exposure

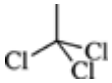
The ACGIH TLV is 10 ppm with an A4 notation, not classifiable as a human carcinogen. The

NIOSH REL is 1 ppm and the STEL is 2 ppm. NIOSH considers this chemical a carcinogen. The OSHA PEL is 50 ppm while the ceiling is 100 ppm and the 5 min peak in any 3 hours is 200 ppm.

Other Occupational Exposure Values: Australia: 10 ppm (substance under review) (1990); Federal Republic of Germany: no MAK, Group 2, probably human carcinogen (1998); Sweden: 1 ppm, 15-min short-term value 5 ppm, skin, carcinogenic (1989); United Kingdom: 10 ppm, 10-min STEL 15 ppm, carcinogenic substance, R45-may cause cancer (1991).
3.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Methyl Chloroform
4.0.1 CAS Number:
[*71-55-6*]
4.0.2 Synonyms:
1,1,1-Trichloroethane, methyltrichloromethane, alpha-trichloroethane, chloroethene, chlorothene, 1,1,1-TCE
4.0.3 Trade Names:
Aerothene TT, Chloroetene, Chloroethene NU, Chlorothane NU, Chlorothene (inhibited), Chlorothene NU, Chlorothene VG, Chlorten, Inhibisol, NCI-C04626, RCRA Waste Number U226, Solvent 111, Strobane, Alpha-T, Tri-ethane, UN 2831, Trichloroethane, 1,11-Trichloroetano, Tri-ethane
4.0.4 Molecular Weight:
133.42
4.0.5 Molecular Formula:
$C_2H_3Cl_3$
4.0.6 Molecular Structure:



4.1 Chemical and Physical Properties
Methyl chloroform is a colorless, nonflammable liquid with an chloroformlike odor and an odor threshold of 120 ppm. It burns only in excess oxygen or in air if a strong source of ignition is present. Because of its reactivity with magnesium, aluminum, and their alloys, inhibitors (usually 1,4-dioxane, 1,3-dioxolane, isobutyl alcohol, or nitroethane) are often added to increase the stability of the solvent.

Physical state	Colorless liquid
Specific gravity	1.3376 at 20°C
Boiling point	74.1°C
Melting point (°C)	–32.5
Vapor pressure	127 torr (25°C)
Refractive index	1.43765 (21°C)
Percent in “saturated” air	16.7 (25°C)
Solubility	0.09 g/100 mL water at 20°C; soluble in ethanol and ethyl ether

Flammability (see following note)

Note: The flammable characteristics of methyl chloroform are similar to those of trichloroethylene. It has no flash point or fire point by ASTM procedures for Tag closed-up and Cleveland open-cup tests. Limits of flammability of vapors of inhibited 1,1,-trichloroethane have been found to be 10–15.5% in air with hot wire ignition. A considerable amount of energy is required for ignition. It will not sustain combustion (91).

4.1.1 General An ATSDR Toxicological profile exists for 1,1,1-trichloroethane (3).

4.1.2 Odor and Warning Properties Although methyl chloroform has a typical sweetish odor, it is not striking enough to be considered a good warning. The odor may be noticeable at concentrations near 100 ppm, well below those known to cause physiological response. However, the odor at 500 ppm and even 1000 ppm is not so unpleasant as to discourage exposure. The odor has been described as strong and unpleasant at 1500–2000 ppm. Stewart et al. (92) reported that female test subjects exposed to 350 ppm objected to the odor; however, this has not been an industrial problem.

4.2 Production and Use

According to the NTP database, methyl chloroform is used in cold-type metal cleaning, in plastic cleaning, in vapor degreasing, as a chemical intermediate for vinylidene chloride, in aerosols (as a vapor pressure depressant, solvent, and carrier), in adhesives (as a resin solvent), and as a lubricant carrier to inject graphite, grease, and other lubricants. It is used alone and in cutting oil formulations as a coolant and lubricant for drilling and tapping alloy and stainless steels. It is also used to develop printed circuit boards, in motion picture film cleaning, in stain repellants for upholstery fabrics, in wig cleaning, in textile processing and finishing, and as a solvent in drain cleaners, shoe polishes, spot cleaners, insecticide formulations, and printing inks. It is also used as a solvent for cleaning precision instruments.

Methyl chloroform is used almost exclusively as a solvent with a few percent used as an intermediate. As a solvent for adhesives, 69% of the U.S. production is consumed in metal degreasing. Another 23% is used in the manufacture of vinylidene chloride (93). Because of the environmental issue of depletion of stratospheric ozone, future use can be expected to decline.

Most commercial methyl chloroform, which is sold under several trade names, contains inhibitors to prevent reaction of the solvent with aluminum and alloys. This reaction produces hydrogen chloride and in confined vessels may produce high pressures.

4.3 Exposure Assessment

4.3.3 Workplace Methods NIOSH Method 1003, for halogenated hydrocarbons, is recommended for determining workplace exposures to methyl chloroform.

4.3.5 Biomonitoring/Biomarkers Stewart et al. (92) have produced a series of graphs making it possible to quantify exposure based on expired air samples. Analysis of urine for metabolites probably has limited value. Monster (94) has also published extensive studies on biologic monitoring of 1,1,1-trichloroethane. Although it has been suggested that urinary trichloroacetic acid and trichloroethanol may be of value in quantifying exposure to methyl chloroform, and the ACGIH in 1992–1993 recommended biological exposure indices, such indices are of most value in discerning average exposure levels and not peak exposures. Thus it is possible that “acceptable false negative” urinary levels of these substances may be found following exposure considered excessive from the standpoint of anesthetic effects. The same caveat must be considered in considering expired air samples collected at the end of the workday or workweek.

4.4 Toxic Effects

Extensive testing and human experience indicate 1,1,1-trichloroethane is probably the least toxic of the chlorinated solvents, but its high volatility and careless use and abuse have resulted in deaths from gross exposure usually in confined spaces or due to deliberate inhalation.

Methyl chloroform is harmful by inhalation, ingestion, and skin absorption. It can be absorbed through the lungs, gastrointestinal tract, and skin. It is an irritant of the skin, eyes, mucous membranes, and upper respiratory tract. It may be narcotic in high concentrations. It may also cause slight lacrimation. When heated to decomposition, it emits irritating gases and toxic fumes of carbon monoxide, carbon dioxide, hydrogen chloride gas, chlorine, and phosgene.

The principal and first response from acute or chronic exposure to excessive amounts of methyl chloroform is depression of the central nervous system. Possibly as a result of very little metabolism of the compound, it has little capacity to produce organ injury from either single or repeated exposures but at high levels can sensitize the heart to epinephrine, possibly leading in some cases to death. Overall the available human and animal data indicate that the compound is not teratogenic, mutagenic, or carcinogenic, although the 1,1,1-trichloroethane isomer is considerably less toxic than the 1,1,2-trichloroethane isomer. Owing to an error in the literature, several authors have indicated the reverse, as documented by Torkelson et al. (95).

Concentrations in excess of 14,000–15,000 ppm are fatal to animals. Human fatalities due to anesthesia (and/or cardiac arrhythmia) have occurred in confined spaces when exposures to high concentrations have not been promptly terminated. In cases where the victim has been alive when removed from the high concentration, recovery has generally been rapid and complete. Abuse (sniffing) has also resulted in deaths.

Several reviews have been published (5, 62, 96–100).

4.4.1 Experimental Studies 4.4.1.1 Acute Toxicity Torkelson et al. (95) reports that the oral toxicity is low with an LD_{50} in rats, mice, rabbits, and guinea pigs ranging from 5.7 to 12.3 g/kg. The LD_{50} for rabbits (skin absorption) is 16 g/kg.

Wolverton et al. (101) report that the inhalation toxicity is also low with an EC_{50} for motor control loss (mice) for 30 min at 5173 ppm. No significant toxic responses were reported for rats, 500 ppm, 6 h/d, 4 d (102), mice to 1300 ppm, 1 h, rats to 3000 ppm for 0.5–4 h (103) baboons, 1400 ppm 4 h (104).

Inhalation: As an anesthetic, methyl chloroform can cause dealth in excess of 14,000–15,000 ppm (105).

Adams et al. (106) reported on the response of animals to acute inhalation exposure. Maximum time concentrations in air survived by rats were as follows: 6 min at 30,000 ppm, 1.5 h at 15,000 ppm, and 7 h at 8000 ppm. Maximum time concentrations in air with no detectable injury in rats were as follows: 18 min at 18,000 ppm and 5 h at 8000 ppm. It should be noted that the maximum level with no detectable injury is very close to the maximum level survived. This information has been confirmed by Torkelson et al. (95) using inhibited solvent.

Bruckner et al. (107) performed an acute and subacute study in rats. Several parameters were studied in addition to lethality. Single oral doses up to 4 g/kg in corn oil did not cause death or treatment-related effects on serum enzymes organ weights, or histological findings in the livers and kidneys of Sprague–Dawley rats 24 h after gavage. Rats treated with nine doses in 11 d were scheduled for sacrifice on the twelfth day. Doses of 0, 0.5, 5.0, or 10.0 g/kg were administered. Doses of 5 and 10 g/kg/d caused hyperexcitability and protracted narcosis as well as some fatalities, but there was little evidence of toxicity in the survivors or in the 0.5 g/kg/d group. In a 12 wk oral study doses of 0, 0.5, 2,5, or 5.0 g/kg were given 5 d/wk. Reduced body weight and CNS effects were seen only in the 2.5- and 5.0-g/kg groups and 35% of the rats in these groups died, but only the 5.0-g/kg group showed serum enzyme changes. The 0.5-g/kg (500 mg/kg) group developed no alterations in toxicity during the 12 wk study.

Torkelson et al. (95) reported on eyes, skin, and skin absorption: The material caused only minor, transient irritation in the eyes of rabbits, and no reports of human injury have been reported following eye contact. The skin shows only slight reddening and scaliness from contact. The reaction is somewhat increased on repreated exposures. Confinement of the liquid on the skin results in considerable pain and irritation. Applied under a cuff for 24 h, 3.9 g/kg was survived by all rabbits; 15.8 g/kg failed to kill all the rabbits treated with the undiluted liquid. Others have reported similar low hepato- and renal toxicity in rats and other species (47, 108–110).

Gehring (111) determined that at 13,500 ppm the LT_{50} (lethal time, 50%) was 595 min but that liver function as measured by serum glutamic-oxalic-transaminase (SGOT) was virtually unaffected unless exposures approached those causing anesthetic death.

Klaassen and Plaa reported an intraperitoneal LD_{50} of 3.9 g/kg in rats (110) and an LD_{50} of 120 mmol/kg (16 g/kg) in mice (108).

4.4.1.2 Chronic and Subchronic Toxicity The EPA (2) reports that the oral RfD for 1,1,1-trichloroethane had been withdrawn on 08/01/1991 pending further review by the RfD/RfC Work Group and that no reference concentration is available. Please see the section on carcinogenicity for additional information.

Adams et al. (106) exposed animals 7 h/d, 5 d/wk for 1–3 mo. At 10,000 ppm rats showed staggering gait and weakness in 10 min. By 3 h, they showed loss of color, irregular respiration, and semiconsciousness. Survivors had completely recovered by the following morning. For those that succumbed, death seemed to be due to either cardiac or respiratory failure. At 5000 ppm, there was definite but mild narcotic effect within 1 h. There was reduced activity. Rats survived for 31 exposures over 41 d without apparent injury. Rabbits showed slight retardation of growth at 5000 ppm. At 3000 ppm, rabbits and monkeys showed no response over a 2-mo period. Guinea pigs showed a barely significant retardation of growth at 650 ppm.

Torkelson et al. (95) reported results of exposures of female guinea pigs and male rats for 3 mo, exposed for 0.05–3 h/d at 1000–10,000 ppm. Some pathologic changes in the livers and lungs of guinea pigs exposed for 3 or 1.2 h/d at 1000 ppm and for 0.2 or 0.5 h/d at 2000 ppm. The anesthetic effect was paramount. No significant toxic changes were reported for exposures to the vapor at 500 ppm for 7 h/d, 7 days/week, for 6 m in rats, guinea pigs, rabbits, or monkeys.

Prendergrast et al. (112) performed continuous (24 h/d) exposure for 14 wk and showed that it produced little injury to rats, mice, dogs, and monkeys at 1000 ppm and essentially no effect at 250 ppm except minor, apparently reversible cytoplasmic alterations in the livers of mice. After exposure to 1000 ppm dogs and monkeys were considered unaffected by the exposure, but the rats and mice exhibited significant increases in liver weight and liver triglycerides and fatty and necrotic changes visible microscopically in the livers.

Quast et al. (113) repeatedly exposed groups of 96 rats of each sex to 875 or 1750 ppm, 1,1,1-trichloroethane vapor 6 h/d, 5 d/w for 1 yr with no adverse effects (see section on carcinogenicity).

Several other subchronic studies indicated minor and reversible effects (114–116).

The section on carcinogenicity also describes a 2-yr inhalation exposure study of rats and mice with effects only at 1500 ppm in rats, but not at 500 or 150 ppm. There was no effect on mice at any concentration.

4.4.1.3 Pharamacokinetics, Metabolism, and Mechanisms Absorption from the skin of humans and rodents after topical application (#51, 52, 53, 54) (117–120) has been shown.

Both *in vivo* and *in vitro* systems metabolize methyl chloroform by microsomal P-450 to trichloroethanol (121, 122). This metabolite is conjugated with glucuronic acid and the trichloroethanol-glucuronide appears in the urine (96). The trichloroethanol can also be oxidized to trichloroacetic acid. It can account for considerable metabolites in rodent and human urine (115, 123–126).

Pulmonary absorption by humans is from 30 to 60% depending on the duration and concentration of the exposure (123, 127).

Gehring et al. (62) indicated that the low systemic toxicity of methyl chloroform is related to the small amount of metabolism that occurs in animals and humans. Because of its low toxicity, it has been used as a model compound in absorption–excretion studies (95, 128). In one of the first metabolic studies on this compound, Hake et al. (129) reported 97.6% of radioactive methyl chloroform injected intraperitoneally was excreted unchanged by the lungs, and only 0.85% of the radioactivity was found in the urine. This and subsequent studies on humans and animals indicate that only small amounts of trichloroacetic acid and trichloroethanol may be found in the urine after injection or inhalation (115, 126, 130–132), but that most of the dose is expired unchanged no matter what the route of administration.

As reported by Schumann et al. (126), rats and mice eliminated 96% of their body burden within 24 h following 6 h inhalation exposure to 150 or 1500 ppm [^{14}C]1,1,1,-trichloroethane. Exhalation of the parent compound was very high, 87–97% of the body burden in mice and 94–98% in rats at 150 and 1500 ppm, respectively. The remaining ^{14}C activity (2–13%) was recovered either as CO_2 in expired air or as nonvolatile radioactivity in urine, feces, carcass, or cage wash.

Although quantities were small, mice metabolized two to three time more than rats on a body weight basis. Fat contained the highest concentrations of ^{14}C activity. Prior long-term repeated exposure to nonradioactive 1,1,1-trichloroethane did not increase the rate of metabolism of a radioactive dose. Reitz et al. (133) have developed pharmacokinetic models for interspecies, high-dose/low-dose, and dose route extrapolations, as models for regulatory risk analysis (134).

According to VanDyke and Wineman (135) the small amount of metabolism that takes place appears to occur in a saturable process. Enzymatic dechlorination by rat liver microsomes *in vitro* is very low and apparently not enhanced by enzyme inducers. VanDyke (136) reports that the reaction is catalyzed by cytochrome P450 in the presence of oxygen. Kawai et al. (137) reported that only 2% of absorbed 1,1,1-trichloroethane was excreted in the urine of the 48 male printing workers they studied.

Occupational Exposures: Imbriani et al. (138) examined occupationally exposed persons and found intact methyl chloroform in the urine from 33 to 314 mg/L. Nolan et al. (124) exposed six humans at 35 or 350 ppm for 6 h and calculated the urinary elimination of trichloroethanol and trichloroacetic acid at 27 and 76 h, respectively.

4.4.1.4 Reproductive and Developmental Schwetz et al. (139) reported that pregnant female rats and mice were exposed 7 h/d on days 6 to 15 of gestation and the mothers and fetuses examined for effects. The inhaled vapor concentration was 875 ppm of an inhibited formulation containing 5.5% inhibitors. No effects related to exposure were observed on either the mothers or fetuses.

The NTP (NTP 1987 (140, 141)) found no signs of developmental toxicity at doses where maternal intoxication was present when given to male and female CD rats prior to mating and throughout pregnancy in drinking water at 30 ppm. Bogen and Hall (134) used these data to determine a "virtually safe dose" of 14–28 mg/d based on the delivered dose to the rat embryo.

York et al. (142) repeatedly exposed female Long–Evans rats to 2100–2200 ppm of methyl chloroform vapors 2 wk before breeding and until day 20 of gestation without effect on teratogenicity or subsequent neurobehavioral studies of the offspring allowed to be delivered normally.

Riddle et al. (72) modified a multigeneration reproduction study to include screening for dominant lethal and teratogenic effects. Mice were fed water containing methyl chloroform so that daily dosage levels were 0, 99.4, 264, or 852 mg/kg. According to the authors, "There appeared to be no dose-dependent effects on fertility, gestation, viability, or lactation indices. Pup survival and weight gain were not adversely affected. Gross necropsy of male and female F/0 generation mice treated with 1,2-DCE or 1,1,1-TCE failed to reveal compound or dose-related effects."

George et al. (143) reported that when methyl chloroform was fed in drinking water to CD rats at 0, 3, 10, or 30 ppm using 0.05% Tween 80 as an emulsifying agent for 14 d prior to and 13 d after cohabitation, "there was no indication of an increase in the incidence of cardiac or other malformations."

These data as well as all other studies appear to refute adequately an allegation of teratological effect reported by Dapson et al. (144).

4.4.1.5 Carcinogenesis The EPA (IRIS) reports that there are no human carcinogenic data and classifies this material as D, not classifiable as to human carcinogenicity and that the animal carcinogenicity data are "Inadequate." In 1987, IARC reviewed the existing information and concluded that there was inadequate evidence for carcinogenicity in animals (74, p. 73). Three animal studies are relevant an NCI bioassay (gavage) and two inhalation studies by Quast et al., (145, 146), none of which gave clear evidence of carcinogenic activity.

The NCI (147) treated Osborne–Mendel rats (50/sex/dose) with 750 or 1500 mg/kg technical-grade 1,1,1-trichloroethane 5 times/wk for 78 wk by gavage. The rats were observed for an additional 32 wk. Twenty rats of each sex served as untreated controls. Low survival of both male and female treated rats (3%) may have precluded detection of a significant number of tumors late in life. Although a variety of neoplasms was observed in both treated and matched control rats, they were common to aged rats and were not dose related. Similar results were obtained when the NCI (147) treated B6C3F1 hybrid mice with the time-weighted average doses of 2807 or 5615 mg/kg 1,1,1-trichloroethane by gavage 5 d/wk for 78 wk. The mice were observed for an additional 12 wk. The control and treated groups had 20 and 50 animals of each sex, respectively. Only 25–45% of those treated survived until the time of terminal sacrifice. A variety of neoplasms was observed in treated groups, but the incidence not statistically different from matched controls.

Quast et al. (145) exposed 96 Sprague–Dawley rats of both sexes to 875 or 1750 ppm 1,1,1-trichloroethane vapor for 6 h/d, 5 d/wk for 12 m, followed by an additional 19 mo observation period. The only significant sign of toxicity was an increased incidence of focal hepatocellular alterations in female rats at the highest dosage. It was not evident that a maximum tolerated dose (MTD) was used, nor was a range-finding study conducted. No significant dose-related neoplasms were reported, but these dose levels were below those used in the NCI study.

In another study, Quast et al. (146) used an inhibited formulation of 1,1,1-trichloroethane. Fischer 344 rats and B6C3F1 mice of both sexes were exposed to 0, 150, 500, or 1500 ppm 6 h/d, 5 d/wk for 2 yr. The authors indicate that there were no indications of an oncogenic effect in rats or mice following 2 yrs of exposure to the 1,1,1-trichloroethane formulation and a no-observed-adverse-effect-level (NOAEL) of 500 ppm for adverse effect of any kind. The ATSDR reviewed this information (56) and determined that the study adequately demonstrated negative evidence of carcinogenicity in animals by lifetime inhalation up to 1500 ppm.

It should be noted that an isomer of methyl chloroform, namely, 1,1,2-trichloroethane, is

carcinogenic in mice, inducing liver cancer and pheochromocytomas in both sexes. Dichloroethanes, tetrachloroethanes, and hexachloroethanes also produced liver cancer in mice and other types of neoplasms in rats and further that 1,4-dioxane, a known animal carcinogen that causes liver and nasal tumors in more than one strain of rats and hepatocellular carcinomas in mice, is a contaminant of technical-grade 1,1,1-trichlorethane.

4.4.1.6 Genetic and Related Cellular Effects Studies According to the EPA (IRIS), mutagenicity testing of 1,1,1-trichloroethane has produced positive results in *S. typhimurium* strain TA100 (148) as well as some negative results (149).

Methyl chloroform was mutagenic for *S. typhimurium* strain TA1535, both with exogenous metabolic activation (150) and without activation (80). 1,1,1-Tricholoroethane did not result in gene conversion or mitotic recombination in *Saccharomyces cerevisiae* (150), nor was it positive in a host-mediated forward mutation assay using *Schizosaccharomyces pombe* in mice. The chemical also failed to produce chromosomal aberrations in the bone marrow of cats (151), but responded positively in a cell transformation test with rat embryo cells (152).

The extensive summary (98) of genotoxic studies on methyl chloroform concludes that the potential for genetic damage is very small at acceptable exposure conditions.

4.4.2 Human Experience Symptoms of exposure to this compound may include irritation of the eyes, dizziness, incoordination, unconsciousness, and death. Irritation of the mucous membranes and respiratory tract may occur. Fainting may also occur. Other symptoms may include decreased reaction time, impaired manual dexterity, ataxia, lightheadedness, positive Romberg test, diarrhea, respiratory arrest, and nausea. It causes a proarrhythmic activity that sensitizes the heart to epinephrine, resulting in cardiac arrhythmias. This sometimes will cause cardiac arrest, particularly when massive amounts are inhaled. Inhalation can cause euphoria. High concentrations may cause narcosis. Exposure can cause headache, drowsiness, burning sensation on the eyes and skin, irritation of the throat, cardiac sensitization, aspiration of vomitus during anesthesia, blood pressure depression, chemical pneumonitis, and pulomary edema with hemorrhage. It can also cause anesthesia, cardiac fibrillations, slight reddening of the skin, central nervous system impairment, helplessness, loss in equilibrium, and mild eye and nasal discomfort. Other symptoms are hallucinations, distorted perceptions, motor activity changes, irritability, aggression, hypermotility, and other gastrointestinal changes. Impaired judgement has been reported. Increased reaction time has also been reported. Repeated skin contact may result in a dry, scaly, and fissured dermatitis due to its defatting properties. Prolonged skin contact may result in considerable pain and irritation. Other symptoms may include difficult breathing, asphyxiation, slight lacrimation, and slight smarting of the eyes and respiratory system. It may cause impaired psychophysiological functions. It may also cause irregular heart beat, lassitude, and coma. High concentrations cause central nervous system depression. Hemorrhage in the brain may also result from exposure to high concentrations. Eye contact may lead to superficial and transient injury to the eyes. It may also lead to mild conjunctivities. Chronic exposure may result in liver and kidney damage. Exposure to and/or consumption of alcohol may increase its toxic effects.

Findings in laboratory animals is consistent with humans (105). Numerous deaths due to CNS depression or cardiac arrhythmias have been reported from poorly ventilated areas (153–162).

Several authors (163, 164) have evaluated methyl chloroform as a surgical anesthetic, but for several reasons, including lack of potency and effects on cardiac function, it was abandoned from serious consideration. If the subject has been alive when removed from exposure, recovery has generally been rapid and complete.

Table 63.4 on the probable effects of exposure to humans to the vapor of methyl chloroform has been published for establishing emergency exposure limits.

Table 63.4. Probable Result of Single Exposure to the Vapors of 1,1,1-Trichloroethane (210)

Exposure time (min)	Concentration in Air (ppm)	Expected Effect in Humans[a]
5	20,000	Complete incoordination and helplessness (R)
	10,000	Pronounced loss of coordination (R)
	5,000	Definite incoordination (R, M)
	2,000	Disturbance of equilibrium. Odor is unpleasant but tolerable (H)
15	10,000	Pronounced loss of coordination (R)
	2,000	Loss of equilibrium (H)
	1,000	Possible beginning loss of equilibrium (H)
30	10,000	Pronounced loss of coordination (R)
	5,000	Incoordination (R, M)
	2,000	Loss of equilibrium (H)
	1,000	Mild eye and nasal discomfort; possible slight loss of equilibrium (H)
60	20,000	Surgical anesthesia, possible death (R)
	10,000	Pronounced loss of coordination (R)
	5,000	Obvious loss of coordination (R, M)
	2,000	Loss of coordination (H)
	1,000	Very slight loss of equilibrium (H)
	500	No detectable effect, but odor is obvious (R, H)
	100	Apparent odor threshold (H)

Laboratory Studies: Numerous laboratory studies in humans have permitted confirmation of many of the toxicologic data derived in animals. Stewart et al. (92), in a series of papers have evaluated the use of expired air for monitoring employee exposure and have produced a series of graphs based on expired air concentration following known exposures to various concentrations for different periods of time. These studies have also investigated metabolism and urinary excretion and evaluated clinical chemical parameters. Most important, however, are their studies to evaluate equilibrium, coordination, alertness, and other signs of anesthetic action. Based on these studies it has been concluded that, except for possible objections to odor, no untoward responses are observed even after repeated prolonged exposures of human subjects to 350 ppm. A few subjects may respond as concentrations approach 500 ppm, and if allowed to inhale 800–1000 ppm, some subjects show minor CNS impairment.

Other investigators (165) have found similar results, but Gamberale and Hultengren (166) reported effects at lower vapor concentrations. Gamberale and Hultengren, however, used a mask to administer the vapors, and this may have influenced their test results.

Monster (94) has published extensive studies on biologic monitoring of 1,1,1-trichloroethane,

trichloroethylene, and perchloroethylene.

Liquid methyl chloroform has been shown by Stewart and Dodd (167) as well as Fukabori et al. (168) to be absorbed through the intact skin, but Riihimaki and Pfaffli (169) have shown that the vapors are not absorbed in toxicologically significant amounts.

Industrial Experience: Although chronic effects have been shown to be of little consequence in industrial exposure (170), failure to recognize the high vapor pressure of methyl chloroform and to prevent inhalation of high concentrations, has resulted in reports of death. The number of deaths per year (2–3 worldwide) appears to be decreasing relative to consumption, as proper precautions are being taken to avoid exposure. Nonoccupational cases of deliberate sniffing have been reported, but generally a consistent pattern of use of the solvent in a confined space without regard for ventilation is the cause of industrial death.

Stewart (171) discussed the consequencs of overexposure and the treatment of overexposed subjects.

A single report (172) alleging chronic cardiac toxicity following repeated exposure to 1,1,1-trichloroethane is inconsistent with all other reports of rapid recovery as well as epidemiologic evidence (170). Furthermore, there are obvious discrepancies in claiming urinary excretion of 1,1,1- and 1,1,2-trichloroethane long after exposure, suggesting the report is in error. A rather extensive study of an industrial population exposed to methyl chloroform for up to 6 yr confirms the data derived from animals (170). No effect of exposure was found in a matched-pair study of 151 subjects and 151 controls despite particular emphasis placed on hepato- and cardiotoxic effects.

Mattsson et al. (173) conducted an elaborate investigation in which male and female Fischer 344 rats were exposed to 1,1,1-trichloroethane vapors for 6 h/d, 5 d/wk, for 13 wk. Exposure levels were 200, 630, and 2000 ppm. Rats were clinically examined regularly and were given a functional observational battery monthly (FOB, including forelimb and hindlimb grip performance testing). After 13 wk of exposure, the functional integrity of the nervous system was evaluated by FOB and by visual, auditory, somatosensory, and causal nerve evoked potentials. After functional testing, a subgroup of rats had histopathologic examination of brain, spinal cord, peripheral nerves, and limb muscles. No treatment-related findings were discovered in any parameter except for a slightly smaller forelimb grip performance in the 2000-ppm exposure group. A subgroup of rats was examined for grip performance 6 wk postexposure; forelimb grip performance was still smaller in 2000-ppm rats. Forelimb nerves and muscles from these rats then were examined histopathologically, and no treatment-related lesions found. No reason was discovered for this difference in forelimb grip performance. It normally decreases (habituates) over time as a function of experimental conditions, and it is speculated that the daily acute-sedative effect of 2000 ppm 1,1,1-trichloroethane has an interaction with the habituation process. Other than a possible indictor of acute sedation, there was no recognized toxicologic significance to this difference in forelimb grip performance. Furthermore, histopathological examination of rats exposed to 2000 ppm for 13 wk found no effects related to exposure in any organ, including the nervous system.

4.4.2.2.5 Carcinogenesis The EPA (IRIS) classifies methyl chloroform as – D; not classifiable as to human carcinogenicity on the basis that there are no reported human data, and animal studies (one lifetime gavage, one intermediate-term inhalation) have not demonstrated carcinogenicity. Technical-grade 1,1,1-trichloroethane has been shown to be weakly mutagenic, although the contaminant, 1,4-dioxane, a known animal carcinogen, may be responsible for this response.

Carcinogenicity Classification:

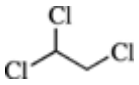
EPA	Group D, Not Classifiable as to Human Carcinogenicity
IARC	Group 3, not classifiable as to its carcinogenicity to humans
ACGIH TLV	A4, Not Classifiable as a Human Carcinogen

4.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV, NIOSH REL ceiling and the OSHA PEL are all 350 ppm. The ACGIH STEL/C is 450 ppm. ACGIH has an A4 designation for this chemical.

Other Occupational Exposure Values: Australia: 125 ppm (1990); Federal Republic of Germany: 200 ppm, short-term level 1000 ppm, 30 min, twice per shift, pregnancy group C, no reason to fear a risk of damage to the developing embryo or fetus when MAK and BAT values are observed (1998); Sweden: 50 ppm, 15-min short-term value 90 ppm (1990); United Kingdom: 350 ppm, 10-min STEL 450 ppm (1991).
4.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

1,1,2-Trichloroethane
5.0.1 CAS Number:
[*79-00-5*]
5.0.2 Synonyms:
Vinyl trichloride, beta-trichloroethane, 1,2,2-trichloroethane, and ethane trichloride (not recommended because of confusion with 1,1,1-trichloroethane)
5.0.3 Trade Names:
NCI-C04579, RCRA Waste Number U227, RCRA Waste Number U359, beta-T
5.0.4 Molecular Weight:
133.40
5.0.5 Formula:
$C_2H_3Cl_3$, $ClH_2C–CHCl_2$
5.0.6 Molecular Structure:



5.1 Chemical and Physical Properties

Physical state	Colorless liquid
Molecular weight	133.41
Specific gravity	1.4397 at 20°C (20/4°C)
Melting point	36.5°C
Boiling point	113.8°C
Vapor pressure	25 torr (25°C) 19 torr (20°C)
Refractive index	1.4711 (20°C)
Percent in “saturated”air	3.3 (25°C)
Solubility	0.44 g/100 g water at 20°C; soluble in ethanol and ethyl ether; 4.50 g/L at 20°C
Flammability	Not flammable by standard tests in air

5.1.1 General

5.1.2 Odor and Warning Properties Although 1,1,2-trichloroethane is reported to have an odor similar to chloroform, no quantitative data were found concerning odor or warning properties. In view of its high systemic toxicity, odor cannot be used to protect against excessive acute or chronic exposure.

5.2 Production and Use

The use of 1,1,2-trichloroethane is quite restrictive. It is used to a slight extent as a specialty solvent but mostly as a chemical intermediate; a solvent for fats, waxes, natural resins, alkaloids, and various other organic materials; intermediate in production of vinylidene chloride and teflon tubing; component of adhesives. The availability of other less toxic solvents discourages its use. Upwards of 95% of this compound manufactured in the United States is consumed in producing vinylidene chloride. Domestic production is about 410 million pounds. It must not be confused with its much less toxic isomer, 1,1,1-trichloroethane.

5.3 Exposure Assessment

1,1,2-Trichloroethane has been detected in ambient urban air at concentrations up to 0.223 m/m^3 (174). It is degraded in the troposphere by reaction with hydroxyl radicals ($t_{1/2}$ = 24 d) (1) to hydrochloric acid, phosgene, formyl chloride, and chloroacetyl chloride.

5.3.3 Workplace Methods NIOSH Method 1003, for halogenated hydrocarbons is recommended for determining workplace exposures to 1,1,2-trichloroethane.

5.3.5 Biomonitoring/Biomarkers 1,1,2-Trichloroethane is absorbed from the lungs and no doubt also is excreted in the breath. Although no data are available, it seems probable that the low concentrations that could be present in expired air after exposure to levels considered safe for occupational exposure will not be useful for monitoring workers exposure. Qualitative analysis might verify that exposure to 1,1,2-trichloroethane has occurred.

Ikeda and Ohtsuji (130) have shown a positive Fujiwara reaction in the urine of rats and mice treated with 1,1,2-trichloroethane, but the value of this determination in humans does not appear to have been investigated. At the low levels of exposure considered acceptable, it may have limited value.

5.4 Toxic Effects

1,1,2-Trichloroethane is toxic by ingestion or inhalation. It is an irritant of the skin, eyes, mucous membranes, and upper respiratory tract. It may be absorbed through the skin, and in high concentrations, it is narcotic. It is a positive animal carcinogen. When heated to decomposition it emits toxic fumes of carbon monoxide, carbon dioxide, hydrogen chloride gas, and phosgene gas.

The principal physiological responses to 1,1,2-trichloroethane are depression of the central nervous system and liver injury. With regard to the CNS effects, it is considerably more potent than chloroform by inhalation (7, pp. 155–156; 175). At narcotic concentrations, ocular and upper respiratory tract irritation is present.

Similarity in chemical names has resulted in some confusion in older literature that misquoted work by Lazarew (175) and stated that the 1,1,2 compound was less toxic than 1,1,2-trichloroethane. Torkelson et al. (95) have explained the source of the error, which could be serious because 1,1,2-trichloroethane is much more hepatotoxic when given to animals by single or repeated doses. Even current literature occasionally confuses the two substances or fails to distinguish between them. No new published reports of human injury were found.

5.4.1 Experimental Studies 5.4.1.1 Acute Toxicity Concentrations of 13,600 ppm for 2 h exposures produce deep narcosis, respiratory arrest, and death (7, 175). Carpenter et al. (176) indicated that exposure of 2000 ppm for 4 h was lethal to rats. Torkelson and Rowe (105) reported hepatic and

renal necrosis for rats inhaling 250 ppm for 4 h. Smyth et al. (63) and Di Vincenzo and Krasavage (177) reported rat oral LD_{50} values for male and female mice at 378 and 491 mg/kg body weight, respectively. Klaassen and Plaa (109) reported a dog interperitoneal LD_{50} of 648 mg/kg. Wahlberg (178) published that repeated applications of 0.5 mL or more to guinea pig skin caused death in all 20 animals in 3 d.

Wright and Shaffer (179) reported that the oral lethal dose for dogs was 0.5 mL/kg. Irish (180) indicated an LD_{50} for rats of 0.1–0.2 g/kg. Liver and kidney pathology were seen at considerably lower doses. Gehring (111) included 1,1,2-trichloroethane in a series of chlorinated solvents evaluated for hepatotoxicity and considered it less hepatotoxic in the rat than carbon tetrachloride or chloroform, but markedly more toxic than 1,1,1-trichloroethane. Klaassen and Plaa (110) and Plaa et al. (181) have confirmed this in mice as well as rats. Watrous and Plaa (182) have indicated that kidney injury also occurs following oral and subcutaneous treatment of mice.

Inhalation: Pozzani et al. (183) reported that a single 7 h exposure to 500 ppm of the vapor was lethal to about half of the rats so exposed. Carpenter reported the acute lethal concentration for about half of the exposed rats to be 2000 ppm for a 4-h exposure followed by a 14-d observation period (176).

5.4.1.2 Chronic and Subchronic Toxicity The critical effect for oral administration, as determined by the EPA (IRIS), is clinical serum chemistry with a NOAEL of 20 mg/L (drinking water 39 mg/kg/d), giving an oral reference dose (RfD) of 4E-3. This was determined from a mouse subchronic drinking water study with a LOAEL of 200 mg/L (drinking water). References for this study are White et al. (184) and Sanders et al. (185).

The studies by White et al. (184) and Sanders et al. (185) were selected by the EPA as the basis for the derivation of the oral RfD because they are considered adequate studies in which mice of both sexes were exposed to 1,1,2-trichloroethane in drinking water for 90 d. Concentrations provided were 0, 20, 200, or 2000 mg/L, which resulted in intakes of 0, 4.4, 46, and 305 mg/kg/d for males and 0, 3.9, 44, and 384 mg/kg/d for females. Clinical chemistry indications of adverse effects on the liver occurred in both sexes at 2000 mg/L. Effects on the erythrocytes occurred only in females, and depressed humoral immune status occurred in both sexes at 200 and 2000 mg/L. The concentration of 20 mg/L, corresponding to 3.9 mg/kg/d for female rats is the NOAEL at which significant adverse effects were not observed and is chosen as the basis for the derivation of an oral RfD.

The previous oral RfD (2E-1 mg/kg/d) was based on the NCI (186) study in rats. This study's major weakness was its lack of reporting of noncancer effects. Also, doses far below the NCI (186) NOAEL (65.7 mg/kg/d) have been shown to alter levels of clinical serum chemistries, which are indicative of systemic tissue damage.

At present the EPA (IRIS) does not provide a reference concentration (RfC) for inhalation exposure.

5.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Yllner (187) injected ^{14}C-labeled, 1,1,2-trichloroethane intraperitoneally in mice. The site of labeling on the molecule was not stated. When collected over a 3-d period, 73–87% of the activity was recovered in the urine. Less than 2% was in the feces; this may have been the result of contamination by urine. Expired air contained 16–22% of the radioactivity (60% $[^{14}C]CO_2$ and 40% unchanged 1,1,2-trichloroethane).

1–3% of the labeled compound remained in the animal. Metabolism by microsomal cytochrome P450 appeared to proceed through chloroacetic acid (188), indicating oxidative dechlorination or dechlorination followed by oxidation of 1,1,2-trichloroethane at the carbon containing two chlorine atoms.

According to VanDyke (136, 189). This is followed by further oxidation of the chloroacetaldehyde

to the corresponding acid. Cytochrome P450 is probably involved in the dechlorination. MacDonald et al. (190) speculated that glutathione is involved in the metabolism of 1,1,2-trichloroethane.

5.4.1.3.1 Absorption Absorption of the liquid through the skin has shown to occur in guinea pigs (174). Jakobson and other workers also investigated the kinetics of absorption through the guinea pigs' skin as well as the nature of injury to the skin with prolonged contact (174, 191). Wahlberg (178) reported that repeated applications of 0.5 mL or more to the skin killed all the guinea pigs in 3 d, but 0.25 mL killed only 5 of 20 animals treated for a longer period of time. Although absorption does not appear to be a serious problem from acute exposure, prolonged or repeated exposure of the skin may result in manifestations of chronic toxicity.

5.4.1.4 Reproductive and Developmental According to Seidenberg et al. (192) pregnant ICR/SIM mice were intubated on days 8 to 12 of gestation with evaluation of the usual parameter of developmental toxicity. The dose (not stated) was selected to produce minimal toxicity based on weight reduction, mortality, or other signs of toxicity. The test results were reported to be negative. No other details were given.

5.4.1.5 Carcinogenesis According to the NCI (185), 1,1,2-trichloroethane has been included in the NCI bioassay program, in which it was fed by gavage to rats and mice. As in many of these studies with hepatotoxic compounds, hepatocellular carcinomas occurred in mice but not rats fed for 78 wk. Rats were kept an additional 35 wk and mice 13 wk following treatment. Pheochromocytomas were also observed in mice. The doses fed were 92 and 46 mg/kg/d for rats and 390 and 195 mg/kg/d for mice. Mortality was accelerated in female mice but not in the rats or male mice. The NCI report does not indicate the degree of noncarcinogenic histopathology produced by these doses.

In a bioassay conducted by NCI (185), technical-grade (92.7%-pure) 1,1,2-trichloroethane was administered by gavage in corn oil to Osborne–Mendel rats and B6C3F$_1$ mice: (50/species/sex/dose) for each of two doses and 20 animals/species/sex for each of two control groups. Administration was 5 times/wk for 78 wk, during which time doses for rats were increased from 70 and 30 mg/kg/d to 100 and 50 mg/kg/d and doses for mice were increased from 300 and 150 mg/kg/d to 400 and 200 mg/kg/d. By two statistical tests, treatment of mice was found to be associated with increased incidence of hepatocellular carcinomas. A dose-related increase in pheochromocytomas was also confirmed in female mice. Tumors found in treated but not control rats included adrenal cortical carcinomas; transitional-cell carcinomas of kidney; renal tubular adenomas; and hemangiosarcomas of spleen, pancreas, abdomen, and subcutaneous tissue. There was, however, no statistically significant increase in tumor incidence in rats as a function of treatment.

5.4.1.6 Genetic and Related Cellular Effects Studies There are numerous references to mutagenic studies on 1,1,2-trichloroethane. It would appear at most to be weakly positive in some systems but negative in others. Mirsalis et al. (193) show that it did not induce unscheduled DNA synthesis but was positive in an S-phase synthesis. 1,1,2-Trichloroethane was found to be nonmutagenic for *Salmonella typhimurium* (194). In rats and mice acutely exposed to 1,1,2-trichloroethane by inhalation and intraperitoneal injection, trichloroacetic acid, trichloroethanol, chloroacetic acid, and thiodiacetic acid were among the urinary metabolites identified (130, 187).

5.4.2 Human Experience Symptoms of exposure to this compound may include irritation of the skin, eyes, nose, mucous membranes, and upper respiratory tract; eye damage; skin cracking and crythema; central nervous system depression; liver and kidney damage; narcosis; drowsiness; incoordination; unconsciousness; and death. Other symptoms may include headache, tremor, dizziness, peripheral paresthesia, hyposthesia, or anesthesia.

The only human studies found relate to permeability in the skin and distribution in the body after inhalation of a radioactive charge. Morgan et al. (195, 196) calculated a blood–air partition coefficient of 44. They also found that 3% of the inhaled chlorine was recovered in exhaled air,

indicating a relatively slow elimination.

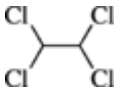
The USEPA (197) determined a permeability coefficient for intact human skin at 8.4×10^{-3} cm/h. Using these data, Tsuruta (198) calculated the dermal uptake of 13.9 mg if both hands were exposed for 1 min.

Wahlenberg (199) determined that a 1.5-mL application to the forearms of adult males for 5 min caused localized hyperemia, transient blanching pain, and burning sensation.

5.4.2.1 General Information 5.4.2.2.5 Carcinogenesis The EPA classifies this compound as - C; possible human carcinogen on the basis of: hepatocellular carcinomas and pheochromocytomas in one strain of mice. Carcinogenicity was not shown in rats. 1,1,2-Trichloroethane is structurally related to 1,2-dichloroethane, a probable human carcinogen. There are no human carcinogenicity data.
5.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV is 10 ppm with an A4 notation. NIOSH considers 1,1,2-trichloroethane as a carcinogen and recommends lowest feasible exposure and an exposure limit of 10 ppm. The OSHA PEL is also 10 ppm with a skin notation.
5.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

1,1,2,2-Tetrachloroethane
6.0.1 CAS Number:
[*79-34-5*]
6.0.2 Synonyms:
Acetylene tetrachloride, 1,1-dichloro-2,2-dichloroethane, sym-tetrachloroethane, 1,1,2,2-TCA
6.0.3 Trade Names:
Bonoform, Cellon, Westron, Acetosol
6.0.4 Molecular Weight:
167.86
6.0.5 Molecular Formula:
$CHCl_2CHCl_2$
6.0.6 Molecular Structure:



6.1 Chemical and Physical Properties

Physical state	Colorless liquid
Molecular weight	167.86
Specific gravity	1.586 (25°C)
Melting point	–44°C
Boiling point	146.3°C

Vapor pressure	6 torr (25°C)
Refractive index	1.4918 (25°C)
Percent in “saturated”air	0.79 (25°C)
Solubility	0.32 g/100 mL water at 25°C; soluble in ethanol and ethyl ether
Flammability	Not flammable by standard tests in air

1 mg/L 145.8 ppm and 1 ppm 6.86 mg/m^3 at 25°C, 760 torr.

This compound has the highest solvent power of the chlorinated hydrocarbons.

6.1.1 General An ATSDR toxicological Profile for 1,1,2,2-trichloroethane is available (3).

6.1.2 Odor and Warning Properties 1,1,2,2-Tetrachloroethane has a mild, sweetish odor similar to several other chlorinated hydrocarbons. Lehmann and Schmidt-Kehl (200) reported 3 ppm to have a noticeable odor and 13 ppm to be tolerated for 10 min. Concentrations of 186 ppm inhaled for 30 min, or 335 ppm inhaled for 10 min, have a disagreeable and marked odor, causing upper respiratory irritation and CNS effects. Because the odor is not particularly striking, and because the acceptable level is 1 ppm, odor does not appear to be of value as a warning property. Amoore and Hautala (10) reported 1.5 ppm was detectable by humans.

6.2 Production and Use

1,1,2,2-Tetrachloroethane was formerly used as a solvent for cleaning and extraction processes and is still used to some extent as a chemical intermediate. Present usage is quite limited because less toxic solvents are available.

6.3 Exposure Assessment

6.3.3 Workplace Methods NIOSH Method 1019 is recommended for determining workplace exposures to 1,1,2,2-tetrachloroethane.

6.3.5 Biomonitoring/Biomarkers The apparent high toxicity of 1,1,2,2-tetrachloroethane would suggest that neither breath nor urine analysis would be adequately sensitive for monitoring exposures at the low level considered acceptable for occupational exposures.

6.4 Toxic Effects

According to Sax and Lewis (201), 1,1,2,2-tetrachloroethane is a poison by inhalation, ingestion, and intraperitoneal routes and is moderately toxic by several other routes. It is considered to be the most toxic of the common chlorinated hydrocarbons. It is considered to be a very severe industrial hazard, and its use has been restricted or even forbidden in certain countries. Its narcotic action is stronger than that of chloroform, but because of its low volatility, narcosis is less severe and much less common in industrial poisoning than in the case of other chlorinated hydrocarbons. It is a lacrimator and irritant of the skin, eyes, nose, throat, mucous membranes, and respiratory tract. When heated to decomposition, it emits toxic fumes of carbon monoxide, carbon dioxide, hydrogen chloride gas, and phosgene.

The most significant injury from subacute or chronic exposures has been reported to be in the liver. The first indication may be a greatly enlarged and palpable liver, which may progress to fatty degeneration, jaundice, and cirrhosis. Injury to the kidneys may also be observed.

This compound also causes CNS depression, dizziness, and incoordination, as do many chlorinated hydrocarbons. In very severe acute exposures, unconsciousness and death from respiratory failure may be seen. Central nervous system depression is not a striking part of the response to usual industrial exposure because of low volatility and because other injurious effects predominate at lower levels. Respiratory irritation may be observed and may lead to pulmonary damage. A significant irritation in the gastrointestinal tract is also observed and may result in nausea, vomiting, and gastric pain.

Literature reviews are available (7, 202, 203), but there is a remarkable lack of quantitative data in animals to support the apparent high toxicity in humans. It is possible, however, that inhaled concentrations have been underestimated, that dermal contact has been more significant than realized, or that the purity of industrial 1,1,2,2-tetrachloroethane available at that time was less than later production.

Limited data on the 1,1,1,2 isomer (204) indicate that this isomer may be less toxic than the symmetrical isomer.

6.4.1 Experimental Studies 6.4.1.1 Acute Toxicity Barsoum and Saad (205) reported that an oral dose of 0.7 g/kg body weight in dogs is a toxic dose, but Wright and Schaffer (179) reported that a lethal dose for dogs was 0.3 mL/kg (0.5 g/kg) given orally. Smyth et al. (63) reported an oral LD_{50} of 200 mg/kg in rats, but did not specify which isomer they used, although a prior publication refers to the 1,1,2,2-tetrachloroethane isomer (45). Gohlke et al. (206) reported deaths of rats treated with 250 mg/kg.

Schwander (207) indicated that 1,1,2,2-tetrachloroethane may be absorbed through the intact skin. However, it does not have a high acute toxicity by this route; Smyth (45) reported an acute dermal LD_{50} of 4 g/kg in rabbits. Based on experience, repeated exposure may be of considerable concern. It has a solvent effect on the skin, but no data on eye irritation by the liquid were found.

Although there are a number of animal experiments with this material, a clean-cut quantitative study of animal response from acute exposure has not been reported. Smyth et al. (63) quoted unpublished work by their laboratory indicating that rats were found to survive a 4 h exposure at 500 ppm but would not survive 4 h at 1000 ppm. They also reported three of six rats exposed to 1000 ppm for 4 h died.

In a report that does not appear to be consistent with oral studies, daily doses of 100–800 mg/kg (17–130 mg/kg/d) were injected intraperitoneally for 7 d in male rats with no toxic symptoms. Liver enzymes and possible hematologic changes were reported (208).

1,1,2,2-TCA is moderately irritating to the skin, and vapors appear nonirritating to the eye of the dog (209). Liver damage involving cytochrome P450 and possibly mediated through free radicals interfering with *in vivo* lipid peroxidation has been reported in mice following single 300 or 600 mg/kg doses (210).

The acute inhalation toxicity of 1,1,2,2-TCA has been thoroughly studied and is relatively low. A 4 h LC_{50} of 1000 ppm for rats has been reported (176); a second investigation found lethality beginning at 1000 ppm (211). The corresponding number for the mouse is 655 ppm, with all mice dying at 786 ppm (212). Narcosis is seen in mice inhaling 625 ppm (49) and in cats at 1000 ppm (175) for 1 h.

Guinea pigs show eye irritation when exposed at 576 ppm, narcosis at 5050 ppm, and death at 6310 ppm (213). Reflex reactivity in mice is reduced within 30 min when inhaling 1091 ppm 1,1,2,2-TCA (175). At the lower end of the dose–response curve, a decrease in spontaneous motor activity was seen in rats inhaling 200 ppm for a single 6 h period (214), and no effects were reported following a 30-min exposure at 576 ppm (213).

6.4.1.2 Chronic and Subchronic Toxicity The EPA (IRIS) has not determined a reference dose or reference concentration for this material (2).

Lehmann and Flury (16) reported data from limited vapor experiments on cats and rabbits, which were exposed to a concentration of 100 to 160 ppm for 8–9 h daily for 4 wk. No typical organ

changes were found. These observations are rather surprising when, as is discussed later, industrial experience indicates that injury to humans has occurred at much lower concentrations.

Navrotskii et al. (215) exposed rabbits to tetrachloroethane (presumably the 1,1,2,2 isomer) vapor for 7–11 m. The 3–4-h daily exposures were to 100 mg/m^3 (14.6 ppm). According to the available abstract, only slight effects on the liver were observed. Schmidt et al. (216) also reported only slight effects in rats exposed to 15 mg/m^3 (2 ppm) for 265 d and considered their results somewhat inconclusive. Some toxicologic parameters deviated during the exposure but were not different from the controls at the end. Mortality was not affected, but histological examination appears to have been inadequate to evaluate chronic effects.

Truffert et al. (217) reported exposing rats 6 h/d, 5 d/wk for 15 wk to 260 ppm with no effect on the respiratory or renal toxicity, but increased deposits were found in the liver.

6.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Studies have shown that 1,1,2,2-trichloroethane is readily absorbed via the lungs or gastrointestinal tract. Some authors have indicated absorption by the skin. It is apparently readily excreted by the lungs.

Yllner (218) injected ^{14}C-labeled 1,1,2,2-tetrachloroethane intraperitoneally in female albino mice at doses of 0.21 to 0.32 g/kg and studied the elimination for 3 days. About half the dose, 45 to 61 percent, was exhaled as carbon dioxide with 28 percent excreted in the urine. About 16 percent remained in the animal and only 4 percent was expired unchanged. Several products were found in the urine with half the urinary activity unaccounted for. Both enzymatic and nonezymatic activity was postulated. Enzymatic hydrolytic fission of chlorine-carbon bonds results in dichloroacetic acid and glycolic acid. Nonenzymatic dehydrochlorination results in trichloroethylene and subsequently trichloroethanol and trichloroacetic acid.

When fed to rats and mice, more than 90 percent of the dose was metabolized (219). Although there was incorporation in mouse DNA, it was not by adduct formation. These authors concluded that their data supported a cytotoxic rather than a genetic mechanism of carcinogenesis observed in mice.

Ikeda and Ohtsuji (130) also found trichloro products in the urine of mice and rats exposed for 8 h to 100 ppm of 1,1,2,2-tetrachloroethane vapor.

6.4.1.4 Reproductive and Developmental A very limited reproduction study by Rosenkrantz (220) indicated no gross reproductive or teratological effect in rats exposed daily for 9 mo prior to mating. A second report by Schmidt (221) describes fetotoxic (lethal) effects in two strains of mice given intraperitoneal injections of tetrachloroethane, presumably the 1,1,2,2-isomer. The doses administered, 300, 400, or 700 mg/kg/d were given singly or on several days of pregnancy. According to the author's summary, the compound was fetotoxic and faintly teratogenic.

The reproductive organs have not been target organs in the limited studies in animals.

6.4.1.5 Carcinogenesis The EPA (IRIS) has classified this material as –C, possible human carcinogen on the basis of increased incidence of hepatocellar carcinomas in mice (222).

The National Cancer Institute (222) has included 1,1,2,2-tetrachloroethane in their bioassay series using rats and mice. Their summary states that the time-weighted average doses (by gavage) were 108 and 62 mg/kg/d for male rats, 76 and 43 mg/kg/d for female rats, and 282 and 142 mg/kg/d for all mice. There was a highly significant positive dose-related trend in the incidence of hepatocellular carcinoma in mice of both sexes. No statistically significant incidence of neoplastic lesions was observed in male or female rats. However, 2 hepatocellular carcinomas and 1 neoplastic nodule, which are rare tumors in the male Osborne–Mendel rat, were observed in the high-dose males. Under the conditions of this bioassay, orally administered 1,1,2,2-tetrachloroethane was a liver carcinogen

in B6C3Fl mice of both sexes. The results did not provide conclusive evidence for the carcinogenicity of 1,1,2,2-tetrachloroethane in Osborne–Mendel rats.

6.4.1.6 Genetic and Related Cellular Effects Studies Mixed results have been obtained in mutagenic studies with most results negative (203). Schumann et al. (219) found little binding to DNA of rats and mice due to adduct formation, indicating a low potential for direct mutagenic activity.

6.4.2 Human Experience Symptoms of exposure to this compound may include irritation of the skin, eyes, nose, throat, mucous membranes, and respiratory tract. Lacrimation may occur. Corrosion may also occur. Other symptoms of exposure include drowsiness, headache, jaundice, abdominal pain or distress, tremor, fatigue, constipation, insomnia, irritability, anorexia, loss of appetite, pulmonary edema, nephritis, albumin and casts in the urine, and kidney damage. Giddiness and unconsciousness have occurred. Central nervous system effects include general anesthesia, somnolence, hallucinations, and distorted perceptions. Other effects include narcosis, acute yellow atrophy of the liver, liver cirrhosis, fatty degeneration of the kidneys and heart, brain changes, changes in the peripheral nerves, hemolysis, salivation, restlessness, dizziness, nausea, vomiting, coma, and death. Monocytosis, dermatitis, liver tenderness and damage, delirium, and convulsions may occur. Oliguria, cyanosis, central nervous system depression, uremia, peripheral paresthesia, and hypesthesia may also occur. Exposure may cause prickling sensation and numbness of limbs, loss of kneejerk, sweating, paralysis of the interossei muscles of the hands and feet, disappearance of ocular and pharyngeal reflexes, peripheral neuritis, liver dysfunction, general malaise, an unpleasant taste in the mouth, mental confusion, stupor, hematemesis, purpuric rashes, and blood changes, including an increase in mononuclear leukocytes, progressive anemia, and slight thrombocytosis. Gastrointestinal disturbances may occur. It may also cause liver necrosis, nervousness, incoordination, respiratory failure, and enlargement and fatty degeneration of the liver. Heart damage has been reported. Neurological disturbances have also been reported. It can cause hepatitis, gastric pain, vertigo, and leukopenia. It can also cause a deep dusky coloration of the skin, weight loss, pain over the liver, dark urine, and bilirubinuria. Pulmonary damage, gastrointestinal irritation, barely perceptible pulse, and shallow and rapid respiration may result. Other symptoms that may occur are polyneuritis (inflammation of the nerves), conjunctivitis, extreme exhaustion, hematuria, mental instability, cardiac irregularity, and epigastalgia. Skin contact may result in dryness, scaling, and inflammation. Severe lesions may occur. Eye contact may result in burning and serious eye damage. Inhalation may cause a burning sensation, wheezing, coughing, laryngitis, and shortness of breath. Ingestion may cause diarrhea and severe mucosal injury.

The review by von Oettingen (7) summarizes much of the old data on human experience and based on numerous cases describes the rather severe effects discussed earlier in this section.

Sherman (223) reported on eight humans who were given 3 mL of tetrachloroethane by mistake. It was given with 30 g of magnesium sulfate and water. Within 1.5–2.5 h, all were comatose. Reflexes were absent and the pulse barely perceptible. Respiration was shallow and rapid. The patients all recovered and showed no after-effects.

Gurney (224) reported a number of cases of chronic exposure to 1,1,2,2-tetrachloroethane. He studied 277 individuals of whom 75 had symptoms and 55 had enlarged livers. There were nearly as many with enlarged livers among those who did not show symptoms as there were among those who did. Coyer (225) reported on six cases, one of which was fatal.

It is evident from clinical reports of exposure to 1,1,2,2-tetrachloroethane that the principal effect involves the liver. Symptoms referrable to gastrointestinal injury may also be observed.

A study of mortality of army personnel who treated clothing with impregnite for protection against mustard gas in World War II has been reported (226). Tetrachloroethane was used as a solvent for the impregnite (N,N-dichlorohexachlorodiphenylurea). The exposed group was compared with a control group that used a water-based system and with unexposed personnel from the same unit.

Overall deaths during the 31 yr follow-up period were less than expected, possibly related to the screening process used in selection of military personnel. The investigators, however, considered that some other cancers may have shown an increase.

The adverse health effects of 1,1,2,2-TCA first became apparent at the beginning of World War I with reports of numerous poisonings of workers in the aircraft industries of several European countries (227, 228), Many deaths were reported, and most cases presented a clinical picture characterized by gastrointestinal, hepatic, and nervous system effects. Although none of a large number of clinical cases contains quantitative exposure data, they consistently indicate primary involvement of the liver (229–232). In domestic airplane factories, complaints of headaches, drowsiness, and nausea, without more serious signs, were attributed to a limited production and short exposure time (lesser exposures) (233). From suicide cases that present similar clinical findings, estimates of a human fatal oral dose ranging from 285 (234) to 6000 mg/kg (235) have been made. The lowest adverse effect level has been estimated to be 100 mg/kg.

Seventy-five workers employed at a plant producing and using 1,1,2,2-TCA were studied for their cardiovascular status. Exposure concentrations ranged from 0.37 to 3.20 ppm, with occasional peaks to 40 ppm. The authors concluded that chronic low-level exposure caused no greater occurrence of cardiovascular lesions than that in the general population (236).

In humans, 97% of an inhaled single-breath dose of 1,1,2,2-TCA is absorbed with very little (3.3%) exhaled as unchanged chemical; urinary excretion was 0.015%/min (195). The metabolism and kinetics in humans have not been as well developed as for chlorinated solvents such as trichloro- and tetrachloroethylene (for which biologic exposure indices exist).

Of 380 workers examined in the workplace where 1,1,2,2-TCA was the solvent for cellulose acetate, 192 were in direct contact, and some of the remaining 188 workers were occasionally exposed to its vapors. The signs of poisoning in the workers were most frequently of the nervous system. These symptoms were characterized by tremor and increased with the amount of solvent in the air. Jaundice was not detected in any of the workers (237).

Early work of Lehman suggests that, in humans, a concentration of 3 ppm 1,1,2,2-TCA may be detected by odor, 13 ppm may be tolerated without effect for 10 min, and inhalation of 145 ppm for 30 min or 334 ppm for 10 min will cause irritation of the mucous membranes, pressure in the head, vertigo, and fatigue (200).

6.4.2.3.5 Carcinogenesis Carcinogenic Classification:

EPA	Group 3, possible human carcinogen.
IARC	Group 3, not classifiable as to its carcinogenicity in humans
MAK	Group B, justifiably suspected of having carcinogenic potential
NIOSH	Carcinogen, with no further categorization
TLV	A3, animal carcinogen

6.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV is 1 ppm with an A3 and skin notation. NIOSH considers 1,1,2,2-TCA a carcinogen and recommends the lowest feasible exposure and an REL of 1 ppm. The OSHA PEL is 5 ppm with a skin notation.

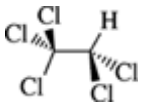
Other Nations: Australia: 1 ppm, skin (1993); Federal Republic of Germany: 1 ppm, skin, Group B, justifiably suspected of having carcinogenic potential (1997).

6.6 Studies on Environmental Impact

None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Pentachloroethane
7.0.1 CAS Number:
[*76-01-7*]
7.0.2 Synonyms:
Ethane pentachloride
7.0.3 Trade Names:
Pentalin
7.0.4 Molecular Weight:
202.29
7.0.5 Molecular Formula:
$CHCl_2CCl_3$
7.0.6 Molecular Structure:



7.1 Chemical and Physical Properties

Physical state	Colorless liquid
Specific gravity	1.6712 (25/4°C)
Melting point	–29°C
Boiling point	162°C
Vapor pressure	3.4 torr (25°C)
Refractive index	1.50250 (24°C)
Percent in “saturated air”	0.45 (25°C)
Solubility	0.05 g/100 mL at 20°C; soluble in ethanol, ethyl ether
Flammability	Not flammable by standard tests in air

7.1.1 General No new information was found since last edition.

7.1.2 Odor and Warning Properties Pentachloroethane has a sweetish odor, not unlike chloroform. The threshold at which the odor is detected has not been determined, and therefore its value as a warning is not known.
7.2 Production and Use
Pentachloroethane has been used as a solvent and chemical intermediate but has had little commercial utilization. Pentachloroethane is used as a solvent for oil and grease in metal cleaning; in the separation of cola from impurities by density difference; as a chemical intermediate, in the manufacture of tetrachloroethylene and dichloroacetic acid; as a solvent for cellulose acetate, certain cellulose ethers, resins, and gums; as a drying agent for timber by immersion at temperatures greater than 100°C; in dry cleaning and soil sterilizing.
7.3 Exposure Assessment
No information found.

7.3.3 Workplace Methods NIOSH Method 2517 is recommended for determining workplace exposures to pentachloroethane.

7.4 Toxic Effects

Sax and Lewis (242) report that pentachloroethane is a poison by inhalation and intravenous routes and is an experimental carcinogen, and moderately toxic by ingestion and subcutaneous routes. It is irritating to the eyes, lungs, corneas, upper respiratory tract, the skin, and mucous membranes. It is very toxic by inhalation, or skin absorption. It has a strong narcotic effect. When heated to decomposition, this compound emits highly toxic fumes of CO, CO_2, and HCl.

Toxicologic data on pentachloroethane are quite limited. Pentachloroethane has a narcotic effect that has been indicated to be even greater than that of chloroform. Exposure to this material may also result in injury to the liver, lungs, and kidneys, but rats and mice have tolerated rather high doses without injury. It has caused liver tumors in mice but not in rats.

7.4.1 Experimental Studies 7.4.1.1 Acute Toxicity Barsoum and Saad (205) reported the lethal oral dose to be 1.75 g/kg of body weight.

Lehmann and Flury (16) indicated that cats inhaled 1 mg/L of air (120 ppm) 8–9 h daily for 23 d without overt symptoms of poisoning. However, they showed significant pathological changes in the liver, lungs, and kidneys. Dogs exposed to the vapor for 3 wk showed fatty degeneration of the liver and injury to the kidneys and lungs.

7.4.1.2 Chronic and Subchronic Toxicity Navrotskii et al. (215) exposed rabbits to 100 or 10 mg pentachloroethane vapor per cubic meter of air 3–4 h daily for 7–11 m. Only limited data are discussed in the available abstract. Antibody titers were reported to be elevated after 1–1.5 m exposure to 100 mg/m^3 (12 ppm). The abstract also states that toxic effects occurred at 10 mg/m^3 but the nature of the toxic effects is not specified.

Pentachloroethane containing 4.2% hexachloroethane was studied by Mennear et al. (243). The material was administered by gavage to rats and mice of both sexes. Prechronic studies of 2 and 13 wk failed to reveal specific target organ toxicity at 10, 50, 100, 500, or 1000 mg/kg. However, all rats fed 1000 mg/kg/d died within 4 d, although the same dose was lethal to only one female mouse. The 500-mg/kg/d dose was lethal to 3/5 rats of each sex between the fourth and tenth day. Decreased motor activity and lethargy were observed but little body weight loss. There were no gross or histological changes.

When fed 5 d/wk for 13 wk at doses of 5, 10, 50, 125, or 250 mg/kg/d to rats or 5, 10, 50, 100, or 500 mg/kg/d to mice, weight loss was the only parameter affected by treatment. All rats survived, and only those fed 250 mg failed to gain weight at the rate of the controls. Only one mouse treated with 500 mg/d died, but weight gain of this group was 29% less than controls. Gross and histopathology were considered normal after 13 wk.

7.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Yllner (244) injected ^{14}C-pentachloroethane subcutaneously in mice at doses of 1.1–1.8 g/kg and determined the excretion over a 3 d period. About 1/3 of the dose (12–51%) was expired unchanged; 16–32% was excreted as 2,2,2-trichloroethanol, and 9–18% as trichloroacetic acid in the urine. The expired air also contained trichloroethylene (3–9% of the dose), indicating both dechlorination and dehydrochlorination.

Town and Leibman (245) reported that a cytochrome P450–dependent monooxygenase system was involved in the dechlorination of pentachloroethane to trichloroethylene and 1,1,2,2-tetrachloroethane. Bronzetti et al. (246) considered P448 to be more important. In a report available only as an abstract, weak covalent binding was reported following intraperitoneal injection (247). Labeled pentachloroethane was reported to be bioactivated by cell-free microsomal and cytosolic enzymes from mouse and rats organs.

The role of a-2m-globulin and protein droplet formation in the male rat kidneys has been studied because it is possibly involved in the production of kidney pathology and cancer in male rats (248).

7.4.1.4 Reproductive and Developmental No information on teratology or reporoduction were found. The reproductive organs were not affected in any of the studies reported previously.

7.4.1.5 Carcinogenesis When fed 5 d/wk to male rats for 104 wk at doses of 75 and 150 mg/kg/d, mortality was excessive and body weight gain was below controls starting at 76 wk. Weight gain was decreased in female rats at both levels starting at 42 wk, but mortality in both sexes was increased only at 150 mg/kg/d. No increase in tumors was found, but there was a dose-related increase in the incidence of chronic renal inflammation of male rats and mineralization of renal papillae.

Survival of mice similarly treated with 250–500 mg/kg/d was significantly shortened, and hepatocellular carcinomas were increased. The only other tumor showing an increase was in female mice, where there was a dose-related increase in hepatocellular adenoma. The cause of death did not appear to be either the renal lesions in male rats or the liver tumors in mice, and no other target organs were found to explain the deaths.

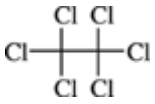
7.4.1.6 Genetic and Related Cellular Effects Studies Mutagenic data are limited and equivocal in yeast (246) and negative in *S. typhimurium* (249).

7.4.2 Human Experience Symptoms of exposure to this compound may include irritation of the eyes, lungs, and upper respiratory tract. It may cause irritation of the skin and mucous membranes. It may also cause drowsiness, giddiness, jaundice, headache, and, in high concentrations, unconsciousness. It may also affect the central nervous system and the blood. Overexposure to this compound may damage the liver and kidneys.
7.5 Standards, Regulations, or Guidelines of Exposure
No standards have been proposed for pentachloroethane. It is probably not possible to set a reliable standard because of the limited toxicologic information and experience reported on this material. It is obvious that a concentration safe for repeated exposure would be well below the 121 ppm that was shown to cause pathological change. The unconfirmed report of Navrotskii suggests that exposures be kept much lower. NIOSH recommends that this substance be handled with caution in the workplace.
7.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Hexachloroethane
8.0.1 CAS Number:
[*67-72-1*]
8.0.2 Synonyms:
Carbon hexachloride, ethane hexachloride, hexachloroethylene, 1,1,1,2,2,2-hexachloroethane, HCE, ethylene hexachloride, and perchloroethane
8.0.3 Trade Names:
A Vlothane, Distokal, Distopan, Distopin, Egitol, Falkitol, Fasciolin, Mottenhexe, Phenohep
8.0.4 Molecular Weight:
236.74

8.0.5 Molecular Formula:
C_2Cl_6, Cl_3CCCl_3
8.0.6 Molecular Structure:



8.1 Chemical and Physical Properties

Physical state	Solid <294> rhombic crystals
Specific gravity	2.091 (20°C)
Melting point	Sublimes at 186.8°C
Boiling point	189°C
Solubility	0.005 g/100 mL water at 22°C; soluble in ethanol, ethyle ether
Flammability	Not flammable by standard tests in air

8.1.1 General An ATSDR Toxicological profile for hexachlorethane is available (250). It is found as colorless crystal.

8.1.2 Odor and Warning Properties Hexachloroethane is reported to have a camphorous odor.
8.2 Production and Use
Hexachloroethane has been used as a chemical intermediate, in pyrotechnics, as an insecticide, and as a parasiticide in animals. It is an undesired by-product of certain chlorination processes and is of environmental concern in soil and water.
8.3 Exposure Assessment
HCE has been employed in veterinary practice as an anthelmintic for livestock, but it is doubtful that it is still used for this purpose. While some may be used as an insecticide and in chemical manufacture, large amounts are used by the United States Army in pyrotechnics and smoke devices (251). It is a by-product of certain chlorination processes, sometimes appearing in waste tars. HCE is produced in France, Spain, and the United Kingdom; it is not manufactured in the United States (252). HCE imported for 1985 was reported to be 1,124,000 kg (253).

8.3.3 Workplace Methods NIOSH Method 1003, for halogenated hydrocarbons is recommended for determining workplace exposures to hexachloroethane (10a).

8.3.5 Biomonitoring/Biomarkers Biologic monitoring of exposed workers may determine if exposure has occurred, but at this time available data appear inadequate to quantify exposure.
8.4 Toxic Effects
According to Sax (254), hexachloroethane has high toxicity via intravenous and moderate via oral, intraperitoneal, and dermal routes. It is irritating to the skin, eyes, mucous membranes, and upper respiratory tract. When heated to decomposition, it emits toxic fumes of CO,CO_2, HCl gas, and phosgene. It is absorbed through the skin. It is a positive animal carcinogen.

Much of the experience with this material has come about because of its use as a parasiticide in animals, although more recent articles indicate renewed interest in this chemical because of environmental concerns, and its use in pyrotechnics. Von Oettingen (7) reviewed the literature available in 1955 and Oak Ridge National Laboratory in 1988 (255). It is possible that some of the effects ascribed to hexachloroethane in the older literature may have been due to impurities in the samples tested. It has been shown to produce liver cancer in mice and kidney cancer in male rats.

The kidneys appear to be the target organ, and males are more affected that female laboratory animals.

8.4.1 Experimental Studies 8.4.1.1 Acute Toxicity Hexachloroethane has a low acute oral toxicity. Thorpe (256) reported the LD_{50} for rats to be 5.9 g/kg, a value consistent with Reynolds and Yee (257), who reported rats survived 6.16 g/kg for up to 24 h, and Barsoum and Saad (205), who reported dogs survived 6 g/kg. A dose of 6 g/kg over a 2-d period was lethal to cats (258). Similar figures are given in Table 63.5 taken from Weeks et al. (251).

Table 63.5. Lethal Dosages for Animals Following Single Administration of Hexachloroethane

Animal	Treatment[a]	Diluent	Dosage (mg/kg)
Rabbit, male	Oral ALD	Methylcellulose	>1,000
Rat, male	Intraperitoneal ALD	Corn oil	2,900
Rat, female	Oral LD_{50}	Corn oil	4,460
		Methylcellulose	7,080
Rat, male	Oral LD_{50}	Corn oil	5,160
		Methylcellulose	7,690
Guinea pig, male	Oral LD_{50}	Corn oil	4,970
Rabbit, male	Dermal LD_{50}	Water paste	≥32,000

The toxicity in larger species such as dogs and cattle is consistent with the laboratory animals.

Twelve daily oral doses of 1000 mg/kg to rabbits cause significant reduction in body weight and increased relative liver and kidney weights. Gross and histology injury occurred in the liver and kidneys. Daily doses of 320 mg/kg caused liver injury, but 100 mg/kg caused no significant effect (251). When fed to rats to determine the maximum tolerated dose in the NTP studies discussed subsequently, the following results were reported (259). In the 16-d studies (dose range, 187–3000 mg/kg), all rats that received 1500 or 3000 mg/kg and 1/5 males and 2/5 females that received 750 mg/kg died before the end of the studies. Final mean body weights of rats that received 750 mg/kg were 25% lower than that of vehicle controls for males and 37% lower for females. Compound-related clinical signs seen at 750 mg/kg or more included dyspnea, ataxia, prostration, and excessive lacrimation. Other compound-related effects included hyaline droplet formation in the tubular epithelial cells in all dosed males and tubular cell regeneration and granular casts in the tubules at the corticomedullary junction in the kidney in males receiving 187 and 375 mg/kg.

Weeks et al. (251) reported reversible injury when crystalline hexachloroethane was applied to the cornea of rabbit eyes for a prolonged period. It produced little or no skin irritation and did not appear to be significantly absorbed percutaneously. The dermal LD_{50} was greater than 32 g/kg by this route. The compound did not sensitize the skin of guinea pigs.

Rats exposed to 2.5 mg/L (260 ppm) of the vapors for 8 h showed no adverse effects, but 57 mg/L caused severe injury, including death. The higher concentration was supersaturated and contained particles of hexachloroethane (251).

Barsoum and Saad (205) indicated that an intravenous dose of 325 mg/kg in dogs resulted in death.

A corresponding dose for pentachloroethane was found to be 100 mg, and for chloroform, 90 mg. This would indicate that hexachloroethane is intrinsically less toxic than the other materials, or is absorbed much more slowly. Weeks et al. found the approximate lethal dose (ALD) when injected intraperitoneally in male rats to be 2900 mg/kg, and Baganz et al. (260) determined an LD_{50} for white mice of 4500 mg/kg by this route.

Weeks et al. (251) published the oral lethal dose (approximate) for rabbits as greater than 1000 mg/kg, the oral LD_{50} for rats at 4460 mg/kg (corn oil) Applied to the shaved skin of rabbits, the dermal LD_{50} was 32,000 mg/kg, and it did not sensitize guinea pigs. Rats exposed for 8 h at a calculated 59,000 ppm vapor showed severe toxic signs and death, but no toxic effects were observed for 8 h at 260 ppm.

8.4.1.2 Chronic and Subchronic Toxicity The EPA (IRIS) considers the critical effect for oral exposure is "atrophy and degeneration of the renal tubules, with a NOAEL of 1 mg/kg/d and a LOAEL of 15 mg/kg/d and a reference dose (RfD) of 1E-3. This is based on a rat subchronic dietary study by Gorzinski et al. (261), as summarized here:

Groups of 10 male and 10 female Fischer 344 rats were treated with diets containing hexachloroethane for 16 wk. Dosages were 0, 1, 15, or 62 mg/kg/d, as determined by the investigators. The rats were evaluated for overt signs of toxicity, body weight gain, food consumption; urinalysis, hematological and clinical chemistry parameters; organ weights; and gross pathology. Comprehensive histologic examination was performed on the control and 62 mg/kg/d groups, while histologic examination of the 1- and 15-mg/kg/d groups was limited to the liver and kidney. At 15 and 62 mg/kg/d, male rats had dose-related increased incidences of renal lesions, including renal atrophy, degeneration, hypertrophy, and dilation. At 62 mg/kg/d, males had increased absolute and relative kidney weights and peritubular fibrosis; females had slight renal tubular atrophy and increased liver weights. No other effects were observed. Thus 15 mg/kg/d is the LOAEL and 1 mg/kg/d is the NOAEL.

In a draft report for a subchronic gavage study (262) rats were treated by gavage with 0, 47, 94, 188, 375, or 750 mg/kg/d, 5 d/wk for 13 wk. Body weight gain was reduced at 750 mg/kg/d, behavioral signs of toxicity were seen at 94 mg/kg/d, and increased relative liver and kidney weights occurred at 375 mg/kg/d. Dose-related increased incidences of renal tubular regeneration occurred at 47 mg/kg/d.

In a 6 wk inhalation study, rats, dogs, and guinea pigs were exposed to hexachloroethane 6 h/d, 5 d/wk for 6 wk at 0, 145, 465, or 2520 mg/m^3 (251). Neurobehavioral effects occurred in rats and dogs, and reduced body weights, increased relative liver weights, and deaths occurred in guinea pigs at 2520 mg/m^3. No effects were observed at 465 mg/m^3. Based on this inhalation NOAEL in rats, an RfD of 0.03 mg/kg/d could be calculated using an uncertainty factor of 1000. However, a later 16 wk oral study by Gorzinski et al. (261) is a better basis for the RfD.

When fed for 3 wk at dosages much higher than used by Gorzinski, NTP (259) reported the following results: In the 13 wk studies (dose range, 47–750 mg/kg), 5/10 male rats and 2/10 female rats that received 750 mg/kg died before the end of the studies. The final mean body weight of male rats that received 750 mg/kg was 19% lower than that of vehicle controls. Compound-related clinical signs for both sexes included hyperactivity at doses of 94 mg/kg or higher and convulsions at doses of 375 or 750 mg/kg. The relative weights of liver, heart, and kidney were increased for exposed males and females. Kidney lesions were seen in all dosed male groups, and the severity increased with dose. Papillary necrosis and tubular cell necrosis and degeneration in the kidney and hemorrhagic necrosis in the urinary bladder were observed in the five male rats that received 750 mg/kg and died before the end of the studies; at all lower doses, hyaline droplets, tubular regeneration, and granular casts were present in the kidney. No chemical-related kidney lesions were

observed in females. Foci of hepatocellular necrosis were observed in several male and female rats at doses of 188 mg/kg or higher.

Rats, dogs, guinea pigs, and quail were exposed 6 h/d, 5 d/wk for 6 wk to hexachloroethane vapor (van Haaften (263)). Extensive studies were conducted to determine possible injury including behavioral, reproductive, clinical chemical, hematologic, and histological examinations. Animals exposed to 260 ppm were seriously affected, including death (except for quail). Quail showed no adverse effect at any dosage. There was no evidence of injury of any type in any species at 15 ppm. Exposure to 48 ppm caused minimal injury. The most significant effects appeared to be irritation of the eyes and respiratory tract. Apparently liver and kidney injury were not significant at these levels of exposure.

8.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Jondorf et al. (264) reported that an oral dose of 0.5 g/kg of body weight in a rabbit was slowly metabolized. Approximately 5% appeared in the urine in a period of 3 d and from 14 to 24% in the expired air. These authors used chromatographic and isotopic dilution techniques to determine the nature of the metabolities in the urine. These were reported as percent of the dose given: trichloroethanol, 1.3; dichloroethanol, 0.4; trichloroacetic acid, 1.3; dichloroacetic acid, 0.8; monochloroacetic acid, 0.7; and oxalic acid, 0.1.

Fowler reported different results for sheep and Leghorn cockerels (265, 266), but the differences in the methods used make it impossible to compare the data from these species with those from rats. Interestingly, hexachloroethane is reported to be a metabolite of carbon tetrachloride but not chloroform. For details see the section on metabolism of chloroform.

Gorzinski et al. (261) analyzed liver, kidneys, blood, and adipose tissue from rats fed hexachloroethane in a 110 d dietary feeding study described in a preceding section. After 57 d the authors reported that the “concentration of HCE in the kidneys of male rats was significantly higher at all dose levels when compared to females (mg HCE/g of kidney with increasing dose <294>males: 1.4, 24.3, 95.1; females: 0.4, 0.7, 2.0); this is consistent with the more pronounced renal toxicity noted for male rats. However, the results of the tissue analysis indicated that HCE was cleared in an apparent first-order manner with a half-life estimated to be 2–3 days.”

The metabolism (reductive dechlorination) of hexachloroethane in rats and mice is mediated by microsomal cytochrome P450 with oxidation of NADPH. Dechlorination with loss of two chlorines in a two-step process produces the major metabolite tetrachloroethylene. Much less pentachloroethane and trichloroethylene are produced. Further metabolism results in some of the same substances as tetrachloroethylene itself.

Hexachloroethane, being fat soluble, enters those tissues that are lipoid in nature, but has been shown to be present at higher concentrations in male rat kidneys than in females. This is consistent with greater toxicity in males (261).

Gorzinski (261) fed doses of 0, 1, 15, or 62 mg/kg/d in the diet for 16 wk (see preceding section on oral toxicity for details). Clearance, due to metabolism and elimination, was first order at 62 mg/kg/d, indicating nonsaturation. The half-time was approximately 2.5 d for fat, liver, kidney, and blood. They concluded that elimination from the rat was more rapid than that reported for other species.

Table 63.6 taken from Gorzinski (261), shows the organ concentration after 16 wk on the respective diets.

Table 63.6. Concentration of Hexachloroethane in the Tissues of Rats Fed Hexachloroethane in the Diet for 16 Weeks

Sex	Dose (mg/kg/d)	mg HCE/g Tissue[a]			
		Blood	Liver	Kidney	Fat
M	1	0.079 ± 0.057	0.291 ± 0.213	1.356 ± 0.29	3.15 ± 0.37
	15	0.596 ± 0.653	1.736 ± 1.100	24.33 ± 5.73	37.90 ± 6.10
	62	0.742 ± 0.111	0.713 ± 0.343	95.12 ± 11.56	176.1 ± 14.50
F	1	0.067 ± 0.039 (3)	0.26 ± 0.035 (2)	0.369 ± 0.51	2.59 ± 0.72
	15	0.162 ± 0.049 (3)	0.47 ± 0.204	0.688 ± 0.17	45.27 ± 11.33
	62	0.613 ± 0.231	0.631 ± 0.262	2.01 ± 0.66	162.1 ± 7.10

Mitoma et al. (52) fed a series of chlorinated ethanes and ethenes to rats and mice to determine the amount of metabolism. Rats were given the NCI maximum tolerated dose (MTD) in corn oil for 5 d/wk for 4 wk followed by a corresponding radio-labeled dose. In rats 93% was recovered and in mice 95.5%. Their data for hexachloroethane are given in Table 63.3. They concluded the biochemical parameters they measured including protein binding provided no clue to differentiate the carcinogens from the noncarcinogenic compounds.

Lattanzie et al. (267), however, concluded that hexachloroethane "bound" to DNA and other macromolecules of the rat and mouse. They reported it less reactive than tetrachloroethane and similar to 1,2-dichloroethane.

8.4.1.4 Reproductive and Developmental Weeks et al. (251) carried out teratological studies in pregnant rats fed by gavage or exposed by inhalation. Oral doses of 50, 100, or 500 mg/kg were fed on days 6 through 16 of gestation. Separate groups were also exposed 6 h/d to 15, 48, or 260 ppm of the vapors. Although body weight gain of the dams in the 500-mg/kg oral and 260-ppm inhalation groups was lower than the controls, there appeared to be no teratological effects on the fetuses. There were adverse effects on gestation indexes and on the number of fetuses alive at the highest oral dose. The fetal reabsorption rate was increased in this group.

8.4.1.5 Carcinogenesis The EPA (IRIS) (2) classifies hexachoroethane as C, possible human carcinogen on the basis of observation of carcinomas in one mouse strain after oral exposure. There are no human carcinogenicity data. The EPA considers the animal carcinogenicity data as "limited."

Technical-grade hexachloroethane (98% pure) was administered by gavage to Osborne–Mendel rats and B6C3F1 mice (50 each male and female) (268).

Rats were treated with either 250 or 500 mg hexachloroethane/kg/d, 5 d/wk for 23 wk. After this time animals were rested 1 wk and gavaged for 4 succeeding weeks up to week 78; an observation period of 33–34 wk followed. Final TWA treatment doses were 212 and 432 mg/kg/d. There was no evidence of hexachloroethane-induced neoplastic growth in rats. Mice were administered 500 or 1000 mg/kg/d, 5 d/wk, continuously. At week 9 the doses were increased to 600 and 1200 mg/kg/d, and this dosage was maintained until week 78. Mice were observed for 12–13 wk after cessation of treatment. The TWA doses were 590 and 1179 mg/kg/d. Mice of both sexes showed a significant increase in the incidence of hepatocellular carcinoma.

When hexachloroethane was restudied in F344/N rats at doses of 0, 10, or 20 mg/kg/d 5 d/wk to

male rats and 0, 80, or 160 mg/kg doses to female rats, body weight was only slightly depressed toward the end of the 2 yr gavage period (259). Survival was not affected in any group. The following nonneoplastic and neoplastic effects were reported in the 2 yr studies: Incidences of kidney mineralization (vehicle control, 2/50; low dose, 15/50; high dose, 32/50) and hyperplasia of the pelvic transitional epithelium (0/50; 7/50; 7/50) were increased in dosed male rats. Renal tubule hyperplasia was observed at an increased incidence in high-dose male rats (2/50; 4/50; 11/50). These lesions have been described as characteristic of the hyaline droplet nephropathy that is associated with an accumulation of liver-generated a-globulin in the cytoplasm of tubular epithelial cells. The severity of nephropathy was increased in high-dose male rats (moderate vs. mild), and the incidences and severity of nephropathy were increased in dosed females (22/50; 42/50; 45/50). The incidences of adenomas (1/50; 2/50; 4/50), carcinomas (0./50; 0/50; 3/50), and adenomas or carcinomas (combined) (1/50; 2/50; 7/50) of the renal tubule were also increased in the high-dose male group. One of the carcinomas in the high-dose group metastasized to the lung. No compound-related neoplasms were observed in females. The incidence of pheochromocytomas of the adrenal gland in low-dose male rats was significantly greater than that in vehicle controls (15/50; 28/45; 21/49), and the incidences for both dosed groups were greater than the mean historical control incidence (28–11%). The relationship of hyalin droplet formation to kidney tumors in the rat has been the subject of several investigations, because the phenomenon appears to be more important in male rats than in female rats or humans. This is particularly important because the mutagenic potency of hexachloroethane appears to be low.

8.4.1.6 Genetic and Related Cellular Effects Studies Hexachloroethane was tested against one yeast strain, *Saccharomyces cervisiae*, and five strains of *Salmonella typhimurium* with and without rat liver activation with no evidence of mutagenic effects (263). Hexachloroethane was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested with and without exogenous metabolic activation. In Chinese hamster ovary cells, hexachloroethane did no induce chromosomal aberrations with or without metabolic activation but did produce sister chromatid exchanges in the presence of exogenous metabolic activation (259).

8.4.2 Human Experience Symptoms of exposure to this compound include skin, eye, mucous membrane, and upper respiratory tract irritation. Chronic effects include liver damage and nervous system disturbances. High concentrations can cause narcosis.

A report of inhalation exposures to humans describes the effects of a military smoke bomb in a fraternity house (269). However, it is probably not appropriate to ascribe the effects specifically to hexachloroethane because a variety of chemicals would be present in the smoke.

Exposure of workmen to the fumes of hot hexachloroethane has been reported to cause blepharospasm, photophobia lacrimation, and reddening of the conjunctiva but no corneal injury and no permanent damage (270, 271). However, the available citation does not give details of the exposure conditions or duration.

8.4.2.2.5 Carcinogenesis There is no human carcinogenicity data. EPA (IRIS) (2) classifies hexachloroethane as C, possible human carccinogen on the basis of observation of carcinomas in one mouse strain after oral exposure. (See animal section on carcinogenesis.)

Carcinogenic Classification:

IARC	Group 3, agent is not classifiable as to its carcinogenicity in humans
NIOSH	Carcinogoen without further classification
NTP	Reasonably anticipated to be a human carcinogen (RAHC)

ACGIH TLV A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans

8.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV for hexachloroethane is 1 ppm with a notation indicating possible skin absorption.

The NIOSH considers hexachloroethane a potential carcinogen and recommends the lowest possible exposure, and an REL of 1 ppm. The OSHA PEL is also 1 ppm.

Other countries: Australia: 10 ppm, proposed change 1 ppm (1990); The former Federal Republic of Germany: 1 ppm (1998); United Kingdom: vapor 5 ppm (50 mg/m^3), total inhalable dust 10 mg/m^3, respirable dust 5 mg/m^3 (1987).
8.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

1-Propyl Chloride
9.0.1 CAS Number:
[*540-54-5*]
9.0.2 Synonyms:
n-Chloropropane
9.0.3 Trade Names:
NA
9.0.4 Molecular Weight:
78.541
9.0.5 Molecular Formula:
$CH_3CH_2CH_2Cl$, C_3H_7Cl
9.0.6 Molecular Structure:

9.1 Chemical and Physical Properties

Physical state	Colorless liquid
Specific gravity	0.8910 (20/4°C)
Melting point	–122.8°C
Boiling point	46.4°C
Vapor pressure	350 torr (25°C)
Refractive index	1.38838 (20°C)
Percent in “saturated”air	44.5
Solubility	027 g/100 mL water at 20°C; soluble in ethanol, ethyl ether
Flammability	Flash point <–18°C; explosive limits 2.6–11.1% in air

9.1.1 General

9.1.2 Odor and Warning Properties No data were found concerning odor or warning properties.
9.2 Production and Use
No information found.
9.3 Exposure Assessment

No information found.
9.4 Toxic Effects
Very little information is available on *n*-propyl chloride because it has found so little use in industry. Von Oettingen (7) reviewed the data available prior to 1955.

9.4.1 Experimental Studies 9.4.1.1 Acute Toxicity Abreu et al. (272) exposed rats to 1.7 mmol/L (40,000 ppm) 1 h/d for 4 d and then examined the livers and lungs. Slight alveolar hemorrhage and "significant" focal necrosis of the liver were observed. This concentration was reported to be anesthetic in mice.

9.4.1.2 Chronic and Subchronic Toxicity No information found.

9.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Barnsley (273) found 2-hydroxypropylmercapturic acid in the urine of rats injected subcutaneously with a 40% w/v solution of 1-chloropropane in arachis oil. VanDyke and Wineman (135) reported that enzymatic dechlorination occurs *in vitro* using rat liver microsomes. Cytochrome P450 may be involved based on *in vitro* data (274). Hepatic microsomes from phenobarbital-induced rats produced a variety of metabolites: propene, 1,2-epoxypropane, 1,2-propandiol, propienic acid, and an unidentified species bound to protein (275). If glutathione was added, there was conjugation with it.

9.4.1.4 Reproductive and Developmental No information found.

9.4.1.5 Carcinogenesis No information found.

9.4.1.6 Genetic and Related Cellular Effects Studies *n*-Propyl chloride was studied at 1000 mg/kg orally in rats and found not to produce a dominant lethal response (276).

9.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization No information found.

9.4.2 Human Experience No information found.
9.5 Standards, Regulations, or Guidelines of Exposure
None has been established for propyl chloride.
9.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Isopropyl Chloride
10.0.1 CAS Number:
[*75-29-6*]
10.0.2 Synonyms:
2-Chloropropane
10.0.3 Trade Names:
NA
10.0.4 Molecular Weight:
78.541
10.0.5 Molecular Formula:
$CH_3CHClCH_3$, C_3H_7Cl
10.0.6 Molecular Structure:

10.1 Chemical and Physical Properties

Physical state	Colorless liquid
Specific gravity	0.862 (20.°C)
Melting point	–117°C
Boiling point	35.74°C
Vapor pressure	523 torr (25°C)
Percent in “saturated”air	68.7 (25°C)
Solubility	0.31 g/100 mL water at 20°C; soluble in alcohol, diethyl ether
Flammability	Flash point –45°C (tag open cup)

10.1.1 General No new information on this compound was found since the last edition.

10.1.2 Odor and Warning Properties Warning properties may be inadequate to protect against excessive repeated exposure. Several subjects did not detect 500 ppm of the vapors.
10.2 Production and Use
Isopropyl chloride has had minimal use as a solvent and chemical intermediate, and to some extent as an anesthetic. Its flammability has limited its use despite its apparent favorable toxicity.
10.3 Exposure Assessment
No information was found.
10.4 Toxic Effects
Isopropyl chloride has a potent anesthetic action and has been proposed for medical usage.

Von Oettingen in 1955 reviewed the literature on the use of this material as an anesthetic (7). Vomiting and cardiac arrhythmia have been observed. It may also cause histopathological changes in the liver and kidneys but is rather low in potency.

Very little information has been published on this compound.

10.4.1 Experimental Studies 10.4.1.1 Acute Toxicity Twenty 6-h exposures to 1000 ppm in rats caused no evidence of injury during exposure, but extensive vacuolation and necrosis were seen in the liver of male and female rats. Similar exposures to 250 ppm caused no injury (277).

10.4.1.2 Chronic and Subchronic Toxicity No information was found.

10.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms VanDyke and Wineman (135) report that 2-chloropropane was enzymatically dechlorinated *in vitro* by rat liver microsomesed. Cytochrome P450 may be involved based on *in vitro* studies (274).

10.4.1.4 Reproductive and Developmental No information was found.

10.4.1.5 Carcinogenesis No information was found.

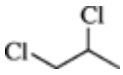
10.4.1.6 Genetic and Relatled Cellular Effects Studies Simmon et al. (278) reported that isopropyl chloride was mutagenic in *S. typhimurium* when tested in desiccators.

10.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization No information found.

10.4.2 Human Experience No information on human experience was found.
10.5 Standards, Regulations, or Guidelines of Exposure
No standards have been established for isopropyl chloride. Based on the limited available data from animals, it is suggested that time-weighted average exposures should be controlled below 500 ppm.
10.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Propylene Dichloride
11.0.1 CAS Number:
[*78-87-5*]
11.0.2 Synonyms:
1,2-Dichloropropane, alpha,beta-dichloropropane, alpha,beta-propylene dichloride, Dichloro-1,2-propane, PDC
11.0.3 Trade Names:
AI3-15406, Caswell No. 324, CCRIS 951, ENT 15,406, HSDB 1102, NCI-C55141
11.0.4 Molecular Weight:
112.99
11.0.5 Molecular Formula:
$C_3H_6Cl_2$
11.0.6 Molecular Structure:



11.1 Chemical and Physical Properties

Physical state	Colorless liquid
Specific gravity	(20/4°C) 1.1558 (1.159 at 25°C)
Melting point	–100°C
Boiling point	95–96°C
Vapor pressure	143 torr (25°C)
Refractive index	1.437 (25°C)
Percent in “saturated” air	3.4 (25°C)
Solubility	0.27 g/100 mL water at 20°C; soluble in alcohol, ethyl ether
Exposure limits	3.4–14.5% in air
Flash point	60°F, 16°C (Closed cup), 21°C (Open cup)

11.1.1 General

11.1.2 Odor and Warning Properties The odor may be adequate to warn against acute injury, but it

appears doubtful if it will prevent excessive repeated exposure. It has a chloroformlike odor.

11.2 Production and Use

Propylene dichloride has been used as a solvent, chemical intermediate, and fumigant. Flammability has significantly limited its use as a solvent.

11.3 Exposure Assessment

No information was found.

11.3.3 Workplace Methods NIOSH Method 1013 is recommended for determining workplace exposures to propylene dichloride (10a).

11.3.5 Biomonitoring/Biomarkers There appears to be inadequate data to determine the feasibility of biologic monitoring of exposure to propylene dichloride following industrial exposure, although Ghittori et al. (279) have presented limited data showing a relationship of urinary metabolites to inhaled exposure concentrations in workers.

11.4 Toxic Effects

Propylene dichloride is toxic by ingestion, inhalation, and skin absorption. It causes CNS depression, injury to the liver and kidney, and possibly hemolytic anemia and disseminated intravascular coagulation. There are indications of adrenal and possibly testicular injury in animals after repeated exposure. At high concentrations the vapors are irritating to the eyes and nose, and irritation of the nasal (olfactory) tissue of animals has been observed. It appears to be weakly mutagenic and carcinogenic, but available data indicate no reproductive effect. When heated to decomposition, it emits toxic fumes of carbon monoxide, carbon dioxide, chlorine, hydrogen chloride gas, and phosgene.

Von Oettingen in 1955 summarized the literature prior to that date (7). A more recent summary published in 1989 contains details of several extensive unpublished toxicologic studies conducted by The Dow Chemical Company, the data from which have been provided to the EPA (60).

11.4.1 Experimental Studies 11.4.1.1 Acute Toxicity The lethal dose of propylene dichloride to guinea pigs is between 2 and 4 g/kg of body weight. Repeated oral feedings of doses as low as 0.2 g/kg of body weight were survived for some period of time, but the animals showed liver injury. An oral LD_{50} for rats of 1.9 g/kg (1.7–2.1 g/kg) has been reported (63).

As part of their procedure for establishing dosage for lifetime studies, NTP conducted 14-d and 13-wk studies in rats and mice (280). All five male and female rats fed 2000 mg/kg/d for 14 d died. On gross necropsy, the renal medullae were red at this dose but not at lower doses. Body weight was depressed 14–15% at 1000 mg/kg in both sexes and at 500 mg/kg in male rats.

Mice were slightly more susceptible because 9/10 mice fed 1000 mg/kg for 14 d died and red renal medullae were observed in 3/5 males at 500 mg/kg and in 1/5 female mice at 125, 250, and 500 mg/kg. Body weight was depressed at 500 mg/kg in male mice and possibly at 250 mg/kg in female mice.

An acute inhalation LD_{50} for 8-h exposures of rats to propylene dichloride was reported by Pozzani et al. (183) as 14 mg/L (3000 ppm).

Mice were exposed to analytically determined concentrations of propylene dichloride vapor in order to study the relationship of lethality to anesthesia and to liver injury (as measured by SGPT in the blood) (111). Based on 10-h exposures, an LC_{50} of 720 ppm was determined. The anesthetic ET_{50} (ET = effective time) at that concentration was 350 min, and the ET_{50} for increased SGPT was 186 min. Based on these data propylene dichloride has much less potency toward causing liver injury than carbon tetrachloride, because its anesthetic, hepatotoxic, and lethal conditions are quite similar. Gehring reported the ratio of ET_{50} anesthesia to ET_{50} for carbon tetrachloride as 136, as compared

to 1.9 for this ratio for propylene dichloride (111). The ratio of LT_{50} to ET_{50} for carbon tetrachloride was 5480 and for propylene dichloride 2.7. It was concluded by the investigator that in mice, respiratory injury, rather than liver injury, was the primary cause of acute death. Anesthetic effects were observed, but they were considered secondary to obstructive respiratory failure.

In limited unpublished study reported to the EPA "male rats and mice were exposed to 0, 500, or 1500 ppm propylene dichloride (PDC) for a single 6-h exposure. Rats exposed to 1500 ppm were lethargic during exposure, lost weight after the exposure, and exhibited pale livers upon gross necropsy. All mice exposed to 1500 ppm died within 24 h postexposure and exhibited nonspecific changes typical of animals which die in acute studies. Several mice exposed to 500 ppm PDC died and exhibited various degrees of liver toxicity upon gross and histological examination" (281).

Early longer-term toxicologic studies on this material were published by Heppel and co-workers (282, 283). These data have been summarized by Von Oettingen (7) for repeated exposure to concentrations of 2200 to 400 ppm. "Exposure for 7 hours daily on 5 days per week to 1,000 ppm (4.4 mg/L) caused in guinea pig no signs, other than drowsiness; rabbits were not affected; and rats showed some incoordination and it appeared that the animals developed some tolerance to the exposure. On the other hand many rats and mice died after a few hours' exposure. Liver function tests performed in dogs showed no definite abnormal values but nevertheless histological examination of their organs gave evidence of liver damage. None of the animals studied gave evidence of injury of the blood or blood-forming organs."

Heppel et al. (283) reported that "repeated exposure to 400 ppm for 7 hours daily on 5 days per week for a total of 128 to 140 (exposures) caused no other ill effects except a decrease in weight gain of rats, whereas mice showed a high incidence of mortality." A group of C3H strain mice exposed to 400 ppm propylene dichloride showed rather high mortality. Hepatomas were observed in some of the animals that survived.

In an incomplete report Shaipak (284) claims impaired spermatogenesis in rats exposed continuously to 9 mg/L (3.6 ppm). The duration of the study was not given in the available abstract but is described as "long periods," possibly 7 d. This report is not consistent with most of the data cited above, or subsequent studies that indicate the testes were not affected by inhalation of higher concentrations. However, Bruckner et al. (285) also reported testicular effects.

Results of repeated inhalation of propylene dichloride were also reported to the EPA (281, 286). Male and female rats and male rabbits were exposed to 0, 100, 300 or 1000 ppm PDC for 6 h/exposure for 9 exposures in 2 wk; male and female mice were exposed to 0, 30, 100, or 300 ppm PDC for the same time period. Body weight gains of rats exposed to PDC (all levels) were decreased from control values. The olfactory mucosa of the nasal turbinates in rats was observed histologically to be affected at all exposure levels. The extent and severity of degeneration of the olfactory mucosa was directly correlated with exposure level. Male and female mice exposed to 300 ppm PDC had increased liver weights and decreased thymic weights. Some mice exposed to 100 or 300 ppm PDC had degenerative changes in the olfactory mucosa, but these changes were not as severe as observed in rats at the same exposure level. Only minor liver changes were observed histologically in mice exposed to 300 ppm PDC. Male rabbits exposed to 1000 ppm PDC had equivocal degenerative changes in the olfactory mucosa. While a no-observable-effect level (NOEL) was not established in rats, a NOEL of 30 ppm for mice and 300 ppm for rabbits was established in a 2 wk study (281).

Skin: Propylene dichloride on the open skin causes only mild irritation. Single short contact will probably be without any effects. The intensity of the reaction is greatly increased when it is held close to the skin by clothing. The LD_{50} for percutaneous absorption has been reported as 8.15 g/kg (63).

Eye: Propylene dichloride causes some pain and irritation when splashed into the eyes of rabbits, but

it would not be expected to cause serious or permanent injury. It should be washed out immediately with water.

11.4.1.2 Chronic and Subchronic Toxicity The EPA (IRIS) provides no oral reference dose but does provide a reference concentration for inhalation, based on the critical effect of hyperplasia of the nasal mucosa with a LOAEL of 69.3 mg/m^3 (15 ppm). This was based on the study by Nitchke et al. (286). Male and female F344 and B5C3F$_1$ mice (10/group) were exposed to 0, 15, 50, or 150 ppm dichloropropane (0, 69.3, 231, or 693 mg/m^3) for 6 h/d, 5 d/wk for 13 wk (duration-adjusted concentrations = 0, 12.4, 41.3, and 124 mg/m^3). New Zealand rabbits (7/sex/group) were exposed to 0, 150, 500, or 1000 ppm dichloropropane (0, 693, 2310, or 4621 mg/m^3) according to the same regimen (duration-adjusted concentrations = 0, 124, 413, and 825 mg/m^3). The animals were observed daily after exposure for overt signs of toxicity as well as changes in behavior pattern and nervous system activity. Body weights were measured weekly. Hematology, clinical chemistry, and urinalysis were done prior to exposure and 2 weeks before study termination. Histopathology was conducted on 52 tissues in the control and high-concentration groups for all three species. The nasal tissues, larynx, trachea, and lungs were evaluated in all concentration groups for all three species. Histopathological examinations were also made on the liver and kidney in mice and on the liver, bone marrow, and spleen in rabbits at all exposure concentrations. The number of sections of the nasal cavity was not stated; it was assumed that four sections were taken as was done in the preliminary 2-wk study in the same lab. No treatment-related deaths were observed in any species. Body weights were statistically significantly reduced in the male rats (90% of control) and female rats (92–94% of control) exposed to 150 ppm, and slightly reduced at 50 ppm dichloropropane. No significant treatment-related effects on any hematological, clinical chemistry, or urinalysis parameters studied were noted in the rats or mice. Histopathological effects were seen in the upper respiratory tract of the rats that were concentration-related in incidence and severity. Very slight to slight hyperplasia of the respiratory epithelium of the nasal cavity was observed (0/10, 2/9, 5/10, and 9/10 in males and 0/10, 3/10, 7/10, and 9/10 in females at 0, 15, 50, and 150 ppm, respectively). This hyperplasia occurred primarily in the anterior regions of the nasal cavity. Very slight to slight degeneration of the olfactory mucosa in the rostral portion of the nasal cavity was noted for all male and female rats exposed to 50 or 150 ppm dichloropropane, but not in the control and 15-ppm groups. Statistical analysis of these results was not reported. Slight inflammation of the larynx was also noted in several male rats exposed to 150 ppm dichloropropane; no other treatment-related effects were observed in the respiratory tract of rats. No effects were observed in the liver, spleen, or bone marrow in rats exposed to 150 ppm.

No treatment-related pathological effects were observed in the mice. Anemia was seen in the rabbits exposed to dichloropropane in a concentration-related manner. Red blood cell counts (RBC), hemoglobin concentration, and percent packed cell volume were statistically significantly decreased in the animals exposed to 150 ppm (red blood cell count only), 500, or 1000 ppm dichloropropane. Animals in the 500- and 1000-ppm groups exhibited evidence of a regenerative response (bone marrow hyperplasia and hemosiderin-laden macrophages). Minimal degeneration of the olfactory epithelium was also observed in the nasal cavity of some rabbits from all exposure groups and the controls, but the incidence and severity were higher in the 1000-ppm male animals. This study demonstrates that respiratory effects are apparently the most sensitive endpoint of dichloropropane-induced toxicity, and that species vary considerably with regard to their susceptibility to these effects. A LOAEL of 15 ppm [LOAEL(HEC) = 1.3 mg/m^3] can be estimated for this study, based on nasal epithelial hyperplasia in female rats. This LOAEL should be considered minimal because of the low incidence and severity of the lesions seen at this concentration. Despite the minimal nature of the effects, they are considered to be adverse because of the increase in incidence and severity with increasing exposure concentration. This relationship is additionally supported by the short-term data (described later). Based on the exposure concentrations used in this study, rats are more than 10 times more sensitive than mice and 100 times more sensitive than rabbits to the nasal effects.

In an NTP (280) 13-week study rats were fed 0, 60, 125, 250, 500, and 1000 mg/kg/d. Five of 10 male and female rats died at 1000 mg/kg and 5/10 males at 500 mg/kg. Body weight was depressed 16% at 500 mg/kg. Centrilobular congestion of the livers occured in 5/10 males and 2/10 females receiving 1000 mg/kg. Hepatic fatty changes and contrilobular necrosis were observed in 2/10 females receiving 1000 mg/kg. Mice were fed 0, 30, 60, 125, 250, and 500 mg/kg. One female mouse fed 500 mg/kg died at 12 wk, and one male fed 60 mg/kg died in the first week. Body weights were little affected, and no compound-related histopathological effects were recorded.

In another study on male rats fed 0, 100, 250, 500, or 1000 mg/kg in corn oil for 1, 5, or 10 doses, a larger number of biochemical parameters were measured in addition to histopathological examination 24 h after treatment (285). There was evidence of development of resistance to propylene dichloride by the tenth dosage. No deaths occured, but a no-observed-effect level was not established because cytochrome P450 levels were incresed in the liver even at 100 mg/kg. However, "doses of 500 and 1000 mg/kg were required to produce significant liver injury."

The same dosage, 100 mg/kg, the lowest dose fed, was found to be an observed effect level in a 13-wk gavage study as well. When fed to male rats for 13 wk at 0, 100, 250, 500, or 750 mg/kg/d, members of the 750-mg/kg group died or were sacrificed, as did 50% of the 500-mg/kg group Bruckner et al. 1989 (285). Although cause of death was not stated and may have been anesthetic, histopathology was only moderate to mild. Hepatitis, hemosiderosis of the spleen, vacuolation of the medulla and lipidosis of the cortex of the adrenals, degenerate spermatogonia, reduction in spermatozoa in the epididymis, and testicular degeneration were observed at 750 mg/kg. At 500 mg/kg testicular and adrenal changes were reported in some of the rats with reduced sperm production and degenerate spermatogonia in the epididymis. There was an increase in fat storage in the adrenal cortex. No such effects were seen in the 100- or 250-mg/kg groups. Dose-dependent depression of weight gain occured at all levels. Nephrotoxicity was not apparent, and liver toxicity as measured by serum enzymes was very limited. Possibly hemolytic anemia occured. All animals in the 500-ppm group were sacrificed the day after exposure, but groups of 100 and 250 mg/kg rats examined 1 wk after treatment stopped had recovered significantly. It is interesting that the testicular changes reported following gavage in this study have not been reported in other studies.

In response to a TSCA section 4(a) test rule, 1,2-dichloropropane (PDC) was evaluated for potential neurotoxic effects in groups of 15 Fischer 344 rats/sex given 0 (corn oil controls), 20, 65, or 200 mg PDC/kg body weight/d, 5 d/wk for 13 wk (287). Specific tests required by the test rule included monthly evaluation of a functional observational battery, hindlimb grip strength, motor activity, and comprehensive neuropathology at the end of the study. Other parameters evaluated included weekly clinical observations, weekly body weights, and body temperatures after 13 wk of treatment.

Transient clinical effects were noted in a dose-responsive manner shortly after gavage for rats receiving all dose levels of PDC. The rats adapted rapidly to PDC such that these effects were no longer noted after the fourth daily dose. Body weights were depressed throughout the study for male rats given 200 mg/kg/d. Males receiving 65 mg/kg/d and females given 200 mg/kg/d had slightly decreased body weights that were also attributed to PDC ingestion. No effects attributable to PDC were noted upon the functional observational battery, hindlimb grip strength, or motor activity at any of the monthly intervals throughout the study. After 13 wk of gavage, the temperature of rats receiving 200 mg/kg/d was slightly lower, particularly females. The body temperature was within the range of normal daily variation and the decrease was not considered toxicologically significant. No gross or histopathologic effects on the nervous system, either central or peripheral, were demonstrated by any of the techniques employed.

All rats not selected for the 13-wk termination were held without further treatment for an additional 9 wk. Parameters noted to be affected in the 13-wk portion were evaluated in these rats. The body weight differences persisted for the 9 wk post-treatment period. Body temperature differences for the female rats, but not male rats, receiving 200 mg/kg/d also remained throughout this period. Female rats previously receiving 65 mg/kg/d also tended to have slightly decreased body temperature during

the recovery period.

In summary, aside from early transient clinical signs and minor body weight and temperature decreases, there were no effects attributable to DCP in the functional observational battery, grip strength, motor activity, and neuropathology.

11.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms It has been shown that rat liver microsomes *in vitro* are capable of metabolizing 1,2-dichloropropane (136). More information on metabolism is discussed on 1,3-dichloropropane (288). Jones and Gibson have proposed a metabolic pathway (289) that has been expanded by Timchalk et al., who studied the disposition and metabolism of [^{14}C]1,2-dichloropropane (propylene dichloride) in Fischer 344 rats following oral and inhalation exposure (290): The objective of this study was to compare the disposition and metabolism of [^{14}C]1,2-dichloropropane ([^{14}C]DCP) following oral and inhalation exposure since these two routes are of interest with regards to occupational and and accidental exposure. [^{14}C]DCP was administered orally to groups of four rats of each sex as a single dose of 1 or 100 mg/kg and as a multiple 1 mg/kg nonradiolabeled dose for 7 d followed by a single 1-mg [^{14}C]DCP/kg dose on day 8. In addition, four rats of each sex were exposed to [^{14}C]DCP vapors for a 6-h period in a head-only inhalation chamber at target concentrations of 5, 50, and 100 ppm. [^{14}C]DCP was readily absorbed, metabolized, and excreted after oral or inhalation exposure. For all treatment groups the principal routes of elimination were via the urine (37–65%) and expired air (18–40%). The tissues, carcass, feces, and cage wash contained <11, 9.7, and 3.8% of the dose, respectively. The major urinary metabolites, as a group, from the oral and inhalation exposures were identified as three, *N*-acetylcysteine conjugates of DCP, *N*-acetyl-*S*-(2-hydroxypropyl)-L-cysteine, *N*-acetyl-*S*-(2-oxopropyl)-L-cystein, and *N*-acetyl-*S* (l-carboxyethyl)-L-cystein. The majority (61–87%) of the expired volatile organic material was found to be parent DCP in all samples analyzed. Increasing the dose/concentration of [^{14}C]DCP resulted in an increase in the amount of exhaled [^{14}C]-volatile organics. The peak DCP blood concentrations (inhalation exposure) were not proportional to dose, indicating a dose dependency in the blood clearance of DCP. Nonetheless, upon termination of exposure, DCP was rapidly eliminated from the blood. In all treatment groups, following oral and inhalation exposure the majority of the radioactivity was eliminated by 24 h postdosing, and no differences were noted between sexes. Therefore, it can be concluded that in the rat the pharmacokinetics and metabolism of [^{14}C]DCP are similar regardless of route of exposure or sex.

These authors proposed a metabolic pathway (Fig. 63.2) quite similar to Jones and Gibson and concluded that incorporation into macromolecules is due to metabolism and not alkylation.

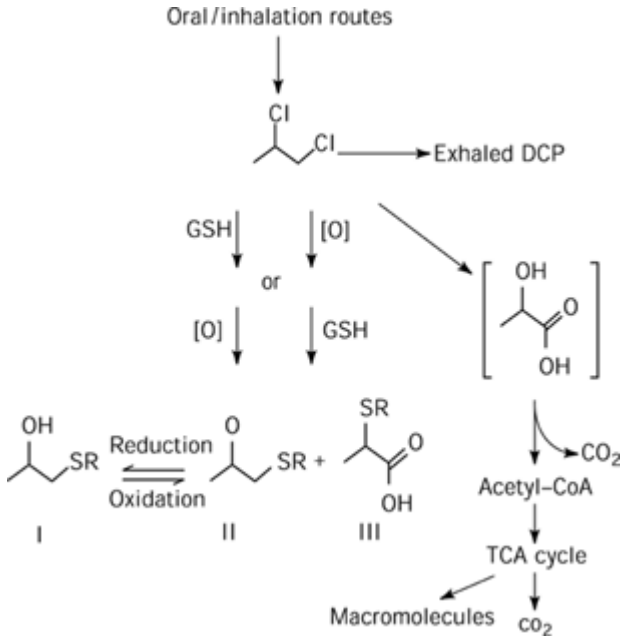


Figure 63.2. Proposed metabolic scheme for 1,2-dichloropropane in the rate (R = *N*-acetylcysteine) [from Timchalk et al. (290)].

11.4.1.4 Reproductive and Developmental Thirty bred female Sprague–Dawley rats were fed propylene dichloride in oil by gavage at dose levels of 0, 10, 30, or 125 mg/kg/d on days 6 to 15 of gestation. The usual teratological parameters were evaluated Kirk et al. (291). Administration of PDC to pregnant rats at a dose level of 125 mg PDC/kg body weight/d produced transient decreases in respiration, movement, muscle tone, and extensor thrust reflex, and increases in salivation and lacrimation within 1 h of dosing on day 6 of gestation. Rapid accomodation to PDC exposure was observed in these animals on the second day of dosing (day 7 of gestation), as evidenced by a decrease in the frequency and severity of clinical observations. Decreased feed consumption and significant decreases in maternal body weight gain resulting in significantly lower maternal body weights were also observed at 125 mg PDC/kg body weight/d. There were, however, no adverse effects on any reproductive parameter measured in any of the dose levels tested. Fetal examination revealed a significant increase in the incidence of delayed ossification of the bones of the skull in the 125 mg PDC/kg body weight/d dose group. This increase was considered to be a reflection of at most slight fetotoxicity, secondary to the reduced maternal growth. There were no adverse effects on any parameter in rats exposed to 10 or 30 mg PDC/kg body weight/d. Based on these results, PDC was not teratogenic at a dose level that produced obvious maternal toxicity (125 mg PDC/kg body weight/d), and 30 mg PDC/kg body weight/d was considered the no-observed-effect level for maternal and fetal effects.

In a similar study 18 inseminated New Zealand white rabbits were administrated 0, 15, 50, or 150 mg/kg/day on days 7 through 9 of gestation (292). Administration of 150 mg PDC/kg/d resulted in anorexia in the majority of animals in this dose group producing significant decreases in maternal body weight gain during the treatment period (days 7–20 of gestation). One maternal death resulting from anorexia was also recorded in the 150-mg/kg/d dose group. Measurement of hematologic parameters revealed anemia (decreased red blood cell counts, hemoglobin concentration, and hematocrit) in rabbits given 150 mg/kg/d, with microscopic examination revealing slight-to-moderate anisocytosis, poikilocytosis, and/or polychromasia, indicative of a regenerative anemia. Despite the obvious maternal effects, there were no adverse effects on any of the reproductive parameters measured in any dose group, nor were there indications of teratogenicity in any of the dose groups. Fetal examination revealed low, but statistically significant, increase in the incidence of delayed ossification of the bones of the skull in the 150-mg/kg/d dose groups. Based on these results, 150 mg/kg/d was considered maternally toxic and produced evidence of slight fetotoxicity.

Therefore, the no-observed-effect level for both maternal and fetal effects was 50 mg/kg/d.

A two-generation reproduction study in rats produced no effect on reproductive parameters, although there was an obvious effect on water consumption and body weight (293). The investigators summarize the study as follows. Groups of 30 male and 30 female Sprague–Dawley rats each were provided with drinking water containing PDC at concentrations of 0 (control), 0.024%, 0.10%, or 0.24% (w/v) over two generations. A concentration of 0.24% PDC in water represented the maximum practicable attainable concentration based on solubility. Adult rats were evaluated for body weights, water and feed consumption, reproductive performance, and gross pathologic and histologic changes. The resultant litters were evaluated for size, neonatal growth, and survival.

Administration of PDC via the drinking water to male and female Sprague–Dawley rats over two generations produced concentration-related palatability effects in adults at 0.24%, 0.10%, and 0.024%. Decreases in water consumption, reflective of a rejection due to palatability, were observed at all levels tested in both the f0 and f1 generations in males and females. These decreases in water consumption at 0.24% PDC (50% below controls) resulted in consistent body weight effects. These differences in water consumption and body weights were also evident among females during gestation and/or lactation. Slight decreases in water consumption 0.024% PDC were associated only with slight decreases in weight gain in females during gestation and had no adverse effects on these animals. There were no treatment-related gross pathologic changes noted in any dose group. Histologic changes related to PDC exposure were limited to increased hepatocellular granularity in males and females of both generations at all dose groups. These histologic changes were considered reflective of a physiologic, adaptive response to PDC and not an indication of toxicity. There were no treatment-related histologic changes in the reproductive tracts of either sex in their generation.

Despite the obvious effects of continuous exposure to PDC on water consumption and body weights, reprodutive function was unaffected in either generation. The substantial decreases in water consumption among females at 0.24% PDC resulted in significantly lower neonatal body weights and slightly increased neonatal mortality in their litters. These neonatal effects were considered secondary to the substantial decreases in maternal water consumption, rather than a direct effect of PDC. There were no neonatal effects at PDC concentrations of 0.10% or 0.024% in either generations.

It should be noted that the concentrations of PDC in the drinking water administered to these animals were at the limit of solubility, and were approximately 100,000-fold higher than levels detected in the environment. Despite the exaggerated levels, neonatal growth and survival were only affected at a PDC concentration of 0.24%, which also resulted in significant reduction in parental water consumption and body weight changes. These effects on the neonates were thus considered secondary to the effects on the adults. Significantly, there were no adverse effects on reproductive performance as measured by fertility and litter sizes at any dose level tested. Thus the no observed adverse effect level for adults was 0.024% PDC, the no observed effect level for neonatal effects was 0.10% PDC, and the reproductive NOEL was 0.24% PDC, the limit of solubility.

It was difficult to calculate with any precision the daily dosage because consumption varied greatly with age of the rats and whether the females were pregnant or lactating. Roughly the lowest level ranged from 20 to 25 mg/kg/d for males and 35 to 45 mg/kg/d for females. The intermediate dose resulted roughly in 65 to 90 mg/kg/d for male rats and 110 to 140 for females. The highest water concentration resulted in roughly 130 to 160 mg/kg/d in males and 190 to 270 mg/kg/d in females.

11.4.1.5 Carcinogenesis The EPA (IRIS) (2) states: “this substance has not undergone a complete evaluation and determination under US EPA’s IRIS program for evidence of human carcinogenicity potential.”

Propylene dichloride was fed by gavage to rats and mice, 5 d/wk for 103 wk. Dosages were 0 (corn oil controls), 125, and 250 mg/kg for mice and 0, 62, and 125 mg/kg for rats (280). Survival was

reduced in high-dose female rats and mice (possibly due to infection in female mice). Body weight was reduced in high-dose rats of both sexes, and clear-cell changes and necrosis of the livers were found in high-dose female rats. The investigators concluded that dose-related increases were observed for adenomas of the liver in both male (control, 7/50; low dose, 10/50; high dose, 17/50) and female (1/50, 5/50, 5/50) mice. The increase in the frequency of liver carcinomas supported the evidence that there was a neoplastic response in the mouse liver for both sexes (males: 11/50, 17/50, 16/50. females: 1/50, 3/50, 4/50). Hepatocytomegaly and hepatic necrosis were increased in male mice, but not in female mice.

A dose-related increase in adenocarcinomas of the mammary gland was observed in female rats (control, 1/50; low dose, 2/50; high dose, 5/50), with the majority of these tumors being found at the end of the study (1/37, 3%; 2/43, 5%; 4/16, 25%). The incidence of mammary adenocarcinomas was increased when compared to the historical controls for this laboratory (3/150, 2.0%) and for all laboratories combined (11/895, 1.2%). Mammary fibroadenomas were decreased in the high-dose treated female rats (15/50, 20/50, 7/50).

Under the conditions of these 2-yr gavage studies, there was no evidence of carcinogenicity for male F344/N rats receiving 62 or 125 mg/kg. For female rats there was equivocal evidence of cacinogenicity in that 250 mg/kg 1,2-dichloropropane caused a marginally increased incidence of adenocarcinomas in the mammary gland; these borderline malignant lesions occurred concurrent with decreased survival and reduced body weight gain. There was some evidence of carcinogenicity for male and female B6C3F1 mice exposed to 1,2-dichloropropane, as indicated by increased incidences of hepatocellular neoplasms, primarily adenomas (280).

11.4.1.6 Genetic and Related Cellular Effects Studies Published mutagenicity tests on microbial systems were summarized by NTP (294). Generally responses were weak to negative in *Drosophila, Salmonella, Streptomyces*, and *Aspergillus*. NTP also conducted studies on *Salmonella* TA100, TA98, TA1537, and TA1535 in the presence or absence of liver S-9 fraction, and no clearly positive responses were obtained. Chromosomal aberration and sister chromatid exchange studies in Chinese hamster ovary cells resulted in an increase with and without S9 activation. ATSDR concluded dichloropropane poses a genotoxic threat to humans ATSDR (60).

A dominant lethal study in Sprague–Dawley rats fed drinking water containing 0, 0.024, 0.10, and 0.24% for 14 wk produced no evidence of mutagenicity (294).

Among PDC-treated males, concentration-related decreases in water consumption were noted at all levels treated, and decreased body weights were noted in males given 0.10% or 0.24% in the water. Mating performance was unaffected in these animals. Evaluation of the resorption rates among these groups revealed that the weekly values for the females mated to PDC-treated males ranged from 2.2% to 8.1%, well within the historical control range expected for this strain. Resorption rates among the concurrent controls were low, ranging from 3.5% to 5.4%. Statistically significant increases from concurrent control values identified during the first week of breeding in the resorption rates in the 0.024% and 0.24% PDC-treated groups were considered a reflection of the normal variability in this strain. In contrast, single oral administration of cyclophosphamide at a dose of 100 mg/kg resulted in a 10-fold increase in the resorption rate, consistent with the acknowledged mutagenic potential of this compound. The concentrations of PDC in the drinking water administered to these animals were at the limit of solubility in water, and were approximately 10,000-fold higher than levels detected in the environment. Despite these exaggerated levels, PDC was not mutagenic in a dominant lethal assay in male Sprague–Dawley rats exposed continuously to concentrations up to 0.24% in the drinking water (136).

11.4.2 Human Experience Symptoms of exposure to this compound may include irritation of the skin, eyes, and respiratory tract. It may also cause irritation of the mucous membranes of the nose, throat, and lungs. Other symptoms may include dermatitis by defatting of the skin and more severe irritation if confined against the skin. Exposure can cause slight smarting of the eyes or respiratory

system and smarting and reddening of the skin. Exposures may also lead to hemolytic anemia, disseminated intravascular coagulation, necrosis and failure of the kidneys, liver failure, and death. Liver and kidney damage occur. Heart damage may also occur. Prolonged exposure may cause nausea, headache, vomiting, and central nervous system depression. High concentrations may cause nacrosis. Drowsiness and lightheadedness have been reported. Cardiac effects have also been reported. Eye contact may cause burning, tearing, reddening, and swelling of the eye and surrounding tissue. Skin contact can cause burning and swelling. Inhalation may lead to coughing, burning sensation, runny nose, sore throat, and dizziness.

Liver, kidney, and hemocytic anemia and disseminated intravascular coagulation appear to be characteristic responses to excessive exposure to propylene dichloride. Pozzi et al. (295) reported finding three publications regarding human exposure to propylene dichloride and discussed three subjects they had examined. All the cases were from Italy, indicating propylene dichloride may have had more usage in that country. One of the three subjects who drank an undisclosed amount of propylene dichloride died of septic shock after developing renal failure and liver damage. Many other changes including hemolytic anemia were observed.

11.4.2.2 Clinical Cases 11.4.2.2.1 Acute Toxicity A young woman who admitted sniffing a cleaning solution containing 98% propylene dichloride complained of vomiting and abdominal pain, widespread ecchymoses, hematuria, and metrorrhagia on first admission. Several months after she was readmitted with oliguria, epistaxis, hematuria, metrorrhagia, and periorbital and conjunctival hemorrhages. She again had vomited and had severe abdominal pain followed by fever, facial edema, and erythemas. She showed evidence of severe renal failure, acute liver damage, and hemolytic anemia. Renal biopsy showed acute tubular necrosis. The patient survived.

The third case, a 55-year-old woman, who had glomerulonephritis and had been on hemodialysis for 3 yr, was admitted with abdominal pain. It was subsequently found she had spent 6 h cleaning her flat with 2 L of solvent (composition not stated) 3 d prior to admission. She developed anorexia, abdominal pain, and nocturnal sweating prior to admission. Severe liver failure, hemolytic anemia, and other blood changes were observed. The patient survived.

Larcan et al. (296) reported an accidental ingestion of 50 mL of a cleaning substance by a 46-year-old man. According to the available abstract, the man was in deep coma within 2 h, with mydriases and hypertonia. Artificial hyperventilation and osmotic diuresis were applied and consciousness was recovered in 24 h. The patient suddenly developed a picture of irreversible shock with cardiac failure, lactic acidosis, and hepatic cytolysis at the thirty-sixth hour. He died after developing acute delirium with tremors. Necropsy evidenced centri- and mediolobular acute hepatic necrosis. The abstract indicated gas chromatography was used to confirm the identity of propylene dichloride, but no details were presented.

A similar response involving a 73-year-old woman has also been reported in a 1992 letter to the editor (297). In addition to the hemolytic anemia, there appeared to be persistent changes in liver enzymes.

A workman was sprayed on one side of his face with propylene dichloride when a pipeline burst (271). There was smarting of the eye on that side that persisted for several hours. The corneal epithelium was damaged in several small areas in the palpebral fissure, but recovery was prompt with no special treatment.

Two interesting cases of dermatitis suggestive of sensitization have been reported in women using a complex (aerosol spray) mixture containing propylene dichloride (298). When tested against the components of the mold-release spray, one women tested strongly positive and the other slightly positive. Few details are given.

In another report of alleged allergies due to Shell DD*f* Fumigant Mixture, which contains about

27% propylene dichloride, two subjects tested negative for the mixture and one subject positive for the mixture but not propylene dichloride alone (299).

The health effects in humans (truck drivers, highway patrol officers, fire fighters, and hospital employees) who were exposed to dichloropropane following the accidental spill of 2000 gallons from a truck were described by Rubin (300). The exposed individuals complained of chest discomfort, dyspnea, and cough, and some had persistent chest pain or discomfort and fatigue. These symptoms indicate that dichloropropane is a respiratory irritant. The level of exposure to dichloropropane was not quantified.

No epidemiologic studies were found in which propylene dichloride was the subject of the study.

11.4.2.3.5 Carcinogenesis Carcinogenicity Classification:

IARC	Group 3, not classifiable as to its carcinogenicity to humans
MAK	Group 3, possible human carcinogen
NIOSH	Carcinogen, with no further categorization
ACGIH TLV	A4, Not Classifiable as a Human Carcinogen

11.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV TWA is 75 ppm with a STEL/C of 110 ppm. NIOSH considers propylene dichloride a carcinogen and recommends the lowest feasible concentration. The OSHA PEL is 75 ppm.

Other Occupational Exposure Values: Australia: 75 ppm, 15-min STEL 110 ppm (1990); Federal Republic of Germany: no MAK, Group 3, possible human carcinogen (1998).
11.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Ethyl Bromide
12.0.1 CAS Number:
[*74-96-4*]
12.0.2 Synonyms:
Monobromoethane, bromic ether, bromoethane, hydrobromic, ether, and monobromoethane
12.0.3 Trade Names:
Halon 2001, Monobromoethane, Bromic ether
12.0.4 Molecular Weight:
108.97
12.0.5 Molecular Formula:
CH_3CH_2Br
12.0.6 Molecular Structure:

12.1 Chemical and Physical Properties
Ethyl bromide is a colorless to yellow, highly volatile, flammable liquid with an ethereal odor. The material turns yellow when exposed to light and air.

Physical state	Colorless liquid
Specific gravity	1.4515 g/mL at 25°C (25/4°C)
Melting point	–119°C
Boiling point	38.4°C
Vapor pressure	475 torr (25°C)
Refractive index	1.42386 (25°C)
Percent in “saturated”air	62.5 (25°C)
Solubility	0.91 g/100 mL water at 20°C; soluble in ethanol, ethyl ether
Flammability limits	6.75–11.25% by volume in air

12.1.1 General

12.1.2 Odor and Warning Properties Ethyl bromide has a definite though not particularly distinctive odor. A threshold of odor response has not been reported. Odor should not be considered a warning property.

12.2 Production and Use

The principal use of ethyl bromide is as a chemical intermediate. Although it has been occasionally proposed as an anesthetic, it has not been used to any extent for that purpose.

12.3 Exposure Assessment

Human exposure has occurred with its use as an anesthetic, but widespread use has ceased.

12.3.3 Workplace Methods NIOSH Method 1011 is recommended for determining workplace exposures to ethyl bromide (10a).

12.3.5 Biomonitoring/Biomarkers Determination of bromide ion in the blood may be of value in determining whether exposure to ethyl bromide has occurred. However, the available data do not permit a quantification of exposure based on blood bromide; nor is it known if measurable concentrations will be present at currently acceptable levels of exposure.

12.4 Toxic Effects

Ethyl bromide may be harmful by ingestion or inhalation. It is an irritant of the skin, eyes, mucous membranes, and upper respiratory tract. It is narcotic in high concentrations. When heated to decomposition, it emits toxic fumes of carbon monoxide, carbon dioxide, bromine, and hydrogen bromide gas.

The primary acute response from exposure to ethyl bromide is CNS depression, as in the case of ethyl chloride. In contrast, however, ethyl bromide causes irritation of the lungs and injury to the liver, muscle, kidneys, and other organs. It has caused cancer in female mice and possibly in male mice and both sexes of rats.

12.4.1 Experimental Studies 12.4.1.1 Acute Toxicity Oral, Skin, and Eyes: The liquid is apparently irritating to the skin and eyes of rabbits and is reported to be absorbed through the skin (301).

Inhalation: Sayers et al. (302) reported acute studies on the response of guinea pigs to ethyl bromide (see Table 63.7).

Table 63.7. Physiological Response of Guinea Pigs to Ethyl Bromide in Air (302)

Concentration (%)	Exposure Time (min)	Response

14	10	Unconscious; death in several days
5	98	Unconscious; died 1 h later
6	10	Survived; lung injury
2.4	90	Died in 18 h
	30	Some delayed death; pathological changes in lungs, liver and spleen
1.2	270	Some deaths; histopathological changes
	90	Survived; histopathological changes
	55	Survived; slight histopathological changes
0.65	270	Some deaths
	180	Survived; histopathological changes
0.07	810	One death and histopathological changes
	540	Survival; normal

Vernot et al. (303) determined 1-h LC_{50}s of 27,000 and 16,200 ppm (120 and 72 mg/L) for rats and mice, respectively.

These data are similar to the results in F344/N rats and B3C3F_1 mice given single 4 h exposure to 625-, 1250-, 2500-, 5000-, or 10000-ppm exposures. All animals exposed to 10,000 ppm died. During the initial part of the exposure, clinical signs included an increased rate of respiration, hyperactivity, and incoordination. By the end of the exposure the rats were dyspneic and comatose. It is not clear what clinical signs were observed at lower concentrations or how long the signs persisted after exposures ceased. Male rats did not die after exposure to 5000 ppm or less, but 2/5 female rats died at 5000 ppm. No rats or mice died at 2500 ppm.

Rats and mice were also given 10 repeated 6-h exposures to 0, 250, 500, 1000, 2000, or 4000 ppm (304). All animals exposed repeatedly to 4000 or 2000 ppm died or were sacrificed in extremis. All animals exposed to 1000 ppm or less survived. Deaths occurred as early as days 2 and 3 at 4000 ppm and as late as day 10 at 2000 ppm. Growth of survivors was not affected by exposure. Prostration, dyspnea, lacrimation, and twitching were observed during exposure. Pulmonary congestion and hemorrhage were observed at 2000 ppm and to a lesser degree at 1000 ppm.

Intraperitoneal: The available abstract of a report by Kosenko (305) gives LD_{50} values of 2850 and 1750 mg/kg for mice and rats given single intraperitoneal injections. The abstract further states the material was rapidly detoxified and not accumulated significantly in mouse tissues.

Waite and Yant (306) studied the microscopic pathology of guinea pigs exposed to ethyl bromide vapor. Ethyl bromide exposure concentrations of 60,000 to 180,000 ppm were used with 5- to 19-min exposure times, and concentrations of 3,200–24,000 ppm were used with exposure times of 90–810 min. The exposed animals that died and those that survived up to 8 d postexposure were autopsied to determine any resulting pathology. The high-concentration exposures mainly produced pulmonary damage in the bronchioles and alveoli. Bronchiolar cells showed swelling, distention, and cytoplasmic vacuolation with an exudate containing erythrocytes, epithelial cells, and leukocytes. Swelling of the alveolar walls was noted. Alveolar spaces were found to contain a sero-fibrinous exudate, endothelial leukocytes, and fine granules. At the lower exposure concentrations, the pulmonary reactions were similar to those at the higher concentrations, but to a lesser degree. In some cases, congestion of the kidneys and liver caused by large numbers of erythrocytes was also observed. At the lower concentrations, kidney effects were the most prominent with apparent

compression of the capillary tufts and tubular damage. There was also central liver lobule necrosis in many cases.

Similar toxicity has been reported in rats (307), dogs (308), cats (309), rabbits (310), and mice (272). Oral doses of 200 mg/kg body weight of ethyl bromide administered in 61 daily doses were reported to cause no apparent toxicity in rabbits (311). Sixty-two daily oral doses administered to rabbits at 300 or 600 mg/kg resulted in paralysis but were not fatal.

12.4.1.2 Chronic and Subchronic Toxicity According to the available abstract, rats were exposed 4 h daily for 6 mo to 2.4 mg/L (about 540 ppm), with some evidence of liver injury and disrupted liver function (312).

More recently, rats and mice were exposed 6 h/d, 5 d/wk for 14 wk (65 exposures) to 0, 100, 200, 400, 800, or 1600 ppm (304). In mice, a single death occurred at 200 ppm but none at 800 ppm. Body weight gains did not appear to be affected except at 1600 ppm, at which concentration ataxia, posterior paresis, dyspnea, and tumors were observed. At autopsy, lesions were observed only at 1600 ppm. Mineralization of granular layer of the cerebellum, degeneration of the spinal cord, hemosiderosis of the spleen, depletion of the hematopoietic cells of bone marrow, atrophy of skeletal muscle, severe atrophy of the testes with complete absence of germinal epitheleum, and minimal atrophy of the uterus were observed in rats. Mice were less affected than rats, but atrophy of the uterus, involution of the ovary, and atrophy of skeletal muscle were reported.

12.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Ethyl bromide, given to rats and mice rapidly detoxified and did not accumulate after repeated administration (313). Cohn et al. (314) suggested that some of the ethyl bromide in anesthetized patients is converted to ethyl sulfide since there is evidence of a lingering garlic odor on the breath for several days postexposure.

Ethyl bromide is enzymatically dehalogenated *in vitro* by rat liver extract (315). Ethyl bromide is a substrate for glutathione *S*-transferase. Female Wistar rats given 1.16 millimoles of ethyl bromide in oil by gavage were sacrificed 2 h later, and livers were assayed for glutathione; ethyl bromide-treated rats showed liver glutathione levels 52% that of controls (316). Ethylmercapturic acid is also an ethyl bromide metabolite as shown by its apperance in the urine of rats administered 1.25 g/kg subcutaneous doses of ethyl bromide. This finding was supported by the presence of *S*-ethyl-cysteine in acid-treated urine (317). Ethyl bromide reduces cytochrome P450 activity by degradation of the enzyme's heme group. Hepatic microsomes from phenobarbital-induced Wistar rats, treated with 44.4 millimolar ethyl bromide, showed a 27% reduction in cytochrome P450 activity. The enzyme binding was by the type I manner. Activities of cytochrome b_5 and cytochrome c were not affected. Speculation suggests that deactivation of the cytochrome P450 by heme degradation could be a mechanism that would trap reactive species that could damage cellular components.

Absorption and excretion through the lungs is rapid, but it may be hydrolyzed to some degree in the body, resulting in the formation of inorganic bromide (318).

12.4.1.4 Reproductive and Developmental No data for teratogenicity were found.

12.4.1.5 Carcinogenesis: ACGIH considers this chemical an animal carcinogen with unknown relevance to humans. There is no EPA (IRIS) file.

In the lifetime carcinogenic/toxicology study (304), groups of rats and mice were exposed 6 h/d, 5 d/wk for 104 wk to 0, 100, 200, or 400 ppm by inhalation. Survival of rats was unaffected or in the case of the 100 ppm female rats was significantly above the control group. Body weights were also unaffected.

Likewise survival of mice was little affected by exposure except for a decrease in survival at

400 ppm in female mice, which also had body weights 6–16% lower than controls after the twenty-ninth week. No clinical signs were apparent in any group, but at autopsy there was evidence of respiratory irritation at 400 ppm. It was concluded there was clear evidence of an increase in neoplasms (endometrial adenomas, adenocarcinomas, and squamous cell carcinomas) in the uteri of female mice. The tumors contributed to the decreased survival of the female mice exposed to 400 ppm. The terminal rats of uterine tumors were 0, 3, 14, and 61% in the 0-, 100-, 200-, and 400-ppm groups.

There was equivocal evidence of carcinogenic activity in the lungs of male mice, and a marginally increased incidence of neoplasms in the brain and lungs of female rats. Male rats were considered to have some evidence of a slightly increased incidence of tumors in the adrenals, brain, and lungs. Although there was a clear dose–response relationship in female mice, the dose response in male mice and rats of both sexes was not as clear.

These results are somewhat similar to the results of the study on ethyl chloride, but obviously ethyl bromide is a more potent uterine carcinogen in female mice, causing uterine cancer at much lower concentrations.

Simmon and Poirier (319) and Poirier et al. (320) gave intraperitoneal doses to strain A mice in three groups of 20 animals each at 1, 1/2, and 1/5 of the MTD once per week for 24 wk. They reported no increased incidence of pulmonary tumors over background (background was ca. 20%). The authors speculated that the inactivity may be due to metabolic inactivation when administered intraperitoneally.

Dipple et al. (321) gave rats single subcutaneous injections and observed over 90 wk for sarcomas at the injection site. Doses were 1.36, 0.46, and 0.14 g/kg and showed no activity. The authors speculated that the inactivity may be due to the slow reaction rate of ethyl bromide for sufficient alkylation of vital cellular components.

12.4.1.6 Genetic and Related Cellular Effects Studies Because of its alkylating properties, ethyl bromide has been tested for mutagenicity in microbial systems. Based on several studies including those at NTP, ethyl bromide appears to be a direct alkylating agent in bacterial systems (304). In cultured Chinese hamster ovary cells it induced increased sister chromatid exchange but did not increase the frequency of chromosomal aberrations (322).

12.4.2 Human Experience Symptoms of exposure to this compound include irritation of the skin, eyes, mucous membranes, and upper respiratory tract. Other symptoms include anesthesia, narcosis, lung irritation, acute congestion and edema, liver damage, and kidney damage. It can cause nausea, dizziness, headache, and nervous system disturbances. Central nervous system depression, cardiac arrhythmias, and cardiac arrest may occur. Loss of balance, slurred speech, unconsciousness, and death can occur. Ingestion can cause burning of the digestive tract, vomiting, and moderate gastrointestinal upset. Skin rash may occur. This compound can affect motor control after repeated exposures. Heart damage has been reported. Persons with pre-existing skin disorders or eye problems, or impaired kidney or respiratory function, may be more susceptible to the effects of this substance.

Ethyl bromide has toxic effects on the skin, pulmonary, hepatic, renal, cardiovascular, and neurological systems of humans. In some instances, the toxic effects can be delayed. Individuals with pre-existing disease of the above organ systems probably would be at increased risk from ethyl bromide exposure. There is a lack of data on the human carcinogenicity of ethyl bromide. Skin absorption may also contribute to the overall exposure to ethyl bromide.

Limited human experience during surgical anesthesia has indicated that, in addition to CNS depression, there is a possibility of lung congestion and degeneration of the liver and kidney tissues.

12.4.2.2 Clinical Cases There are no detailed epidemiological or human toxicological studies concerning ethyl bromide, but there are reports of human exposures. In the late eighteenth century, the use of ethyl bromide as an anesthetic was advocated for a number of medical procedures. Probable ethyl bromide concentrations used during some of these procedures approached 100,000 ppm. Von Oettingen (7, pp. 134–138; 323) and Scherbatscheff (308) have reviewed the adverse effects encountered from the use of ethyl bromide for this purpose. In addition to central nervous system (CNS) depression, narcosis, and anesthesia, ethyl bromide administration causes excitation and an initial increase in pulse rate, followed by a slowed pulse and marked vasodilation. Patients have been reported to experience tinnitus, heart palpitations, muscle rigidity and spasms, abdominal wall cramping, hemorrhaging, and a garlicky odor on their breath. Fatalities have occurred from respiratory or cardiac arrest immediately following anesthesia or up to over 24 h post-treatment. Symptoms in fatal cases include vertigo, weakness, difficult breathing, weak and rapid pulse, and unconsciousness, followed by cardiac failure. The autopsy of one fatal case showed ecchymosis of the pericardium, hyperemia and edema of the lungs, and fatty degeneration of the heart and liver. Blindness and conjunctival hyperemia and hemorrhaging have also been reported as occasional results of ethyl bromide anesthesia.

Sayers et al. (302) found that 12,000 ppm ethyl bromide caused immediate eye irritation in human volunteers, and a 5-min exposure at 6500 ppm lead to eye irritation, headache, and vertigo.

Reznikov (324) related clinical cases of occupational ethyl bromide intoxication observed between 1937 and 1942. The course of ethyl bromide poisoning was described in three stages. The first stage lasted 2–4 d and involved a garlicky odor on the breath, sleepiness, fatigue, sharp pain and paresthesia of the lower legs, and a staggering gate. During the second phase that lasted 2–5 d, the symptoms of the first phase grew more severe. The third phase was characterized by spastic paresthesia of the legs, disturbance of the peripheral nervous system, and atrophy of the lower leg. CNS disturbances can also occur at high ethyl bromide exposures. Prognosis for recovery is good for most patients. Blood bromine concentrations of patients suffering from ethyl bromide poisoning at the time of admission were reported to be 15–53 mg/100 mL. Spinal fluid bromine concentrations were 4–7 mg/100 mL. After 5–10 d without exposure, the patients' blood bromine levels were 5–7 mg/100 mL; however, after 2–3 wk, these returned to background levels of 0.61–1.81 mg/100 mL. No background levels for spinal fluid bromine concentration are reported. Blood bromine levels are suggested as a diagnostic and monitoring tool for ethyl bromide exposure. It was pointed out that the blood bromine levels did vary and not all workers supposedly poisoned by ethyl bromine showed greatly elevated levels.

Watrous (325) reported that a group of workers intermittently exposed to ethyl bromide air concentrations up to 1500 ppm complained of no systematic symptoms over a period of several years, but the possibility of undetected chronic toxicity was not ruled out. The abstract of a study of 262 pregnant workers exposed to ethyl bromide vapor reported a significant number of early and late pregnancy toxemias. These workers were also exposed to toluene, ethyl chloride, butyl alcohol, and orthosilicic ester; therefore, these observations cannot be solely attributed to ethyl bromide.

In addition to irritation, repeated or prolonged contact of ethyl bromide with the skin may also lead to absorption of the compound. The Dow Chemical Company (326) states that a single prolonged skin exposure can lead to the absorption of harmful amounts of ethyl bromide. The National Institute for Occupational Safety and Health (NIOSH) (327) states that ethyl bromide can be absorbed through human skin.

12.4.2.3.5 Carcignogenicity Carcinogenicity Classification:

IARC 3, not classifiable as to carcinogenicity to humans

MAK 2, probably human carcinogen

ACGIH A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans

12.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV TWA is 5 ppm with an A3 and skin notation. NIOSH questions whether the OSHA PEL of 200 ppm is protective enough for workers. The NIOSH IDLH is 2000 ppm.

Other Occupational Exposure Values: Australia: 200 ppm, STEL 250 ppm (1990); Federal Republic of Germany: no MAK, A2, clearly carcinogenic only in animal studies (1997); United Kingdom: 200 ppm, STEL 250 ppm (1995).
12.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Ethylene Dibromide
13.0.1 CAS Number:
[*106-93-4*]
13.0.2 Synonyms:
1,2-Dibromoethane, Sym-dibromoethane, dibromoethane, alpha, beta-dibromoethane, glycol bromide, and glycol dibromide, ethylene bromide
13.0.3 Trade Name:
Bromofume, Celmide, DBE, Dowfume 40, Dowfume EDB, Dowfume W-8, Dowfume W-85, Dowfume W-90, Dowfume W-100, EDB, EDB-85. E-D-BEE, ENT 15,349, Fumo-Gas, Iscobrome D, Kopfume, NCI-C005220, Nephis, Pestmaster, Pestmaster EDB-85, RCRA Waste Number U067, Soilbrom-40, Soilbrom-85, Soilbrom-90, Soilbrom-100, Soilbrome-85, Soilbrome-90EC, Soilfume, UN 1605, and Unifume
13.0.4 Molecular Weight:
187.88
13.0.5 Molecular Formula:
$C_2H_4Br_2$
13.1 Chemical and Physical Properties
Ethylene dibromide is a colorless, nonflammable, heavy liquid with a sweetish odor.

Physical state	Colorless liquid
Specific gravity	2.172 at 25°C (25/4°C)
Melting point	9.97°C
Boiling point	132°C
Vapor pressure	11 torr (25°C)
Refractive index	1.53789 (20°C)
Percent in “saturated” air	1.5 (25°C)
Solubility	0.43 g/100 mL water at 30°C; soluble in ethanol, ethyl ether
Flammability	Essentially nonflammable by standard tests in air; it has been used as a fire extinguisher

13.1.1 General

13.1.2 Odor and Warning Properties The odor of ethylene dibromide is not unpleasant and has been termed “chloroformlike.” The odor is not detectable at a low enough concentration to be considered a good warning of excessive exposure.

13.2 Production and Use
Ethylene dibromide was previously used extensively in leaded antiknock gasoline and in fumigant mixtures, but both of these uses have virtually disappeared in the United States. It is used to some extent as a chemical intermediate, special solvent, and gauge fluid. The most significant human exposure appears to have been the result of its use as a fumigant. The high boiling point, low vapor pressure, and high heat of vaporization greatly reduce the probability of high concentrations accumulating rapidly in the work atmosphere.
13.3 Exposure Assessment
No information found.

13.3.3 Workplace Methods NIOSH Method 1008 is recommended for determining workplace exposures to ethylene dibromide (10a).

13.3.5 Biomonitoring/Biomarkers Increased bromide ions may be found in the blood after exposures but is of limited value in biologic monitoring because of the low concentrations present at acceptable levels of exposure. It is not clear if any of the other metabolites is of use for the same reason.
13.4 Toxic Effects
Ethylene dibromide may be toxic by inhalation, ingestion, or skin absorption. It is irritating to the skin, eyes, mucous membranes, and respiratory tract. It may also cause narcosis. It is absorbed through the skin. When heated to decomposition, it emits toxic fumes of carbon monoxide, carbon dioxide, and hydrogen bromide gas. It may also emit ionic and oxidized halogen.

The toxicity of ethylene dibromide has long been recognized and probably because of its low vapor pressure and control of exposure, a relatively small number of cases of acute human injury have been reported despite rather widespread usage. Exposure to high concentrations of the vapors of ethylene dibromide may result in some CNS depression, although the anesthetic action is weak. Deaths from acute exposure at high concentrations are usually due to pneumonia developed as a result of injury to the lungs. Following acute exposures, injury may be observed in the lungs, liver, and kidneys. Chronic exposure over a long period to levels significantly above the threshold also results in a response very similar to that seen from acute exposure. It should be particularly noted that in experimental animals the difference between the concentration causing severe injury and death and that which is tolerated for long-term exposure is not great. Ethylene dibromide has been shown to be carcinogenic in animals, to be mutagenic in many test systems, and to cause adverse effects on the sperm of laboratory and domestic animals. EPA (IRIS) (2) considers it a probable human carcinogen on the basis of increased incidences of a variety of tumors in rats and mice in both sexes by three routes of administration but that the human data are “inadequate.”

Several reviews are available, one of the more comprehensive by Alexeeff et al. (328). Certainly extreme caution must be used in handling ethylene dibromide, to prevent inhalation, ingestion, and skin contact.

13.4.1 Experimental Studies 13.4.1.1 Acute Toxicity Although there are newer references, the acute and short-term animal data cited in previous editions of this volume remain valid. Alexeeff et al. (328) cites many of the more recent reports. There is new evidence of toxic effects at dosages lower than those causing death.

Rowe et al. (329) reported the single-oral-dose LD_{50} for several species of animals: female mice, 420 mg/kg; male rats, 148 mg/kg; female rats, 117 mg/kg; guinea pigs, 110 mg/kg; unsexed chicks, 79 mg/kg; and female rabbits, 55 mg/kg.

Rowe et al. (330) and McCollister et al. (331) compared ethylene dichloride, carbon tetrachloride, and ethylene dibromide, as components of fumigant mixtures. With regard to oral toxicity, ethylene dibromide was, by far, the most toxic of the three. Also ethylene dibromide was more toxic in inhalation exposures of less than 7 h. The minimum lethal concentration for rats in the 8-h exposure

as 200 ppm. The highest concentration not producing detectable injury for 8 h was 50 ppm.

Eyes: Rowe et al. (329) also reported experiments on the effects of ethylene dibromide in the eyes of rabbits. Undiluted ethylene dibromide caused obvious pain and conjuctival irritation, clearing in 48 h. A slight, superficial necrosis of the cornea was observed. Nevertheless, healing was prompt and complete. A 10% solution in propylene glycol was also tested and produced a more severe reaction than did the undiluted material. However, the eye healed without scarring or apparent injury. It is obvious that, in handling ethylene dibromide, the eye should be protected. If the material gets into the eye, it should be washed out promptly.

Skin: Ethylene dibromide is definitely irritating and injurious to the skin. Rowe et al. (329) reported that a 1% solution of ethylene dibromide in butylcarbitol acetate applied 10 times in 14 d to a rabbit's ear caused slight irritation characterized by erythema and exfoliation. The same repeated application, when bandage on to the shaved abdomen, produced erythema and edema, progressing to necrosis and sloughing of the superficial layer of the skin.

Skin Absorption: Thomas and Yant (330) indicated that ethylene dibromide could be readily absorbed through the skin in toxic amounts. Rowe et al. reported quantitive measurements of the toxic dose absorbed through the skin in rabbits for a contact period of 24 h. A dose of 0.21 g/kg body weight was survived by 14 out of 15 animals; 1.1 g/kg body weight killed five of five animals.

Inhalation: A quantitative expression of acute vapor toxicity of ethylene dibromide is found in the data of Rowe et al. (329). The maximum survival exposures of rats to ethylene dibromide vapor in air were as follows: 3000 ppm for 6 min, 400 ppm for 30 min, and 200 ppm for 2 h. Guinea pigs survive 400 ppm for 2 h and 200 ppm for 7 h. The maximum exposure without adverse effect on female rats are 800 ppm for 6 min, 100 ppm for 2.5 h, and 50 ppm for 7 h. The pathological changes following acute exposure described by Rowe et al. were congestion, edema, hemorrhages, and inflammation of the lungs. The liver showed cloudy swelling and central lobular fatty degeneration and necrosis. The kidneys showed slight interstitial congestion and edema with slight cloudy swelling of the tubular epithelium in some cases.

13.4.1.2 Chronic and Subchronic Toxicity EPA (IRIS) indicates that there is no reference dose available for oral exposure for ethylene dibromide, nor is there a reference concentration for inhalation exposure.

Alexeeff et al. (328) reported finding 20 studies in which cats, chickens, guinea pigs, mice, quail, rabbits, and rats were repeatedly exposed to ethylene dibromide. Generally the results are similar to those found following single exposures.

Oral: Aman et al. (33) gave 3–20 mg/kg dosages fed daily to rats and guinea pigs for 95 d were reported to cause no effect on body weight, nor were clinical signs apparent.

These data are consistent with a study by NCI (73) in which rats and mice were intubated 5 d/wk for 6 wk and then observed for an additional 2 wk. All rats survived 63 mg/kg/d, but one male and one female fed 100 mg/kg/d died. Male mice fed 159 mg/kg/d or less survived, but one female mouse dosed with 100 mg/kg/d and two dosed with 250 mg/kg/d died. Body weight of mice was unaffected at dosages 159 mg/kg/d.

Repeated vapor exposure in animals has been reported by Rowe et al. (329). Animals were exposed 7 h/d, 5 d/wk for periods up to 6 mo. At 100 ppm in air, rats and rabbits were in poor condition, and some deaths occurred within the first week or two of exposure. The rats showed injury to the lungs, liver, and spleen. The rabbits showed definite liver injury. At 50 ppm, the rates showed a fairly high mortality (approximately 50%) due to pneumonia and infection of the upper respiratory tract, which may be related to the effect of ethylene dibromide on the lung. A number of them, however, lived through the full 6-mo period. They had increase in lung, liver, and kidney weight and some

histopathological changes in the lungs. Guinea pigs subjected to 57 7-h exposures in 80 d showed some depression of growth but no increase in mortality. Lung, liver, and kidney weights were increased. There were slight histopathological changes in the liver and kidneys. An exposure of 25 ppm was tolerated by rats, guinea pigs, rabbits, and monkeys. The male rats, however, showed high mortality due to pneumonitis and infections of the upper respiratory tract, which the authors apparently considered the result of the chemical exposures. Testicular pathology was not exceptional in these animals, and testicular weights were not consistently affected. Changes in the testes of certain species are discussed in the next sections.

Plotnick and Conner (332), however, saw adverse effects in Sprague-Dawley rats exposed to 20 ppm of the vapor 7 h/d for their lifetimes. Half the rats that also had 0.5% disulfiram (Antabuse) in their diet were very severely affected by 10 mo of exposure. The section on carcinogenesis contains more details of this study.

NTP (335) exposed rats and mice to 0, 3, 15, or 75 ppm of the vapor 6 h/d, 5 d/wk for 13 wk. No deaths occurred in either male or female rats, but male weight gain was depressed in a dose-related manner at all levels. Female rats failed to gain weight only at 75 ppm. Swelling and/or vacuolization of the adrenal cortical cells of the zona fasiculata was found in 8/10 rats and a slight decrease in the follicular size of the thyroid in 6 of 10 rats at this dosage level. A dose-related depression of weight gain was observed in both sexes of mice at all dosage levels. One death occurred in female mice exposed to 75 ppm, and four deaths occurred in the lowest-exposure group of male mice, although there were none at the two higher levels. There was apparently eye irritation in mice exposed to 75 ppm, and megalocytic cells were found lining the bronchioles at that concentration.

Other short-term repeated studies include Short et al. (336), Rezanick et al. (337), and Nitschke et al. (338), discussed in the following.

Reznick exposed rats and mice 6 h/d for 13 wk to 0, 3, 15, or 75 ppm. Rats exposed to 15 or 75 ppm and mice exposed to 75 ppm had cytomegaly, focal hyperplasis, squamous metaplasia, and loss of cilia in the dorsal region of the nasal cavity.

Short et al. exposed pregnant rats and mice to 0, 20, 38, or 80 ppm ethylene dibromide 23 h/d for 10 d starting on day 6 of pregnancy. There were adverse effects on maternal welfare as measured by lack of weight gain or food consumption in both species at all doses. Mortality occurred in rats exposed to 80 ppm and in mice exposed to 38 and 80 ppm. The fetus was affected but only at exposures causing maternal toxicity, and was not considered tetratological.

Nitschke et al. exposed rats to 0, 3, 10, or 40 ppm 6 h/d, 5 d/wk, with scheduled sacrifices after 1, 6, or 13 wk of exposure and after 88–89 d recovery following exposure.

Exposures to 3 ppm were without “consistent effect in any parameter measured.” Ten ppm caused slight epthelical hyperplasia in the nasal turbinates of 1, 6, and 13 wk but not after 88 d recovery. Rates exposed to 40 ppm exhibited decreased body weight gain throughout the 13-wk exposure period and increased liver and kidney weights after 6 and 13 wk. Hyperplasia and nonkeratinizing squamous metaplasia of the respiratory epithelium of nasal turbinates were also seen after 13 wk exposure with apparent recovery of 19/20 rats during the 88-d recovery period. The authors concluded that 3 ppm was a NOEL.

13.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Alexeeff et al. (328) suggest that the route of metabolism may have a pronounced effect on the site and nature of toxic action. Further, it is speculated by these authors that the rat may not be the best animal model because it uses a mercapturic acid pathway little used in humans. Figure taken from the above reference, is based primarily on rat studies.

It has been shown by Stott and McKenna (339) that rats about 50–60% of inhaled ethylene

dibromide and none of the retained compound was excreted unchanged.

The role of ethylene dibromide versus its metanolites in binding with macromolecules and with toxicity and/or carcinogenicity at sites remote from the site of treatment is not clear, but may be influenced greatly by glutathione. Alexeeff et al. (328) indicate the complexity by stating the following: “Thus, the studies on EDB's potential mechanism of action indicate that GSH may be a major factor for preventing the noncarcinogenic action of EDB. The studies also indicate GSH may be involved in the metabolic activation of EDB producing a genotoxic intermediate. These findings represent a potential paradox. GHS may be important in the prevention of the noncarcinogenic effects of EDB, but the resulting EDB–GSH conjugate may be reponsible for the carcinogenic action of EDB. These conclusions are further complicated by studies indicating that while single doses of EDB deplete GSH, multiple doses increase GSH levels. The conjugation pathway appears secondary in the liver but may be primary in the extrahepatic tissues where most of the carcinogenic action of EDB is observed. Humans differ quantiatively in comparison to rodents in the hepatic production of genotoxic metabolites; human tissue appears to produce more genotoxic metabolites via the oxidative pathway than rodent tissue.

13.4.1.4 Reproductive and Developmental According to Short et al. (336), although it caused maternal toxicity at 20, 38, or 80 ppm when inhaled 23 h/d, ethylene dibromide did not appear to be teratogenic in rats and mice.

According to IRAC (340), it has been shown to have rather marked effects on the reproductive systems of some birds and mammals. Ingestion of ethylene dibromide by chicken hens for a prolonged period reduced the number and size of the eggs.

Alumot et al. (341) showed that male chickens were less affected than hens, and bulls, but not cows, rams, or ewes, were markedly affected by repeated exposure to ethylene dibromide. The number of sperm, their morphology, and their motility were affected in bulls and rams, as shown by examination of testes and ejaculates. Rat spermatogenesis was reversibly impaired by five daily intraperitoneal injections of 10 mg/kg (341).

When Epstein et al. (342) studied a dominant lethal test system using mice, ethylene dibromide was found to be negative. Doses of 50 or 100 mg/kg were given orally and intraperitoneally.

13.4.1.5 Carcinogenesis The EPA (IRIS) classified ethylene dibromide as B2; probale human carcinogen on the basis of increased incidences of a variety of tumors in rats and mice in both sexes by three routes of administration at both the site of application and at distant sites. Ethylene dibromide is mutagenic in various *in vitro* and *in vivo* assays and structurally similar to 1,2-dibromo-3-chloropropane, a probale human carcinogen and to ethylene dichloride, a probale human carcinogen.

The EPA (IRIS) considers the human data, with regard to carcinogenesis, as Inadequate. Mortality studies of workers occupationally exposed to EDB (343) found neither total deaths nor total malignancies of individuals exposed to EDB exceeded the control rate. The studies are inconclusive due to their small cohort size; lack of, or poorly characterized, exposure concentrations; and/or concurrent exposure to other potential or known carcinogens.

The EPA (IRIS) considers the animal carcinogenicity data as sufficient—ethylene dibromide has been tested for carcinogenicity by gavage, inhalation, and dermal adminstration.

Gavage Study: The NCI (344) administered TWA doses of 27 and 29 mg EDB/kg bw/d to male and 26 and 28 mg EDB/kg bw/d to female rats by gavage for 49 and 61 wk for the low- and high-dose groups, respectively. High treatment-related mortality prompted the early termination of the study (planned for 110 wk) and alterations of the dosing regime, regimen, resulting in similar TWA dosage for high- and low-treatment groups. Significant increased incidences of squamous cell carcinomas of

the stomach (both sexes), hepatocellular carcinomas and neoplastic nodules of the liver (females), and hemangiosarcomas of the circulatory system (males) were observed upon histologic examination. The stomach tumors developed after a short latency period and were observed to metastasize to multiples sites. Male and female B6C3F1 mice received TWA doses of 44 or 77 mg EDB/kg bw/d by gavage for 53 wk and were observed for their lifetime (344). The incidence of squamous cell carcinomas and alveolar/brochiolar adenomas of the lung was significantly increased over the controls in all the mice. As in the rat bioassay, no tumors were observed in the controls, and high treatment-related mortality prompted dosing regimen alterations.

Inhalation Study: Fischer 344 rats and B6C3F1 mice of both sexes were exposed to EDB vapors at 0, 10, or 40 ppm, 6 h/d, 5 d/wk for their lifespans (335). The incidence of nasal cavity carcinomas and adenocarcinomas in the rats of both sexes and alveolar/bronchiolar carcinomas in female rats and mice of both sexes was significantly increased over the controls. The chronic inhalation of EDB was also associated with circulatory system hemangiosarcomas in both sexes of rats (high-dose only), mammary gland fibroadenomas of female rats, mammary gland adenocarcinomas of female mice, subcutaneous fibrosarcomas of female mice, and tunica vaginalis mesotheliomas of males rats. Stinson et al. (1981), in a chronic inhalation study of experimental design indentical to the NTP study (with B6C3F1 mice only), reported an elevated incidence of nasal cavity carcinomas in the female mice exposed to 40 ppm EDB. Both sexes had dose-related epithelical hyperplastic lesions of the nasal cavity. Histologic and pathologic exams were conducted only on the nasal cavity.

Inhalation: Wong et al. (345) exposed Sprague–Dawley rats of both sexes by inhalation to 0 or 20 ppm EDB, 7 h/d, 5 d/wk for 18 mo. Splenic hemangiosarcomas and adrenal gland tumors of both sexes, subcutaneous mesenchymal tumors in males, and mammary gland tumors in females were significantly increased over the controls. Histologic examination excluded the nasal cavity.

Dermal: Lifetime dermal application of EDB to female He:ICR Swiss mice caused both skin papillomas at 50 mg and lung papillomas at 25 and 50 mg, a significant increase by comparison to the controls (79). A single dermal application of EDB followed by thrice weekly treatment with phorbol myristate acetate (PMA) did not result in an increased papilloma incidence.

13.4.1.6 Genetic and Related Cellular Effects Studies EDB has been studied for mutagenic potential by a variety of *in vitro* and *in vivo* test systems. Reverse and forward mutations have been consistently produced in bacterial assays and in *in vitro* assays using eukaryotic cells. EDB caused an increase in unscheduled DNA synthesis in cultured mammalian cells (346–348) and single-strand DNA breaks in *in vitro* cultured cells and in *in vivo* rat liver cells (350). Direct evidence of intractions with DNA have been provided by the formation of nonextractable radiolabeled DNA following both *in vivo* and *in vitro* exposure to radiolabeled EDB.

13.4.2 Human Experience Ethylene dibromide may cause skin, eye, mucous membrane, and respiratory tract irritation. It may also cause demage to the lungs, liver, and kideys. Inhalation may result in delayed pulmonary lesions. The vapor may have a narcotic action. Prolonged skin contact with the liquid may cause erythema, blistering, and skin ulcers (may be delayed 24–48 h). Dermal sensitization to the liquid may develop. Inhalation may cause severe acute respiratory injury, central nervous system depression, and severe vomiting. Other symptoms include abdominal pain, nausea, diarrhea, dark and scant urine, anuria, mild icterus, marked agitation, jaundice, moderate anemia, systemic effects, and chemical burns. Pulmonary congestion may result after exposure by inhalation, and ingestion may cause gastrointestinal distress and pulmonary edema. After short exposure to very high concentrations, drowsiness occurs. Other symptoms include tychypnea, diffuse inflammation of the gastric and intestinal mucosa, massive central lobular necrosis of the liver, and patchy necrosis of the tubular epithelium. It may cause vesiculation. It may also cause skin burns. Inhalation may be fatal as a result of spasm, inflammation, and edema of the larynx and bronchi. Other symptoms include chemical pneumonitis and eye damage. High concentrations are extremely destructive to tissue of the mucous membranes, upper respiratory tract, skin, and eyes. Anesthesia, conjunctivitis, pharyngeal and bronchial irritation, severe loss of appetite, headache, and depression have also been

reported. Eye contact may cause a temporary loss of vision. Death may result from respiratory or circulatory failure. Lung injury may result in pneumonia and eventually cause death. Persons with pre-existing skin disorders or eye problems, or impaired liver, kidney, or respiratory function may be more susceptible to the effects of this material.

Von Oettingen (74 p. 152) noted cases of poisening when ethylene dibromide was mistakenly used in place of ethyl bromide as an anesthetic.

Kochman (351), in reporting a subacute poisoning case from accidental inhalation, stated that a concentration of 50 ppm could be dangerous to humans.

Kochmann (351) reported poisoning in a chemical plant worker engaged in manufacturing ethylene dibromide who suffered from conjunctivitis, pharyngeal, and bronchial irritation, severe loss of appetite, headache, and depression. When he was removed from the exposure, his condition improved.

The liver and kidneys are target organs as in animals.

Olmstead (352) reported on a death following ingestion of 4.5 mL or 140 mg/kg by a 43-year-old woman, and Letz et al. (353) on two workers who entered a tank. However, it is not clear from the nature of their response that the two worker were in fact injured by ethylene dibormide or by some other agent such as *Clostridia* (354).

Serious skin injury can occur from clothing (particularly shoes) wet with ethylene dibromide. This is true not only when material is spilled inside the shoe but also when it wets the outside, for it penetrates leather. Pflesser (355) observed a case of prolonged contact with the skin when liquid ethylene dibromide was accidently spilled into the shoes. There was reddening, blistering, and burning pain.

Calingaert and Shapiro (356) have observed that ethylene dibromide can penetrate through serveral types of protective clothing, particularly neoprene rubber and several types of plastic gloves. Nylon was found to be the most resistant material but lacking in good physical characteristics.

Ott et al. (343) performed an epidemiological study of 161 employees who manufactured ethylene dibromide. Concentration in one plant ranged from 1 to 10 ppm in 1950; in 1952, concentrations were from 19 to 31 ppm (area samples) and up to 13 ppm in drum filling. Twenty years later, time-weighted-average concentrations averaging 2 and 3.5 ppm were found for two groups of workers (343). Three episodes of exposure to concentrations of ethylene dibromide vapor believed to be between 100 and 200 ppm were reported. These excursions resulted in gastrointestinal discomfort, vomiting, and respiratory involvement, which apparently were caused by exposures above 100 ppm for an hour or less or by longer exposures at lower concentrations (e.g., 75 ppm). In one plant, 5 malignant neoplasms were reported versus 2.2 expected. In the other plant, there seems to have been no excess over the number expected. The exposure to ethylene dibromide vapor at one of these plants, at least, appears to have been greater than at two other facilities engaged in the manufacture of ethylene dibromide (and in one case, vinyl bromide). Of 68 sample results in these plants during 1975 and 1976, only 1 sample, at 18 ppm, exceeded 5 ppm and only 10 others were above 1 ppm. IARC (74) reviewed this and two other studies of workers but determined that there was inadequate evidence for carcinogenicity to humans.

The reproductive history of 297 male employees manufacturing ethylene dibromide was also summarized by Wong et al. (357). In this limited study, reproduction generally appeared to be unaffected by exposure to ethylene dibromide, although in one of four plants, the subjects had fewer children than predicted, possibly due to a high number of vasectomies.

Other studies, however, suggest the number and quality of sperm from 46 exposed workers may

have been affected by exposure (358). However, there are inconsistencies in the results, such as a lack of a clear relation to extant of exposure.

13.4.2.1 General Information 13.4.2.2.5 Carcinogenesis The EPA(IRIS) considers the human data with regard to carcinogenesis as inadequate (see later section on human experience—carcinogenesis). Mortality studies of workers occupationally exposed to EDB (343) found neither total deaths nor total malignancies of individuals exposed to EDB exceeded the control rate. The studies are inconclusive due to their small cohort size; lack of, or poorly characterized, exposure concentrations; and/or concurrent exposure to other potential or known carcinogens.

13.5 Standards, Regulations, or Guidelines of Exposure

No TLV for ethylene dibromide was recommended by the ACGIH in1992–1993, although it was included in their list of their animal carcinogens. It would appear prudent to limit vapor exposure with careful control to minimize dermal contact as well.

NIOSH REL	Ca TWA 0.045 ppm C 0.13 ppm (15-min)
OSHA PEL	TWA 20 ppm C 30 ppm 50 ppm (5-min maximum peak)
IDLH	Ca (100 ppm)

ACGIH-TLY Recommendation: Ethylene dibromide is a severe mucuous membrane, eye and skin irritant. It causes liver and kidney damage and is carcinogenic in experimental animals.

Evidence of carcinogenicity was reported in animals exposed to ethylene dibromide through several routes of administration. Based on these data and the redefination of the carcinogenicity classifications by the TLV Committee, the A2 classification no longer applies. Therefore, an A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans, is assigned to ethylene dibromide, with no set TLV at this time. Because of the potential for systemic toxicity resulting from skin absorption, a skin notation is also recommended.

Carcinogenic Classification

EPA	Group B2, Probable human carcinogen; sufficient evidence from animal studies; inadequate evidence or no data from epideologic studies
IARC	Group 2A, Probably carcinogenic to human
MAK	Group 2, Probably a human carcinogen
NIOSH	Carcinogen, with no further categorization
NTP	Group 2, resonably anticipated to be a carcinogen
TLV	A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans

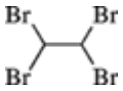
Other Occupational Exposure Values: Australia: no exposure standard, Category 2 carcinogen, probable human carcinogen, skin (1990); Federal Republic of Germany: no MAK, skin, Group 2 carcinogen, probably a human carcinogen (1997); Sweden: Group B carcinogen, may be produced, used, or otherwise handled only after permission has been obtained from the Labour Inspectorate (1984); United Kingdom: 0.5 ppm, skin, carcinogenic substance, R45—may cause cancer (1991); U.S. NIOSH: 0.045 ppm, 15-min ceiling 0.13 ppm, carcinogen, IDLH 100 ppm; U.S. OSHA: 20, STEL 30 ppm, 5-min peak per 8-h shift 50 ppm (113).

13.6 Studies on Environmental Impact

None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

1,1,2,2-Tetrabromoethane
14.0.1 CAS Number:
[*79-27-6*]
14.0.2 Synonyms:
Acetylene tetrabromide, tetrabromoacetylene, and 1,1,2,2-tetrabro--moethylene
14.0.3 Trade Names:
Muthmann's liquid, TBE, and UN 2504
14.0.4 Moleculer Weight:
345.65
14.0.5 Molecular Formula:
$CHBr_2CHBR_2$
14.0.6 Molecular Structure:



14.1 Chemical and Physical Properties

Physical state	Colorless to yellow liquid
Molecular weight	345.7
Specific gravity	2.966(20/4°C)
Melting point	–1.0°C
Boiling point	Decomposition 253.5°C
Vapor pressure	0.04 torr (24°C)<0.1 torr at 20°C
Refractive index	1.63795(20°C)
ppm v/v in air “saturated” at 25°C	80(theoretical)
Solubility	0.065 g/00 mL water at 30°C; soluble in ethanol, ethyl ether, chloroform
Flammability	Not flammable by standard tests in air

1mg/L 70.4 ppm and 1 ppm 14mg/m^3at 25°C, 760 torr

14.1.1 General

14.1.2 Odor and Warning Properties The odor of 1,1,2,2-tetrabromomethane is sweetish and has been compared with chloroform or camphor. The odor is not distinctive enough to be considered a good warning property, although it may give sufficient warning to avoid serious acute exposure.
14.2 Production and Use
Because of its high density, this compound is used in separating minerals by specific gravity or density. It is also used as a solvent for fats, oils, and waxes, as solvent in microscopy, and as a fluid inliquid gauges.
14.3 Exposure Assessment
14.3.3 Workplace Methods Si gel; tetrahydrofuran; gas chromatography/flame ionization detection; IV[#2003]: (4), sample workup with silica gel; IV indicates the 4th edition of NIOSH Mannual of Analytical Methods (DHHS) [NIOSH] publication No. 94-113.

14.3.5 Biomonitoring/Biomarkers Few data are available, but some metabolism may occur, since Hoollingsworth et al (359) reported a slight increase in blood bromide of chronically exposed animals.

14.4 Toxic Effects

Virtually no new reports were found of toxicologic studies since the last revised edition of this volume.

According to SAX, this compound is a poison by inhalation and ingestion, an experimental neoplastigen, an eye and skin irritant, and a narcotic. This compound is a very potent mutagen (360).

Acute/chronic hazards: This compound may be fatal if swallowed (361). It is harmful if inhaled or absorbed through the skin. It is an irritant of the skin and respiratory tract (361). When heated to decomposition, it emits highly toxic fumes of carbon oxides, carbonyl bromide, bromine, and hydrogen bromide gas (361, 362).

1,1,2,2-Tetrabromomethane is a CNS depressant and liver and kidney toxicant. If given in sufficiently large doses, it may cause narcosis, coma, and eventually death from respiratory failure. There may be lung irritation, and pathological changes may be observed in the liver and kidneys. Because the vapor pressure is exceedingly low at room temperature, inhalation exposure may be controlled by reasonable precautions and ordinary ventilation. However, contact with the skin should be avided as well.

14.4.1 Experimental Studies 14.4.1.1 Acute Toxicity Gray (363) reported the LD_{50} for rabbits and guinea pigs to be approximately 0.4 g/kg of body weight. Rats survived 0.6 g/kg and succumbed to 1.6 g/kg (359).

Based on studies using rabbits, contact with the open skin does not result in any skin reaction if it is washed off in a resonable period of time. If the material is bandaged onto the skin and allowed to remain there for a period of hours, a slight redness appears. In 24 h there is some edema and blistering. It can be concluded that ordinary contact does not represent a skin problem. However, wet clothing or shoes that may contain the material should be removed and cleaned before reuse.

No data were found on skin absorption, but given the rather high inhalation toxicity, it should be assumed enough can be absorbed on repeated exposure to be toxic.

Arkhangel-Skaya and Yanushkevich (364) reported on the exposure of rats to aerosols of 1,1,2,2-tetrabromomethane. A concentration varying from 3.7 to 4.2 mg/L for a single exposure of 2 h gave only slight and ill-defined symptoms of toxicity. Concentrations varying from 5.9 to 7.2 mg/L caused excitation followed by sleepiness. Repeated daily exposure to aerosol concentrations of 3.7 to 4.2 mg/L resulted in death of the animals. Ingestion due to preening may have increased the exposure.

Merzbach (365) and Glaser and Frisch (309) exposed animals to vapors of 1,1,2,2-tetrabromomethane. It is a bit difficult to determine the significance of their findings, for Gray (363) indicated that the concentrations reported by these authors were, in most instances, well above a saturated atmosphere.

Gray reported exposure of animals to the vapors of 1,1,2,2-tetrabromomethane at near saturation in a static chamber. Rabbits were exposed for up to 2.5 h and rats for up to 3 h with no deaths. Guinea pigs exposed 0.5 h survived. One out of two survived an exposure of 1 h but all exposed succumbed to exposures of 1.5 h or more. In the guinea pigs that died, injury was seen in the liver and kidneys. The guinea pigs recovered consciousness in a period of 5 h but died in periods of from 1 to 5

following exposure.

14.4.1.2 Chronic and Subchronic Toxicity Gray (363) exposed mice, rats, guinea pigs, and rabbits for 15 min daily for 47–92 d to a "saturated atmosphere." One mouse out of 43 died of an unknown cause; the rest survived without adverse effects. Four out of 36 albino rats were ill from lobar pneumonia, a complication that was considered unrelated to the exposure. The rest of the animals survived without injury. The rabbits were observed taking significant amounts of the condensed 1,1,2,2-tetrabromomethane orally by licking it from their bodies. They were therefore not considered significant to the experiment. It should also be recognized that a certain amount of oral intake would have been possible in the case of the other animals as well, but even so, the chronically exposed animals showed no significant pathological change.

Hollingsworth et al. (359) reported that the concentration in air could not be maintained above approximately 14 ppm by analysis. The theoretically saturated concentration should have been about 79 ppm. Rats, guinea pigs, rabbits, and a monkey were exposed 7 h/d, 5 d/wk for periods ranging from 100 to 106 d. The average concentration was 14 ppm by analysis. All animals survived and apperared normal. There was growth depression in guinea pigs. All animals showed an increase in liver weight. Histopathological changes were observed in the liver and lungs. At 4 ppm, some animals showed slight histopathological changes in the liver and some in the lungs. At 1.1 ppm, animals appeared normal.

14.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Few data are available, but some metabolism may occur, since Hollingsworth et al. (359) reported a slight increase in blood bromide of chronically exposed animals.

14.4.1.4 Reproductive and Developmental No reports were found.

14.4.1.5 Carcinogenesis 1,1,2,2-Tetrabromomethane was applied to tumor-prone H2: ICR Swiss mice in a skin application study (79). Doses of 45 mg/application/mouse were applied 3 d/wk as in action solution to the dorsal skin. Apparently no increase in tumors was found at the site of application, but there were a statistically significant greater number of stomach papillomas.

14.4.1.6 Genetic and Related Cellular Effects Studies Brem et al. (366) reported that the compound was not mutagenic to *S. typhimurium* and that it inhibited the growth of *E. coli*.

Rosenkrantz et al. (367) subsequently reported that 1,1,2,2-tetrabromoethane was negative in the standard (Ames) assay but strongly mutagenic against *S. typhimurium* when tested in suspension.

14.4.2 Human Experience Symptoms of exposure to this compound include irritation of the eyes, nose and upper respiratory tract, anorexia, jaundice, central nervous system effects, urobilinuria, bilirubinuria, and monocytosis (368). Other symptoms include nausea, severe headaches, irritation of the mucous membranes and skin, and dizziness (prolonged exposure). It can cause abdominal pains, lung irritation, dermatitis, and kidney damage (361). It can also cause liver damage (369, p.9; 370). Skin contact may result in blisters (370).

Van Haaften (263) describes the only available report of human injury alleged to be due to 1,1,2,2-tetrabromomethane. Although there appears to be little doubt that the chemists involved had exposure to the vapors, skin exposure was very high, and it is impossible to separate the effects. "Near-fatal liver injury" was reported with headaches, anorexia, stomach ache, and heartburn. Although there is no question of a serious response by the liver, the effects were similar to viral hepatitis. Unfortunately no determinations of blood bromide were reported to determine the magnitude of the exposures.

14.5 Standards, Regulations, or Guidelines of Exposure

The TLV for 1,1,2,2-tetrabromomethane recommended by the ACGIH in 1992–1993 is 1 ppm

(14 mg/m^3).

OSHA PEL: TWA 1 ppm (14 mg/m^3)

IDLH 8 ppm
14.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Propyl Bromide
15.0.1 CAS Number:
[*106-94-5*]
15.0.2 Synonyms:
n-Propyl bromide, bromopropane, 1-bromopropane
15.0.3 Trade Names:
NA
15.0.4 Molecular Weight:
123
15.0.5 Molecular Formula:
C_3H_7Br
15.0.6 Molecular Structure:

15.1 Chemical and Physical Properties

Physical state	Colorless liquid
Specific gravity	1.3539 (20/4°C)
Melting point	–109.85°C
Boiling point	71.0°C
Vapor pressure	143 torr (25°C)
Refractive index	1.43411 (20°C)
Percent in “saturated” air	19.3 (25°C)
Solubility	0.25 g/100 mL water at 20°C; soluble in alcohol, ethyl ether
Flammability	No data were found

1 mg/L 198.8 ppm and 1 ppm 5.03 mg/m^3 at 25°C, 760 torr

15.1.1 General

15.1.2 Odor and Warning Properties No data were found.
15.2 Production and Use
Propyl bromide has had but minor use in industry. It has been studied as an anesthetic but has not

found significant use.
15.4 Toxic Effects
Propyl bromide has a depressant action on the central nervous system and, for that reason, has been considered as a possible anesthetic. Exposure of animals to anesthetic concentrations may result in injury to the lungs and liver.

15.4.1 Experimental Studies 15.4.1.1 Acute Toxicity The material is reported to be irritating to the skin and eyes of mice (301) and to have intraperitoneal LD_{50}s of 2.5 and 2.9 g/kg for mice and rats, respectively (371). Orally administered 1-bromopropane was excreted in expired air (318). Barnsley et al. (273) report that rats metabolize 1-bromopropane. Another reference (372) also reports excretion by rats of a mercapturic acid metabolite as well as the parent compound. It has been reported to be negative when tested for dominant lethal activity in rats (276) when studied at 400 mg/kg orally.
15.5 Standards, Regulations, or Guidelines of Exposure
None has been established.
15.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

Ethyl Iodide
16.0.1 CAS Number:
[*75-03-6*]
16.0.2 Synonyms:
Monoiodoethane, 1-iodoethane, ethyl iodide, ethyl iodide, 99% and hydriodic ether, 99%
16.0.3 Trade Names:
NA
16.0.4 Molecular Weight:
155.97
16.0.5 Molecular Formula:
C_2H_5I
16.0.6 Molecular Structure:

16.1 Chemical and Physical Properties

Physical state	Colorless liquid that may become colored with iodine if exposed to the light
Specific gravity	1.9245 (25/4°C)
Melting point	–108.5°C
Boiling point	72.2°C
Vapor pressure	137 torr (25°C)
Refractive index	1.5076 (25°C)
Percent in “saturated” air	18 (25°C)

Solubility	0.4 g/100 mL water at 20°C; soluble in ethanol, ethyl ether, benzene, chloroform
Flammability	No flash point by standard tests in air, but can be made to combust

1 mg/L 156.7 ppm and 1 ppm 6.38 mg/m^3 at 25°C, 760 torr

16.1.1 General Colorless liquid that may become colored with iodine if exposed to the light

16.1.2 Odor and Warning Properties Ethyl iodide has an ethereal odor but may not be an adequate warning of excessive exposure.
16.2 Production and Use
Ethyl iodide is used in small quantities as a chemical intermediate. In the past, it had limited medicinal use.
16.4 Toxic Effects
Most of the information on the toxicity of ethyl iodide has been obtained because of the interest in this material for the treatment of fungus infections and for measurement of cardiac output. No new, relevant data were found since the third revised edition of this volume. It has been administered to humans as a vapor that, when inhaled, is absorbed by the lungs. It can cause CNS depression and may affect the kidneys, thyroid, lungs, and the liver.

16.4.1 Experimental Studies 16.4.1.1 Acute Toxicity Skin Absorption: Von Oettingen (7) cites a 1936 report by Schwander (207) that indicated ethyl iodide was absorbed through the skin, with deaths occurring 7 d after treatment.

Flury and Zernik (373) have reported the physiological effect of various concentrtations on mice. According to Reinhardt et al., who cite data by Herman and Vial, it was not possible to classify ethyl iodide as to its potency as a cardiac sensitizer based on the available data.

16.4.1.6 Genetic and Related Cellular Effects Studies Simmon and Poirier (319) tested ethyl iodide against *S. typhimurium* and *E. Coli* with positive mutagenic results.

Poirier et al. (320) indicate that when injected intraperitonially two to four times in 24 wk at a total dose of 38.4 mmol/kg, ethyl iodide did not result in an increase in lung adenomas in Strain A mice.

16.4.2 Human Experience Discussions of the response of humans to the therapeutic inhalation of the vapors of ethyl iodide are given in the publications of Blumgart et al. and Schwartz. These reports describe skin lesions and peripheral neuritis in patients.
16.5 Standards, Regulations, or Guidelines of Exposure
No standard has been established for ethyl iodide.
16.6 Studies on Environmental Impact
None found.

Saturated Halogenated Aliphatic Hydrocarbons Two To Four Carbons
Jon B. Reid, Ph.D., DABT

1,2-Dibromo-3-chloropropane
17.0.1 CAS Number:
[*96-12-8*]
17.0.2/3 Synonyms and Trade Names

Names DBCP; CBCP; 3-chloro-1,2-dibromopropane; os 1897; Fumazone; Nemafume, Nemagon; 1,3-Dibromo-3-chloropropane; Nemanax; Nemaset; Nematocide; dibromochloropropane; 1-chloro-2,3-dibromopropane; fumagon; BBC 12; fumazone 86; nemabrom; nemagon soil fumigant; nemagon 206; nemapaz; nematox; nemazon; oxy dbcp; Dibromo-3-chloropropane, 1,2- (DBCP)
17.0.4 Molecular Weight:
136.3
17.0.5 Molecular Formula:
$C_3H_5BR_2Cl$
17.0.6 Molecular Structure:
See attachment
17.1 Chemical and Physical Properties

17.1.1 General :

Physical state	Dense yellow or amber liquid. May also appear in granular form.
Specific gravity	209 (20/4°C)
Melting point	5°C
Boiling point	196°C
Vapor pressure	0.8 torr (21°C)
Refractive index	1.5518 (25°C)
Solubility	Less than 0.1 g/100 ml water at 20øC; Soluble in hydrocarbons, alcohols Percent in saturated air is 0.13 at 25°C
Flammability	Not flammable by standard tests in air

17.1.2 Odor and Warning Properties: Pungent odor at high concentrations. Unpublished data indicate the odor is perceptible at 0.01 ppm to 0.03 ppm (374). It appears doubtful that odor will provide significant warning to discourage excessive exposure, since 0.2 ppm was tolerable although disagreeable to a small series of test subjects.
17.2 Production and Use
DBCP is produced by liquid phase addition of bromine to allyl chloride It was first produced commercially in the United States in 1955.

DBCP is a contaminant of the flame retardant tris (2,3-dibromopropyl) phosphate, and was been used primarily as a soil fumigant to control nematodes. Unlike other halogenated nematocides, DBCP could be applied to soil without damaging perennials. Its use in the United States was canceled in 1979. However, it is still used in Hawaii for use on pineapples and in other places in the world.
17.3 Exposure Assessment
17.3.3 Workplace Methods Per the OSHA website, the primary sampling/analytical method is: media-petroleum base charcoal tube (100/50 mg sections, 20/40 mesh); sampling volume-10 liters; sampling rate-0.2 liters/min; analytical method-GC/ECD; Secondary analytical method: PID.

17.3.4 Community Methods A number of methods have been approved for the determination of DBCP in water. These include: AOAC Method 993.15; APHA Methods 6210-C and D, 6230-C and D; CLP Methods 6231-B and LC_VOA; EMSLC Methods 502.2, 504, 504.1, 524,1, 524.2 551 and 608.1 (375).

17.3.5 Biomonitoring/Biomarkers Although an increase in bromide ion in the blood of individuals exposed to DBCP is likely, the small quantities expected at acceptable levels of exposure would not be meaningful for assessing worker exposures (376).
17.4 Toxic Effects

Laboratory studies and human experience have shown DBCP to be a highly toxic material, particularly from chronic exposure. The testes, liver and kidneys appear to be particularly affected. A summary of the toxicity has been published (377). Much of the original data on acute and repeated studies in animals was initially determined by Torkelson et al (378).

17.4.1 Experimental Studies

17.4.2 Acute Toxicity Oral Single dose oral LD_{50s} for male rats have been reported as 170 and 300 mg/kg and for female mice as 260 and 410 mg/kg by two laboratories. Oral LD_{50s} of 210, 180 and 60 mg/kg were reported for male guinea pigs, male rabbits and unsexed chicks. Kidney degeneration and depressed body weight, which took a long time for recovery, were noted after single doses of 126 mg/kg to male rats (379). Slightly higher LD_{50} values were reported by Rakhumatullaev who noted CNS depression and incoordination following acute oral doses. Single oral doses of 100 mg/kg produced inhibition of the CNS system, prolonged weight loss, and decreased spermatogenesis (379).

Eyes Slight pain and irritation of conjuctiva and irises were observed in rabbits treated with a few drops of undiluted DBCP or a 1 percent solution in propylene glycol.

Skin Single applications did not appear to be more than slightly irritating to rabbit skin, but when applied repeatedly there appeared to be extensive necrosis in the dermis although the epidermis showed only slight crustiness.

Skin Absorption When applied to rabbits' skin for 24 hours, LD_{50s} of 1.4 and 0.5 g/kg have been reported for undiluted DBCP and a 10 percent solution in propylene glycol.

Inhalation Values of 368 ppm, 1hr; 323 ppm, 2 hr; 154 ppm, 4 hr; and 103 ppm, 8 hr were reported by one laboratory (378). In this same paper a second laboratory found DBCP to be somewhat more lethal to their strain of rats, with kidney injury and delayed deaths commonly observed. When rats given 15-7 hr exposures to 40 ppm, almost all died. Extensive injury was noted in the kidneys and testes. Six exposures produced poor health, loss of weight, lung congestion, cloudy swelling of the liver, and nephritis in groups of five male or female rats. The testes of one male appeared atrophied.

Intramuscular Injections Rats were reported to have survived two series of intramuscular injections each given 3 consecutive days (total six injections). The daily doses, 25 mg/kg in propylene glycol, did not produce significant alterations in body weight, lymphocyte counts, or in nucleated cells in formoral smears. These data appear somewhat inconsistent with the previously discussed effect of subacute inhalation exposure (378).

17.4.1.2 Chronic and Subchronic Toxicity Oral In a 90 day feeding trials, the lowest dose level causing a decrease in growth rate for female rats was 150 mg/kg and for male rats 450 mg/kg (380).

Daily oral administration of 70 mg/kg body weight to rats was lethal after 3 weeks of dosing. Degenerative effects were noted in the vascular system and in all internal organs. DBCP was given by gavage to 190 rats either in a dose of 10 mg/kg body weight (single dose) or in repeated doses of 10 mg/kg for 5 months. After the single dose, the animals developed nervous system depression and weight loss (381).

In another study by Kodama and Dunlap in which DBCP was fed as part of the diet, chronic toxicity was not as high as in other studies by gavage or inhalation. Rats fed diets containing 1350 ppm by weight of DBCP were injured but rats ingesting diets containing 450 mg DBCP per kilogram of diet showed only slight evidence of injury. A diet containing 150 mg/kg fed for 90 days produced retarded weight gain of female rats but otherwise was reported to have little effect on male and

female rats. The doses in milligrams per kilogram of body weight and the possible loss of DBCP by evaporation from the food prior to eating were not discussed (374).

Inhalation Torkelson et al. reported severe effects following 50 to 66 7-hr exposures of rats, guinea pigs, rabbits, and female monkeys to 12 ppm. Five ppm inhaled 7 hr/day for 70 days (50 exposures) produced severely decreased testicular weights in half the rats, with histological changes in the testes, kidneys, and bronchioles (376).

17.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms When a dose of 20 mg/kg of 1,2-dibromo-3-chloropropane-3-^{14}C was given orally, it was metabolized rather rapidly by male rats (382). Only traces (0.4 percent of the ^{14}C were excreted in the expired air as unchanged DBCP. Essentially all (98.8 percent) was absorbed from the gut and 90 percent of the activity was excreted in 3 days. During the first 24 hr, 49, 14 and 16.5 percent of the activity was excreted in the urine, feces, and expired air, respectively. The radioactivity in expired air was primarily carbon dioxide. The activity in the urine was in the form of an acidic metabolite (8 percent of the activity of the urine) or as a highly polar metabolite(s) (>90 percent of urinary activity). Some accumulation occurred in the body fat in the form of a metabolite.

Single subcutaneous injections of DBCP produced dose-dependent injury to kidney, testis, epididymis and liver in male rats. Pretreatment with enzyme inducer phenobarbital reduced the nephrotoxicity and hepatotoxicity of DBCP and resulting serum creatinine and urea nitrogen concentrations. Cobaltous chloride pretreatment enhanced the necrogenic effect of DBCP on the kidney and potentiated DBCP-induced elevations of serum creatinine and urea nitrogen concentrations. The gonadotoxicity of DBCP was enhanced by cobaltous chloride and reduced by phenobarbital. The modulating effects of cobaltous chloride and phenobarbital could not be ascribed simply to changes in tissue concentration of the protective conjugation substrate glutathione, since cobaltous chloride increased and phenobarbital did not alter renal and hepatic nonprotein sulfhydryl concentrations (383).

Rats treated orally with DBCP excreted a small amount of 2-bromoacrylic acid. Rabbit liver microsomal oxidases also yielded 2-bromoacrylic acid from DBCP. The conversion involves initial enzymic sulfoxidation or hydroxylation at methyl chloride moiety (CH_2Cl) substituents and then facile nonenzymic reaction to liberate 2-haloacroleins which are further oxidized to the 2-haloacrylic acids. 2-Haloacroleins as potent mutagens and intermediary metabolites may contribute to the adverse toxicologic properties of DBCP (384).

Male rats were challenged with a single dose of DBCP showed a significant decrease in cytochrome p450 in microsomes isolated from liver, kidney, testis, lung and small intestine mucosa 48 hr after treatment. Lipid peroxidation was not found in hepatic microsomes. In liver tissue, treatment resulted in decrease in cytochrome p450 in both rough and smooth microsomal fractions and nuclei, but not in mitochondrial fractions. Mixed function oxidase activities in hepatic microsomes decreased parallel with cytochrome p450 content. Thus, treatment with alkyl halides may preferentially affect isozymes of cytochrome p450 (385).

Following intraperitoneal administration of 50 mg/kg of DBCP to rats in propylene glycol, S,S'-(2-hydroxypropane-1,3-diyl) bismercapaturic acid and S-(2,3-dihydroxypropyl)mercapturic acid were found as metabolites in urine. The metabolic pathway for DBCP includes oxidation and hydrolysis to a series of epoxide metabolites and formation of male anti-fertility agents alpha-chlorohydrin and alpha-bromohydrin from epoxides. Subsequent oxidative metabolism of these latter two compounds to oxalic acid presumably causes liver damage (386).

17.4.1.3.1 Adsorption Male Wistar rats were orally given 20-400 mg/kg (387) ^{14}C labeled DBCP. Major sites of radioactivity were found in the liver and kidney. It is suggested by the authors that the macromolecular binding *in vivo* is caused by an activated metabolic intermediate formed on the

microsome (387).

17.4.1.4 Reproductive and Developmental Following repeated treatment by gavage in either doses of 100 mg/kg body weight or repeated doses on 10 mg/kg body weight to rats for 5 months, an effect on spematogenesis was observed in males: the number and viability of spermatozoa were decreased; the estrus was inhibited in females (381).

Male rabbits exposed to 10 ppm DBCP for 8 weeks by inhalation appeared infertile when mated during the 14th week (388).

Male rabbits, about 14 weeks old were exposed continuously to 0.3 to 10 ppm DBCP. Hypertrophy of the adrenals and marked weight reduction of epididymis, testes and seminal vesicles were observed. Reduction in number of spermatozoa in epididymis and reduction in white blood cells also occurred (389).

Although DBCP has a pronounced effect on the male reproductive system, it was not teratogenic when given to female rats at dosages of 0, 12.5, 25, or 50 mg/kg body weight on days 6 through 15 of pregnancy. The investigators reported it was toxic to dams and fetuses at 50 and 25 mg/kg but not at 12.5 mg/kg (390). Reznik and Sprinchan reported that the estrus cycle of female rats was affected by doses of 10 mg/kg fed repeatedly for 4 to 5 months. Morphological changes have not been reported in the ovaries but these authors suggest that decreased hormonal secretion by the ovary produces the altered estrus cycle (391).

The report by Torkelson et al. (378) of severe testicular injury has been confirmed by numerous other investigators (379, 388, 391, 392, 393, 394). The papers by Burek et al (394) and Rao et al (388) indicate significant species differences, with rabbits more sensitive than rats. Male rabbits were exposed 6 hr/day, 5 days/week to 0, 0.1 or 1.0 ppm (14 weeks) or 10 ppm (2 and 8 weeks). Male and female rats were exposed for 14 weeks to 0, 0.1, 1 or 10 ppm DBCP vapor. Two weeks of exposure of rabbits to 10 ppm produced detectable testicular alterations principally on spermatogenesis. Sertoli cells were unaffected in these animals. Six to 8 weeks of exposures to 10 ppm produced nearly complete atrophy of the germinal tissue of rabbits. Rats, on the other hand, showed no detectable changes after similar exposure to 10 ppm for 5 weeks and only moderate alterations after 14 weeks. There was considerable variation between individual animals. At 1 ppm, rats showed no testicular atrophy after 14 weeks but rabbits were moderately affected. At 0.1 ppm, no effect was seen microscopically in either species, but an equivocal, apparently reversible increase in abnormal sperm was seen by electron microscopy of the testes of the rabbits but not of the rats (394). Reproduction was severely impaired at the higher concentrations, as would be expected from the marked effect observed on sperm counts. Furthermore, a dominant lethal effect was observed when male rates exposed to 10 ppm were mated with unexposed females. This effect was reversible since subsequent matings did not show this effect.

17.4.1.5 Carcinogenisis Two groups of 50 male and 50 female B6C3F_1 hybrid mice, 5 to 6 weeks old were fed technical grade DBCP in corn oil by gavage on 5 consecutive days/week. Approximate time weighted average doses were 114 and 219 mg/kg for males and 110 and 209 mg/kg for females. Two groups, each of 20 males and 20 females were used as vehicle controls. Animals were killed at 60 and 78 weeks and high dose animals at 47 weeks because of high mortality related to tumors. In males, 40/50 of the high dose group had died by end of week 47 and 42/50 of the low dose group had died by week 59. In females, 30/50 of the high dose group had died by end of week 47 and 41/50 of the low dose group. By week 60, squamous cell carcinomas of forestomach occurred in 43/46 low dose males, 47/49 high dose males, 50/50 low dose females and 47/48 high dose females. This lesion occurred with frequent metastases to abdominal viscera and lung. No gastric neoplasms occurred in either vehicle or untreated controls (381).

When fed by gavage to male and female rats and mice in a NCI bioassay program, DBCP had been

shown to produce tumors. The high exposure rats were given 24 to 30 mg/kg per day and the low dose rats 12 to 15 mg/kg per day. The dosage to mice was changed during the study so that daily doses ranged from 160 to 260 mg/kg per day as well as half these levels (low dose) in male mice, and 120 to 160 mg/kg per day and half these levels (low dose) in female mice. Treatments were given 5 days/week for 78 weeks. Tumors were present after 10 weeks of treatment. Ultimately 90 percent of the mice and 60 percent of the rats developed squamous cell carcinomas of the forestomach. A high incidence (54 percent) of mammary adenocarcinomas was observed in female rats but not in mice (395). These results have been confirmed in subsequent studies in which DBCP was administered to rats and mice in the diet, by gavage or by inhalation.

17.4.1.6 Genetic and Related Cellular Effects Studies DBCP was evaluated for genotoxicity in the mouse spot test. Male PW mice, homozgous for 5 coat mutation, were mated with C57BL/6 females. On day 10 of the pregnancy, the females received ip injections of 106 mg/kg DBCP dissolved in soybean oil. The offspring were examined for recessive color spots for 14-30 days following birth. Pups from treated animals showed a significantly higher frequency (2.9%) of recessive color spots compared with solvent treated (0.6%) or untreated (0.9%) controls. Most of the spots induced by DBCP were light brown, which suggest that DBCP induced predominately point mutations in the pigment cells. It was, therefore, concluded that DBCP is mutagenic in somatic cells of mice *in vivo*; however, no teratogenic effects were observed (396).

DBCP has been found to be mutagenic in bacterial test systems using S. typhimurium TA 1530 and E. coli but is quite toxic to the latter. The dominant lethal effects reported by Rao et al (388) also suggest mutagenic changes in mammals.

17.4.2 Human Experience

17.4.2.1 General Information In the July 1977, a worker at a chemical plant in California noted and complained of his inability to father a child. During discussions with fellow workers, it was discovered that several other workers were having a similar problem. These workers were tested and found to be sterile. As a result of this testing, the Oil, Chemical and Atomic Workers (OCAW) union requested the National Institute for Safety and Health (NIOSH) to conduct a health hazard evaluation of their plant. Subsequent to, OSHA alerted approximately 80 manufacturers and formulators to the potential hazard of worker exposures to DBCP.

17.4.2.2 Clinical Cases Investigations in the health effects of DBCP began in 1977. Since that time, a number of studies have confirmed the toxic nature of DBCP.

17.4.2.2.1 Acute Toxicity In humans, DBCP produces moderate CNS depression and pulmonary congestion after exposure by inhalation and causes acute gastrointestinal distress and pulmonary edema after ingestion (397).

17.4.2.2.4 Reproductive and Developmental Five to eight years after the initial effects of DBCP exposure were discovered in 1977 and all exposures were terminated, there appeared to be no major changes in testicular function of most of the 44 exposed men as measured by sperm concentration or serum FSH levels. Recovery of sperm production in two of eight originally azoospermic workers was observed and no increase in sperm production could be detected in the other men who had low sperm counts (398).

A group of 22 factory workers who were exposed to DBCP during production were reassessed 8 years after being diagnosed as azoospermic (388) or oligozoospermic (380) when initially evaluated in 1977. A follow-up study after 4 years had indicated that the gonadotoxic effects of DBCP might be reversible. The objective of the eight year reassessment was to confirm this effect as well as to assess the outcome of pregnancies among wives of DBCP exposed workers. It was observed that recovery of spermatogenesis occurred in 4 oligozoospermic and 3 azoospermic men whose plasma FSH hormone concentration was normal during the whole period. A marked increase in this hormone and luteinizing hormone levels above the upper limit of normal was found in azoospermic men who did not recover. No significant changes in FSH hormone levels were detected in both

recovered and non-recovered oligozoospermic workers. It was also concluded that paternal exposure to DBCP was not associated with increased risk of fetal malformations or spontaneous abortions. There were 44 conceptions; 22 occurred during paternal exposure to DBCP and 22 during the recovery period. These 44 conceptions resulted in 36 live births (and one ongoing uncomplicated pregnancy). The spontaneous abortion rate did not differ from the frequency found in the re-exposed or non-exposed pregnancies. The 3 induced abortions were not related to paternal DBCP exposure (399).

Kapp et al (399a) have reported Y-chromosomal nondisjunction in DBCP exposed employees but these data were not confirmed at the time. The Y-chromosome counts were made on ejaculates with extremely low sperm counts; the control sample was from a different location, and the statistical methodology was questioned.

17.4.2.3 Epidemiology Studies The mortality experience of a cohort of 548 workers who had potential exposure to DBCP was updated in 1989. There were 68 total deaths compared with 72.1 expected. There 19 deaths from all malignancies compared to 19.0 expected. There no deaths from stomach, liver, kidney, testes or nasal cavity cancers. There were 7 deaths from cancer of the lung compared with 6.6 expected (400).

A historical prospective mortality study was conducted on 3579 white male workers employed between 1935 and 1976 with potential exposures to brominated compounds, including DBCP. Workers were classified by their work areas or departments to estimate their potential exposures. A significant excess due to diseased of the circulatory system was observed among the workers exposed to DBCP (401).

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17.5 Standards, Regulations or Guidelines of Exposure
There is inadequate evidence in humans for the carcinogenicity of DBCP. There is sufficient evidence in experimental animals for its carcinogenicity. According to IARC, the overall evaluation of DBCP is that of a possible carcinogen to humans (Group 2B) (402).

The OSHA permissible exposure limit is 1 ppb DBCP as an 8 hr time weighted average (403). NIOSH recommends that occupational exposures to carcinogens be limited to the lowest feasible concentration (404).

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17.6 Studies on Environmental Impact
Since the restrictions on the use of DBCP in 1979 as a nematocide and soil fumigant, little release of DBCP presently occurs. The use of DBCP as a laboartory reactant is not expected to result in large quantities being released to the environment. If released to the atmosphere, DBCP will exist solely in the vapor phase in the ambient atmosphese based on measured vapor pressure of 0.58 mm HG at 20° C. Vapor phase DBCP is degraded in the atmosphere by reactionwith photochemically produced hydroxyl radicals with an estimated half life of 37 days. Products of DBCP are formed during this

process.

DBCP released to soil will likely volatilize or leach. In alkaline, but not neutral or acidic soils, hydrolysis may be significant. Biodegradation is possible but is expected to be slow relative to volatilization and leaching.

In water, DBCP is expected to volatilize. It may also hydrolyze. Esitmated volatilzation half lives for a model river and model lake are 14 hours and 9 days, respectively. In groundwater after DBCP is expected to persist due to its low estimated rate of hydrolysis. In surface waters, biodegradation may occur but is expected to be slow relative to the rate of volatilization. Photodegradation is not expected to be an important fate process for this compound. Sorption to sediments and bioconcentration are not expected to be important fate processes based on measured Koc values of 40-149 and measured BCF values of 3.6-19, respectively. Human exposure is expected to result primarily from ingestion of drinking water, particularly from ground water sources containing DBCP (405).

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Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

1.0 1,3-Dichloropropene
1.0.1 CAS Number:
[*542-75-6*]
1.0.2 Synonyms:
3-Chloroallyl Chloride; 3-chloropropenyl chloride; Telone®; Telone II Soil fumigant; 1,3-dichloropropylene; alpha-chloroallyl chloride; chloroallyl chloride; 1,3-dichloro-1-propene; Telone II; alpha, gamma-dichloropropylene; gamma-chloroallyl chloride; 1,3-dichloropropene (mixed isomers); 1,3-dichloro-1-propylene; 1,3-dichloropropene-1; dorlone ii; Tri-Form; 1,3-D; Telone IIR; chloropropenyl chloride; 1,3-dichloro-2-propene; 1,3-dichloropropene, E-Z-; 1,3-Dichloropropene (mixed)
1.0.3 Trade Names:
cis,*trans*-1,3-Dichloropropene, DD*f* Soil Fumigant (Shell Chemical Company), Telone*f* Soil Fumigants (The Dow Chemical Company), Vorlex*f* Soil Fumigants (Schering, A. G. Berlin/Bergkamen)
1.0.4 Molecular Weight:
110.98
1.0.5 Molecular Formula:
$C_3H_4Cl_2$
1.0.6 Molecular Structure:

1.1 Chemical and Physical Properties

1.1.1 General (1) Although a product that contains primarily *cis* isomer is available, 1,3-dichloropropene isomers are not commonly separated. Commercial products often contain varying amounts of other C_3 compounds and epoxy inhibitors. Hence the following data for a 92% material must be considered only approximate.

Physical State	colorless to light straw-colored liquid
Specific Gravity	1.22
Melting Point	–60°C
Boiling Point	104°C 104.3°C (*cis*) 112°C (*trans*)
Vapor Pressure	5720 Pa at 25°C (*cis*); 4522 Pa at 25°C (*trans*) (2)
Relative Vapor Density	3.83 (air = 1) (2)
Percent in "Saturated" Air	3.7 at 25°C
Solubility	<0.01 g/100 ml in water; soluble in acetone, diethyl ether, benzene, chloroform, octane, and toluene (2, 3).
Flash Point	27°C
Explosive Limits	5 to 14.5% at 80°C

1.1.2 Odor and Warning Properties Rick and McCarty (4) reported that an odor concentration of 4.4 ppm to 3.1 ppm (mean ñ SD) was detected by 22 persons. Concentrations that can cause injury from a single exposure will probably have an odor detected by most people; however, the odor cannot be relied upon to warn against concentrations that can cause injury from prolonged repeated exposure. The odor is sharp, penetrating and irritating (3).

1.2 Production and Use

The *cis* and *trans* isomers of 1,3-dichloropropene are used primarily in soil fumigants. A small amount is used as a chemical intermediate. Exposure occurs principally during manufacture or during bulk handling activities. Because it is generally injected into the soil at depths of 15 to 30 cm, airborne concentrations are generally well below 0.5 ppm, even when measured in the middle of a fumigated field. The material is flammable.

1.3 Exposure Assessment

1.3.1 Air Indoor air in Knoxville, TN contained 52.4 mg/m^3 during the winter and outside the mean was 5.0 mg/m^3 (2).

1.3.2 Background Levels 1,3-Dichloropropene is not a natural product, and its presence in the environment results from industrial use.

1.3.5 Biomonitoring/Biomarkers It seems unlikely that analysis of blood urine or expired air will be of significant value for industrial hygiene monitoring at currently accepted levels of exposure but may help determine if exposure has occurred.

1.4 Toxic Effects

1.4.1 Experimental Studies The subchronic inhalation toxicity data for 1,3-dichloropropene are contradictory. Older data indicate that the commercial product studied at that time (1958–1975) was quite irritating and hepatotoxic, but data developed on currently produced fumigants indicate considerably less hepatotoxicity. Although impurities and inhibitors in the samples used in older toxicity studies may account for part of the discrepancy, different strains of animals, different animals' diets, and different methods of handling the samples used in recent studies may also explain

the difference. It is reasonable to rely more on the more recent data, which has been obtained with improved methods and with samples of better characterized purity. Reviews are available (5, 6).

1.4.1.1 Acute Toxicity A 10% solution of a *cis* and *trans* mixture of 92% purity (8% related compounds) had acute oral LD_{50}s of 710 and 470 mg/kg in male and female rats, respectively. The livers and kidneys of treated animals were grossly affected and there was a suggestion of lung injury in surviving animals (7). Stott et al. (8) reported oral LD_{50}s of 640 mg/kg for male and female mice, 300 to 713 mg/kg for male rats, and 224 to 560 mg/kg for female rats.

Severe to moderate injury occurred in the eyes of rabbits in which a couple of drops of liquid 1,3-dichloropropene had been placed. Prompt washing with water greatly reduced the degree of irritation. The vapors were quite irritating to the eyes and caused lacrimation (7). When a more recent sample was tested, marked conjunctival irritation and discharge were noted and some reddening of the iris. All irritation subsided in 14 days (8).

Necrosis and edema occurred when liquid 1,3-dichloropropene was confined on the skin of rabbits, but if it was allowed to evaporate, the effect was greatly reduced. Positive guinea pig skin sensitization was reported using a 0.1% v/v solution in mineral oil (6), an atypical response for a small chlorinated hydrocarbon.

Absorption through the skin occurred particularly when the liquid was confined or when it was dissolved in propylene glycol, which retarded evaporation. A 24 h LD_{50} for dermal exposures to 333 mg/kg under a cuff was been determined. Higher dermal LD_{50}s of 1000 mg/kg for males and between 1300 and 2000 for females were determined for rats. Fourteen days after treatment, there was congestion of the lungs and congestion of the viscera was apparent in animals that died (6).

According to a 1967 publication by Torkelson and Oyen (7), 2700 ppm was extremely irritating to the respiratory tract and caused liver and kidney injury in rats. Rats survived a 1 h exposure but died from a 2 h exposure to 1000 ppm of the vapor. These rats and others exposed to 700 ppm had a peculiar garlic (or skunk) odor following exposure, indicating probable absorption and possible reaction of the 1,3-dichloropropene with the hair or skin of the rats. Guinea pigs, but not rats, succumbed following a single 7 h exposure to 400 ppm; the rats, however, were severely injured, lost weight, and required 8 days to recover lost weight. Lung injury was still present 8 days after exposure.

When a more recent sample was studied, 4 h inhalation LC_{50}s between 1035 and 855 ppm for male rats and 905 ppm for female rats were determined (8). All rats exposed to 1000 ppm for 4 h died, as well as one female exposed to 850 ppm. Eye and nasal irritation were observed, as well as decreased body weight. Although body weight had not returned to normal at the end of the 2 week observation period, there were no exposure-related observations at gross autopsy. These investigators also reported a strong odor, described as mercaptan-like in rats and mice exposed to 90 or 150 ppm.

In an early subacute study to define the conditions for a subsequent chronic study, Torkelson and Oyen found considerable liver and kidney injury grossly evident in small groups of rats exposed 19 times to 50 ppm, 7 h/day in a 28-day period. Less injury from these early chemical samples was seen at 11 ppm (7).

However, much less toxicity was observed from a later sample tested by Stott et al. (8), according to the authors' abstract.

To provide a comprehensive subchronic inhalation toxicity study of the soil fumigant, technical grade 1,3-dichloropropene (DCPT), male and female Fischer 344 rats and $B6C3F_1$ mice were exposed to 0, 10, 30, 90, or 150 ppm DCPT vapors for 6 h/day, 5 days/week for 13 weeks. The

primary target tissues of inhaled DCPT were identified as the nasal mucosa of both sexes of rats and mice and the urinary bladder of female mice. In addition, depressed growth rates of all animals exposed to 90 or 150 ppm DCPT (up to 20% in rats and 12% in mice) resulted in a variety of alterations in hematologic and clinical chemistry parameters and changes in organ weights relative to controls. Nasal mucosal effects consisted of a slight dose-related degenerative effect on nasal olfactory epithelium or a mild hyperplasia of the respiratory epithelium or both in all animals exposed to 90 or 150 ppm and 2 of 10 male rats exposed to 30 ppm DCPT. Some focal areas of respiratory metaplasia were also noted in high-exposure group mice. Urinary bladder effects consisted of a diffuse, moderate hyperplasia of the transitional epithelium in female mice exposed to 90 or 150 ppm DCPT. No treatment-related effects were observed in rats or mice exposed to 10 ppm DCPT vapors.

Parker et al. (9) also found much less effect than Torkelson and Oyen in CD-1 mice and Fischer 344 rats exposed to 0, 5, 15, or 50 ppm for 6 h/day, 5 days/week for 6 or 12 weeks. Their test material was Shell DD*f* soil fumigant, which contained 55% 1,3-dichloropropene and 30% 1,2-dichloropropane. The balance was related compounds, according to the available abstract.

The following parameters were examined: pharmacotoxic signs; body weights; hematology (HGB, HCT, RBC, WBC, and diff. leukocyte count), serum chemistry (BUN, GLU, ALB, GPT, and ALP); urinalysis; gross pathology; histopathology; organ weights and organ weight/body weight ratios of brain, heart, liver, kidneys, testes or ovaries, and adrenals. The only exposure-related effect observed was increased mean liver weight/body weight ratios of male mice and rats and mean kidney/body weight ratios of female rats at the 50-ppm exposure level. Other statistically significant differences were either inconsistent or not dose-related. Slight to moderate diffuse hepatocytic enlargement in 12/21 of the 50-ppm male mice after 12 weeks exposure was the only compound-related histopathological change.

1.4.1.2 Chronic and Subchronic Toxicity When 1,3-dichloropropene was fed by gavage to groups of rats at 0, 1, 3, 10, or 30 mg/kg body weight for 6 days/week for 13 weeks, it was concluded that 3 to 10 mg/kg was a nontoxic effect level. No gross or microscopic pathological changes related to exposure were observed at any level, nor were general condition, demeanor, survival, hematologic indexes, serum enzyme, activity, or urinalysis affected by exposure. The relative weights of the kidneys increased at 30 mg/kg/day in both sexes and at 10 mg/kg/day in males (10). More recent data by Osterloh and Kiwen (11) suggest that the nephrotoxic effects of 1,3-dichloropropene may be mediated through the mercapturic acid metabolites in the kidney rather than glutathione depletion (2). Haut et al. (12) found a no-observed-adverse-effect of 5 mg/kg body weight for rats and 15 mg/kg body weight per day for mice.

1,3-Dichloropropene is included in the NCI bioassay program discussed under carcinogenesis in the next section, and a lifetime study on a microencapsulated sample is under way.

Four species of animals were exposed for 7 h/day, 5 days/week to either 3 or 1 ppm 1,3-dichloropropene in air for 6 months. This study used a sample available in 1977 (7). There was no effect in rats, rabbits, guinea pigs, or dogs exposed to 1 ppm (0.9 ppm recovered analytically) based on demeanor, general appearance, growth, mortality, hematologic examination, final body and organ weights, and gross and microscopic examination of all major organs. The kidneys of the males rats exposed to 3 ppm showed cloudy swelling, which was attributed to exposure. This effect was also seen in a small group of male rats exposed for 4 h/day, but not in rats exposed 2 or 1 h/day.

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms 1,3-Dichloropropene given either orally or via inhalation is absorbed rapidly and eliminated through metabolism (glutathione conjugation) within 24–48 hours (3).

1.4.1.4 Reproductive and Developmental Pregnant Fischer 344 rats and New Zealand white rabbits were repeatedly exposed to 0, 20, 60, or 120 ppm for 6 h/day on days 6 to 15 (rats) or 6 to 18

(rabbits) of gestation (13). There was no evidence of teratological effects despite obvious toxicity the pregnant dams. The authors' abstract states,

Exposure-related decreases in maternal weight gain and feed consumption were observed in rats at all treatment levels. Decreased weight gain was also observed among rabbits at 60 and 120 ppm. A slight, but statistically significant, increase in the incidence of delayed ossification of the vertebral centra in rats exposed in utero to 120 ppm of DCP was considered of little toxicologic significance in light of the maternal toxicity observed at this exposure concentration. No evidence of teratogenic or embryotoxic response was observed in either species at any exposure level tested. Thus, it was concluded that DCP was not teratogenic at exposure levels up to 120 ppm in either rats or rabbits.

A two-generation reproduction study in which rats were routinely given 6 h daily exposure, 5 days/week to 0, 10, 30, or 90 ppm was reported (14). Dams and nonpregnant females were not exposed from day 20 of gestation through day 4 of lactation. Toxic effects were seen only in the parents exposed to 90 ppm and consisted of decreased body weight and histological changes in nasal mucosa. Reproductive parameters, neonatal growth, and survival were unaffected at all levels, including 90 ppm.

When Shell DD fumigant that contained 28% *cis*-1,3-dichloropropene, 25.6% *trans*-1,3-dichloropropene, and 25.6% 1,2-dichloropropane was used in a single-generation study, adverse effects were observed only in the group of rats that inhaled 90 ppm (15).

The effects of inhaled D-D (1,3-dichloropropene/1,2-dichloropropane) on reproduction were studied in rats of both sexes. The rats inhaled nominal concentration of 0, 10, 30, or 90 ppm (v/v) D-D for 6 h/day, 5 days/week for 10 weeks. Treated males of proven fertility were paired with untreated virgin females at intervals during and after exposure. Treated females were paired with untreated males immediately after the 10-week exposure period. Various aspects of reproductive performance and general toxicity were assessed. Exposure to D-D produced no adverse effects on the libido, fertility, or morphology of the reproductive tracts of rats of either sex; no treatment-related dominant lethal effect was observed in male rats. Slight reduction in body weight gains and slight increases in liver and kidney weights were observed in 90 ppm rats of both sexes.

There were no treatment-related effects on testicular weight, sperm count, or sperm morphology in male mice given five injections of 10, 19, 38, 75, 150, 300, or 600 mg/kg intraperitoneally and examined 30 days later (16).

Possibly because of impurities or stabilizers in different samples, contradictory results have been obtained in *in vitro* and *in vivo* test systems. Highly purified 1,3-dichloropropene had no directly acting mutagenicity to *Salmonella typhimurium* TA100 (17). The investigators hypothesized that a minor oxidation product produced in purifying of previous samples was responsible for the direct mutagenic activity seen in some previous studies.

Furthermore glutathione, which is present in much higher concentrations in mammalian cells than in bacteria, has a detoxifying conjugative effect (18). The addition to standard bacteria test systems of a concentration of glutathione, equal to that present in mammalian cells, virtually eliminated mutagenic activity in *S. typhimurium* TA100 (19). In fact, many mammalian systems have produced negative results, including the Chinese hamster ovary HGPRT forward mutation assay, rat hepatocyte unscheduled DNA synthesis, mouse bone marrow micronucleus, and a dominant lethal study in rats (6, 15). It is important to develop a better understanding of the importance of

glutathione and the significance of bacterial test systems that are low in glutathione (18).

1.4.1.5 Carcinogenesis The IARC (2) has concluded that technical grade 1,3-dichloropropene (that contains 1.0% epichlorohydrin) administered by gavage caused urinary bladder, lung, and forestomach tumors in mice and in the liver and forestomach in rats. Further, it concluded that inhalation exposures resulted in bronchioalveolar adenomas in mice, whereas no tumors were seen in rats (2). After injection with the *cis* isomer, malignant tumors occurred at the site of injection (2). These findings led the IARC (2) to conclude that there is sufficient evidence for carcinogenicity in experimental animals, at least when tested with technical grade 1,3-dichloropropene (2).

Van Duuren (20) tested what was reportedly *cis*-1,3-dichloropropene and found it negative in an initiation-potentiation bioassay on mouse skin when tested with 7,12-dimethylbenzanthracene and phorbol myristate. It was not carcinogenic to the backs of Hs:ICR Swiss mice following 3 times/week application of 122 mg/kg for 85 weeks. Subcutaneous injections once a week increased local fibrosarcomas.

NTP (21, 22) tested a 92% commercial product that was stabilized with epichlorohydrin. It is not clear how much epichlorohydrin was present but the concentration may have been as high as 1.8%. Rats were fed 0, 25, or 50 mg/kg/day and mice 0, 50, or 100 mg/kg/day via gavage for 3 days/week for up to 2 years. Ancillary studies were conducted to determine the time-related effects on a group of rats treated for 9 to 27 months, according to the authors' summary.

The primary organs affected were forestomach (rats and mice), urinary bladder (mice), lung (mice), and liver (rats). Compound-related nonneoplastic lesions included basal-cell or epithelial hyperplasia of the forestomach (rats and mice), epithelial hyperplasia of the urinary bladder (mice), and hydronephrosis (mice). Neoplastic lesions associated with administration of Telone II included squamous-cell papillomas of the forestomach (male and female rats, female mice), squamous-cell carcinomas of the forestomach (male rats, female mice), transitional-cell carcinomas of the urinary bladder (female mice), alveolar/bronchiolar adenomas (female mice), and neoplastic nodules of the liver (male rats). Although *cis*- and *trans*-1,3-dichloropropene are the principal components of Telone II, the presence of 1% epichlorohydrin, a direct-acting mutagen and carcinogen added as stabilizer, may have influenced the development of forestomach lesions. The results of the ancillary studies supported the findings of the carcinogenesis studies and demonstrated the time-dependent development of lesions in the forestomach (basal-cell hyperplasia and squamous-cell papilloma).

Perhaps the most pertinent study is that of Lomax et al. (23), who exposed Fischer 344 rats and $B6C3F_1$ mice to 0, 5, 20, or 60 ppm (0, 22.7, 90.8, or 272 mg/m^3) technical grade 1,3-dichloropropene for 6 h/day, 5 days/week for up to 2 years. Ancillary groups were exposed for 6 to 12 months. Exposure resulted in nontumorigenic lesions of the nasal mucosa in both sexes of rats and mice exposed to 60 ppm and female mice exposed to 20 ppm, in the urinary bladder mucosa of both sexes of mice exposed to 60 ppm, and in the forestomach of male mice exposed to 60 ppm. Slight changes in the relative degree of cellular vacuolation in renal and hepatic tissues of male and female mice exposed to 60 ppm, respectively, were also observed following months of exposure. These changes were consistent with changes in the renal lipid and hepatic glycogen content of these mice and were considered related to depression of body weight and did not represent a toxicologically significant effect of exposure. However, in contrast to the results of the oral gavage bioassay, an increased incidence of benign lung tumors in the high-exposure group of male mice was the only tumorigenic response observed. The benign tumors did not progress to malignancy, nor did they have an effect on survival. This apparent difference in results between the lifetime gavage and the lifetime inhalation studies is striking, especially when the total daily dose 5 days/week by inhalation, based on respiratory rates and tidal volumes, would have been considerably more than that from the repeated boluses of oral dose given three times per week. Whether the response in the oral study was due to the administration of boluses or possibly due to some other factor such as the epichlorohydrin that had been added to the sample is not clear. It certainly suggests the need for

caution in extrapolating the results to humans, particularly in the light of the lack of mutagenic activity of 1,3-dichloroprene in mammalian cells. No-effect levels of 5 ppm for mice and 20 ppm for rats were found.

Gehring et al. summarized the available data on metabolism (6). Absorption occurs through the skin, from the gut, or by inhalation. Hutson et al. (24) fed ^{14}C-labeled 1,2-dichloropropane and both isomers of 1,3-dichloropropene to rats and found differences in their metabolism. With all compounds, 80 to 90% of the radioactivity was eliminated in the first 24 h. The major route of excretion of radioactivity was in the urine, where 50.2, 80.7, and 56.5% of the 1,2-dichloropropane, *cis*-1,3-dichloropropene, and *trans*-1,3-dichloropropene activity, respectively, were found. The amount of ^{14}C-carbon dioxide excreted was quite different for the two isomers. The *cis* isomer yielded only 3.9% of the dose and the *trans* isomer 23.6%, and correspondingly less radioactivity was in the urine. As expected with volatile compounds, residual unreacted compounds were not present as significant residues, although metabolites entered the normal metabolic pool. Subsequently Climie et al. (25) showed that 82 to 84% of the radioactivity of the ^{14}C-label at the second carbon was recovered in the urine of rats as *N*-acetyl-*S*-(*cis*-3-chloropropenyl)cysteine.

Both *cis* and *trans* isomers are eliminated rapidly by the rat (half-life less than 30 min) (26). A relatively small amount was found bound to macromolecules in the forestomach and to a lesser degree in the glandular stomach of rats and mice. Macromolecular binding correlated to dose- and time-related depression of nonprotein sulfhydryl of the stomach and liver (27, 28).

Excretion and distribution of 1,3-dichloropropene in rats fed up to 50 mg/kg was independent of dose. More than 80% was excreted in 24 h. Mice had a similar response at doses up to 100 mg/kg. Excretion in rat urine was primarily of the mercapturic acid conjugate and its corresponding sulfoxide, as it was in humans (28).

The *N*-Acetylcysteine conjugate of 1,3-dichloropropene was found in the urine of four men 24 h after field application of Telone II fumigant, consistent with similar findings in animal studies (16).

1.4.2 Human Experience 1.4.2.2.1 Acute Toxicity A brief case report was found in the literature. This article is of dubious value because it contains a significant amount of subjective evidence and presents inadequate control data (29). After accidentally drinking a solution containing a mixture of *cis* and *trans* isomers of 1,3-dichloropropene, a 27-year-old male died 40 hours later after experiencing gastrointestinal distress, adult respiratory distress syndrome, and hematologic and hepatorenal function impairment (30).

A fatality following ingestion reportedly involved abdominal pain and vomiting. The patient became semicomatose, exhibited muscular twitching, and died, despite gastric lavage and therapy for pulmonary edema (31).

1.4.2.2.5 Carcinogenesis In a case report (32) 1,3-dichloropropene and malignant lymphoma were associated in two firemen who died 7 years after a single exposure. A third person, a farmer, was included, but the authors failed to mention that he had been ill for some time before his alleged exposure. The authors correctly drew no conclusions as to cause and effect. IARC (2) concluded that there was no epidemiological data on the carcinogenicity of 1,3-dichloropropene in humans. However, based on the experimental animal data, IARC (2) place classified the technical grade 1,3-dichloropropene as possibly carcinogenic to humans and placed it in its 2B Group. 1,3-Dichloropropene has been classified as may reasonably be anticipated to be a carcinogen (33).
1.5 Standards, Regulations, or Guidelines of Exposure
OSHA has no PEL for 1,3-dichloropropene, whereas NIOSH considers it a carcinogen and recommends a REL of 1 ppm (5 mg/m^3) with a skin notation (34). The ACGIH has recommended 1 ppm as the TLV®, with skin and A4 notations; similar values have been used as guidelines and standards in other countries (35, 36). The WHO has recommended an international drinking water

standard of 20 mg/L (37).

Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

2.0 *cis*- and *trans*-1,2-Dichloroethylene
2.0.1 CAS Number:
[*156-59-2*] *cis* isomer; CAS Number: [*156-60-5*] *trans* isomer; CAS Number: [*540-59-0*] mixed isomers
2.0.2 Synonyms:
1,2-Dichloroethene; acetylene dichloride; *sym*-dichloroethylene; acetylene dichloride; dioform; dichloroethylenes
2.0.3 Trade Names:
NA
2.0.4 Molecular Weight:
96.95
2.0.5 Molecular Formula:
$C_2H_2Cl_2$
2.0.6 Molecular Structure:
cis-

; *trans*-

2.1 Chemical and Physical Properties
2.1.1 General (38)

Physical State	colorless liquid
Specific Gravity	1.284 (*cis*); 1.257 (*trans*)
Melting Point	–57°C; –81.5°C (*cis*); –49.4°C (*trans*)
Boiling Point	48–60°C; 60.3°C (*cis*); 48.0–48.5°C (*trans*)
Vapor Pressure	kPa at 20°C: 24.0 (*cis*); 35.3 (*trans*) 180–264°C (*cis*);
Percent in “Saturated” Air	27.4 at 20°C
Relative Vapor Density	3.4 (air = 1)
Solubility	poor in water, 0.50 g/100 mL; 0.08 g/100 mL (*cis*); 0.63 g/100 mL (*trans*); soluble in ethanol, ethyl ether
Explosive Limits	9.7 to 12.8% in air (*cis*)
Autoignition Temperature	460°C
Flash Point	6°C (c.c.); 2.2 to 3.9°C (c.c.) (*cis*); 6°C (*trans*) (c.c.)

2.1.2 Odor and Warning Properties No definitive data are available. The odor has been described as slightly acrid like a chloroform mixture of isomers.
2.2 Production and Use
The *cis* and *trans* isomers of 1,2-dichloroethylene have had only limited use as solvents and chemical intermediates. Neither of the isomers has developed wide industrial usage in the United States partly because of their flammability.
2.3 Exposure Assessment
2.3.3 Workplace Methods NIOSH Method 1003 is recommended for determining workplace exposures to the 1,2-dichloroethylene isomers (80).

2.3.5 Biomonitoring/Biomarkers The metabolisms of *cis*- and *trans*-1,2-dichloroethylene have been reviewed (39). Metabolism is thought to proceed via epoxidation through dichloroacetaldehyde to dichloroethanol and dichloroacetic acid. Cytochrome P450 is involved in the epoxidation (40, 41). There are differences in the rate of metabolism of the two isomers.

There are no data to evaluate biological monitoring in humans.
2.4 Toxic Effects
2.4.1 Experimental Studies Because neither isomer has found wide usage, toxicological data are limited. The compounds were studied as anesthetics, and von Oettingen (42) summarized the old data. However, some of these data must be considered suspect because the purity of the samples and the ratio of the isomers is not always indicated. Even recent data are inconsistent, and there are considerable variations among studies (39).

Unpublished data indicate low to moderate oral toxicity and rather large differences among studies. Unpublished data cited in the third revised edition of this publication reported an oral LD_{50} of more than 2000 mg/kg for a 60:40 *cis:trans* mixture. Fruendt et al. (43) reported an oral LD_{50} of 1275 mg/kg which was surprisingly low compared to an intraperitoneal LD_{50} of 7650 mg/kg reported for female Wistar rats by the same investigators. Fruendt et al. reported considerable pulmonary pathology, suggesting that some of the dosage may have been aspirated. Hayes et al. (44) reported feeding *trans* isomers to Sprague–Dawley rats and determining acute oral LD_{50}s of 7900 and 9900 for males and females, respectively.

Values of 2100 and 2400 mg/kg were determined for fasting mice gavaged with a 10% aqueous solution containing Emulphor (45). Deaths generally appeared to be due to anesthetic effects.

trans-1,2-Dichloroethylene was fed to rats and mice in drinking water studies (44). There was little effect when it was fed to mice for 14 days at daily doses of 21 and 210 mg/kg body weight. When it was fed for 90 days at average doses of 0, 17, 175, and 387 mg/kg to male mice and 0, 23, 224, and 452 mg/kg body weight to female mice, effects were described as minimal based on gross pathological, hematologic, and clinical chemical parameters. Histopathological examinations were not made, but cell-mediated immune status was reportedly unaffected in both sexes. Humoral immune response was not affected in female mice but was suppressed at all three dosages in male mice (46).

Immunotoxicity was evaluated by feeding *trans*-1,2-dichloroethylene (47) to Charles River CD-1 mice. LD_{50}s of 2221 and 2391 mg/kg body weight were determined for males and females, respectively. Deaths due to CNS depression occurred between 4 and 24 h after treatment. When fed by gavage for 14 days at 0.1 and 0.01 of the LD_{50} levels, there was no effect on body weight. Necropsy 24 h after the last dosing showed no changes in liver, spleen, lung, thymus, kidney, or brain weight. Serum lactic dehydrogenase, SGPT, and urea levels were unaffected. There was a nonstatistically significant trend toward reduction in the ratio of humoral IgM antibody forming cells to spleen red blood cells. When evaluated for cell-mediated immune response by using human serum

albumin, the mice showed a slight effect that was not dose-dependent.

Plaa and Larson (48) evaluated kidney toxicity in mice and concluded that both the *cis* and *trans* isomers were, at most, weak nephrotoxins.

When fed in drinking water to Sprague–Dawley rats for 90 days at doses of 402, 1314, and 3114 mg/kg body weight per day (male rats) and 353, 1257, and 2809 mg/kg/day (female rats), there were no compound-related effects on hematological, serological, or urinary parameters. Female rats showed a dose-related increase in kidney weight, but no gross or histological changes were found in either males or females (44).

The available data conflict on whether there is a significant difference between the toxicity of the two isomers. According to Smyth, the *cis* isomer did not kill or anesthetize rats in 4 h at 8000 ppm. At 16,000 ppm, they were anesthetized in 8 min and were killed in 4 h. He also states that the *trans* isomer was twice as toxic and anesthetic as the *cis* isomer (49), and that the important effect of inhalation is narcosis. Lehmann and Flury (50) reported that disturbance of equilibrium and prostration occur in approximately the same length of time from similar concentrations of the *cis* and *trans* isomers. Both slight narcosis and deep narcosis occurred with the *cis* isomer at concentrations of about half of the *trans* isomer.

More recently, Gradiski et al. (51) reported a 6 h LC_{50} of 22,000 ppm for mice exposed to the *trans* isomer, but Fruendt et al. (43) claimed adverse effects in rats that received a single 8 h exposure to 200 ppm of the *trans* isomer. Fruendt et al. reported that five of six rats had livers that appeared normal when stained for fat accumulation, but one showed fat deposition. Apparently, all six rats showed effects in the lungs, whereas only one control rat was similarly affected. These workers reported fibrous swelling in the cardiac muscle of rats exposed for 8 h to 3000 ppm. Fruendt's data are markedly inconsistent with other inhalation studies.

Fruendt and Macholz (52) reported that a single 8-h exposure to 200 ppm of either *cis*- or *trans*-1,2-dichloroethylene inhibited mixed-function oxidases in rats and the *cis* isomer was more active than the *trans* at high concentrations.

The concentration of 1,2-dichloroethylene required to cause anesthesia is not clear. No gross effects were seen in rats at 200 ppm (43), in several species at 1000 ppm (51), or in rats at 3000 ppm. Old data suggest that concentrations approaching 1 to 2% are required to cause surgical anesthesia in mice or other species (42).

Reinhardt et al. (53) concluded there were inadequate data on which to rank the ability of 1,2-dichloroethylene to sensitize the heart to adrenaline.

Intraperitoneal LD_{50}s of 6 mL/kg (7650 mg) (rats) and 3.2 mL/kg (mice) for the *trans* isomer were reported by Fruendt et al. (43), who surprisingly reported a lower oral LD_{50} (1 mL/kg) for rats.

2.4.1.2 Chronic and Subchronic Toxicity Lehmann and Flury (50) reported the results of repeated exposures of cats and rabbits to vapor concentrations of 0.16 to 0.19% in air. Animals exposed to the *cis* isomer at this concentration showed loss of appetite and some respiratory irritation but no histological changes.

Conflicting data exist on the chronic toxicity of 1,2-dichloroethylene. Torkelson, as cited in the Third Revised Edition of Patty's, reported no adverse effect in rats, rabbits, guinea pigs, or dogs exposed to either 500 or 1000 ppm for 7 h/day, 5 days/week for 6 months. The sample consisted of 60% *cis* and 40% *trans* isomers. The parameters studied included growth, mortality, organ and body weights, hematology, clinical chemistry, and gross and microscopic examinations of the major organs. In contrast, Fruendt et al. (43) claimed marked effects in rats exposed for 8 h daily, 5

days/week for 16 weeks to 200 ppm of the vapors of the *trans* isomer. Liver and lungs were affected and the leukocyte count decreased.

2.4.1.4 Reproduction and Developmental When *cis*- and *trans*-dichloroethylene isomers were incubated in the presence of metabolically active mouse liver enzymes, they were not mutagenic to *E. coli* K-12 or *S. typhimurium* (54, 55).

More recent data give mixed results in a variety of *in vitro* and *in vivo* test systems (39), and the *cis* isomer was apparently more active than the *trans* isomer. Chromosomal aberrations in a mouse bone and gene conversion in a mouse host-mediated assay have been reported (39).

No data on teratogenesis or carcinogenesis were found. *cis*- and *trans*- 1,2-Dichloroethylene have been scheduled in the NTP bioassay program, but no data are available.

2.4.2 Human Experience 2.4.2.1 General Information 1,2-Dichloroethylene was studied as an anesthetic in humans, apparently with some success. Only one old report of one fatality was found (56); death was probably due to anesthesia. Routes of exposure can be by inhalation and ingestion. Harmful contamination of the air is reached rapidly by evaporation at 20°C. Irritation of the eyes and respiratory tract can also occur and central nervous system effects, like narcosis (38) may occur at high levels.

2.4.2.2.2 Chronic and Subchronic Toxicity Long-term or repeated exposure can result in defatting of the skin (38).
2.5 Standards, Regulations, or Guidelines of Exposure
The TLV recommended by the ACGIH is 200 ppm (793 mg/m^3) (35). The NIOSH REL/OSHA PEL is also 200 ppm. The NIOSH IDLH is 1000 ppm.

Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

3.0 Dichloroacetylene
3.0.1 CAS Number:
[*7572-29-4*]
3.0.2 Synonyms:
1,2-Dichloroacetylene; Dichloroethyne; DCA
3.0.3 Trade Names:
NA
3.0.4 Molecular Weight:
94.93
3.0.5 Molecular Formula:
C_2Cl_2
3.0.6 Molecular Structure:

3.1 Chemical and Physical Properties
3.1.1 General (57–59)
Physical liquid (or colorless gas at elevated temperatures)

State	
Melting Point	–66 to –50°C
Boiling Point	32–33°C
Solubility	insoluble in water; soluble in ethanol, diethyl ether and acetone
Flash Point	Spontaneously combustible; severe explosion hazard; Acetylene is used as a stabilizer; in the presence of trichloroethylene its stability is considerably increased

3.1.2 Odor and Warning Properties Dichloroacetylene has a disagreeable sour-sweet odor. Based on the experience in closed environmental systems, it is doubtful that dichloroacetylene has useful warning properties. No data were found for odor thresholds.

3.2 Production and Use

Dichloroacetylene is not commercially available in large quantities. It is reportedly a by-product of the synthesis of vinylidene chloride and is not known to be used commercially (58, 59).

Dichloroacetylene is a highly toxic, spontaneously combustible, undesired, and noncommercial product of the dehydrochlorination of trichloroethylene. It has resulted from exposure of trichloroethylene vapor to Hopcalite in a closed environmental system (submarine) and soda lime in closed circuit (rebreathing) anesthesia machines and from exposure of trichloroethylene liquid to caustic in degreaser tanks. It may also be an undesired by-product during chemical processes such as production of vinylidine chloride (60).

When dichloroacetylene was decomposed in the presence of oxygen, seven substances were found; phosgene, hexachlorobutadiene, chloroform, carbon tetrachloride, trichloroacetyl chloride, tetrachloroethylene, and trichloroacryloylchloride (60).

3.3 Exposure Assessment

3.3.1 Air Dichloroacetylene does not occur as a natural product (58, 59).

3.3.3 Workplace Methods No workplace measurement method is available (61).

3.3.4 Community Methods Dichloroacetylene has been measured in air over the range of 0.4–40 mg/m^3 using gas chromatography with electrolytic conductivity detection.

3.3.5 Biomonitoring/Biomarkers No data were found but in view of the high toxicity of dichloroacetylene, biological monitoring does not appear reasonable.

3.4 Toxic Effects

3.4.1.1 Acute Toxicity Dichloroacetylene is highly toxic and causes nausea; neurological, liver, and kidney injury; and liver and kidney tumors in rodents.

Reichert et al. (62) reported that the LC_{50}s for 1 and 4 h exposures of mice were 124 and 19 ppm, indicating that the vapor is highly toxic. Deaths were due to kidney injury. Degenerative lesions were found in the brain, a finding the investigators thought consistent with rather pronounced sensory loss and effects in facial muscles of humans. Reichert et al. reported similar injury in rabbits. Neuropathological changes were not found following a 2.25 h exposure of groups of rats to about 300 ppm dichloroacetylene (63). However, trigeminal somatosensory evoked potentials were significantly slower than baseline values or concurrent controls. Trichloroethylene/dichloroacetylene-exposed control animals were unchanged.

Rats were exposed for 6 h/day, 5 days/week for 6 weeks to dichloroacetylene at 2.9, 9.8, or 15.5 ppm in a dichloroacetylene–trichloroethylene mixture and for continuous 90 day exposure to 2.8 ppm dichloroacetylene (64). The trichloroethylene vapor concentrations were 3.2, 50, and 150 ppm during

the repeated exposures and 5.3 ppm during the continuous. Approximately 4 ppm acetaldehyde vapor was also present. Although no deaths were reported, rats exposed repeatedly to 9.8 and 15.5 ppm were unkempt in appearance and showed some respiratory distress. No signs of toxicity were seen during repeated exposure to 2.9 ppm, but rats exposed continuously were emaciated and showed weakness in the hind limbs. One rat appeared to be blind at the end of the exposure period. The most striking observation during microscopic examination was in the kidneys of rats exposed continuously to 2.8 ppm and repeatedly to 15.5 ppm. Effects in the lungs were less consistent and not clearly related to exposure. The course of development of the kidney changes with time has been studied in rats exposed continuously to 4.8 ppm for up to 28 days. In addition to rather marked injury to this organ, weakness in the hind legs, self-inflicted bite wounds, weight loss, and some deaths were observed.

Reichert et al. (65) also reported severe kidney injury and some deaths in rabbits exposed for 1 h to 126, 202, and 307 ppm or for 6 h to 17 to 23 ppm.

3.4.1.2 Chronic and Subchronic Toxicity The rat is mildly to markedly susceptible to dichloroacetylene-induced trigeminal nerve dysfunction, as assessed by trigeminal nerve-stimulated somatosensory evoked potential. The kidney is the likely target organ of exposure to dichloroacetylene (66). Data from longer term studies are reported in the section on carcinogenicity. Patel et al. (67) found that glutathione-dependent bioactivation of dichloroacetylene might be related to neurotoxic effect of dichloroacetylene. Barret et al. (68) found that, although dichloroacetylene had only a slight effect on the fatty acid content of the brain, it did have a higher intensity for inducing trigeminal nerve alterations.

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Glutathione conjugation has been shown in rats following inhalation of dichloroacetylene (69). These investigators reported the identification of *S*-(1,2-dichlorovinyl) glutathione (DCVG) as a product of the glutathione (GSH)-dependent metabolism of DCA *in vitro* and the identification of *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine (N-Ac-DCVC) as a urinary metabolite of DCA in rats.

The product, DCVG, was definitively identified by ^{1}H-NMR spectrometry (400 MHz), mass spectrometry, and UV spectroscopy. N-Ac-DCVC was identified as a urinary metabolite from rats by GC/MS after esterification. Urine (collected for 24 h) from male rats exposed to 36 ñ 5 ppm DCA (100 mmol of DCA introduced into the exposure system) for 1 h contained 10.7 mmol of N-Ac-DCVC as determined by HPLC analysis. Formation of DCVG, renal processing to *S*-(1,2-dichlorovinyl)-L-cysteine, and cleavage of this cysteine S-conjugate by cysteine S-conjugate b-lyase in the kidney and the formation of reactive and mutagenic intermediates may account for DCA nephrotoxicity and nephrocarcinogenicity. N-Ac-CDVC is the end product of DCVG processing by the enzymes of mercapturic acid formation.

Using a nose-only dynamic system, Kanhai et al. (70) gave ^{14}C-dichloroacetylene to rats for 1 h at concentrations of 20 or 40 ppm. Retention rates of 17.6 and 15.6% of the radioactivity were reported for 20 and 40 ppm, respectively. Elimination of radioactivity was almost quantitative in 96 h. Elimination of radioactivity in urine was 67.8% at 20 ppm and 60% at 40 ppm. Elimination in feces was 27.5% at 20 ppm and 27% at 40 ppm. Only 3.4 to 3.5% remained in the carcass.

Metabolites in the urine were identified as *N*-acetyl-*S*-(1,2-dichlorovinyl)-L-cysteine, dichloroethanol, dichloroacetic acid, oxalic acid, and chloracetic acid. Only the cysteine conjugate was found in feces. It was formed in the kidneys because only *S*-(1,2-dichlorovinyl) glutathione was found in the bile. Biliary cannulation did not influence renal excretion of the cysteine conjugate.

They concluded that

the results suggest that two metabolic pathways are operative in dichloroacetylene metabolism *in vivo*. Cytochrome P450-dependent oxidation represents a minor pathway accounting for the formation of 1,1-dichloro compounds after chlorine migration. The major pathway is the biosynthesis of toxic glutathione conjugates. Organ-specific toxicity and carcinogenicity of dichloroethyne (acetylene dichloride) is due most likely to the topographical distribution of gamma-glutamyl transpeptidase which is concentrated mainly in the kidney of rats.

3.4.1.4 Reproduction and Developmental The reproductive organs have not been target organs in available studies.

Only limited data on the mutagenic potential of this very reactive compound were found (71). The investigators summarized their study which they concluded clearly demonstrated the mutagenicity of pure dichloroacetylene, as follows: DCA vapor was streamed under analytical control through the bacterial suspensions. DCA is soluble in aqueous solution and was stable under the experimental steady-state conditions of the bacterial exposure. There is a linear correlation between the supply of DCA vapor and solubilized DCA in the range of 1000 and 16,000 ppm. Mutagenic response was observed with strain TA100 if the bacteria were suspended in Oxoid medium. No mutagenicity was detected with strain TA98. DCA mixtures with acetylene, as used as a stabilizer for animal experiments, were not mutagenic in either bacterial strain with or without S9 mix in the cell suspension. One of the degradation products of DCA, trichloroacryloyl chloride, showed pronounced mutagenic properties with and without drug-metabolized enzymes. Other degradation products of DCA, such as trichloroacetyl chloride and hexachlorobutadiene, were not mutagenic, with or without liver homogenate.

3.4.1.5 Carcinogenesis The IARC (58, 59) concluded that there is limited evidence for the carcinogenicity of dichloroacetylene to experimental animals based on treatment-related increases in the incidence of adenocarcinomas of the kidney in male mice, benign tumors of the liver and kidney, and an increased incidence of lymphomas in rats.

Kidney tumors were the most significant carcinogenic response reported in an inhalation study of rats and mice (72). The investigators summarized their data as follows: Groups of 30 male and 30 female rats and mice were exposed to DCA vapor under the following conditions: mice, group I: 9 ppm for 6 h/day, 1 day/week for 12 months; group II: 2 ppm for 6 h/day, 1 day/week for 18 months; group III: 2 ppm for 6 h/day, 2 days/week for 18 months; rats: 14 ppm for 6 h/day, 2 days/week for 18 months; controls: under identical conditions except for the addition of DCA to breathing air. The most important result is a striking increase in the formation of kidney cystadenomas of the proximal tubuli in all DCA-exposed animals. The median latency time of this tumor varied widely in both mice and rats. Renal cystic adenocarcinomas were found in statistically significant numbers in male mice. In addition to kidney tumors, the development of cystadenomas of the Harderian gland in mice and of liver cholangiomas in rats were highly significant findings. DCA failed to induce liver tumors in mice. Our results confirm that DCA possesses high carcinogenic potential, pronounced organotropic properties, and distinct species differences for the number and nature of the induced tumors. The risk associated with handling chlorinated aliphatic hydrocarbons is essentially increased by the decomposition product, DCA.

The investigators commented on the rapid induction of tumors at low concentrations and in only 1 to 2 days/week of exposure. Cystic adenocarcinomas were found in 42% of the male mice after exposure to 2 ppm for 1 day/week for 18 months.

3.4.2 Human Experience 3.4.2.2.2 Acute Toxicity Deaths possibly due to kidney injury have been reported. Defolgue (73) summarized human experience during anesthesia from trichloroethylene before 1961. IARC (59) has summarized more recent data, most of which has come from Henschler and co-workers in Wurzburg, Germany, who concluded that dichloroacetylene “possesses the

highest carcinogenic potential of all representatives of the class of chlorinated, aliphatic hydrocarbons" and "that it is by far the most toxic compound of this class of xenobiotics" (72).

Deaths ascribed to dichloroacetylene have been reported following use of trichloroethylene with soda lime in closed-circuit anesthesia machines, but the precise inhaled concentrations were not determined (64). Saunders (74) described human experience in an incident in a closed environmental system in which alkaline materials were present in the life support system.

3.4.2.3 Epidemiology Studies 3.4.2.3.1 Acute Toxicity Dichloroacetylene can cause headaches, dizziness, nausea, vomiting, eye irritation, mucous membrane irritation, and neurological disorders such as paresis and neuralgia in several cranial nerves. Nausea has occurred at concentrations as low as 0.5 to 1.0 ppm.

3.4.2.3.2 Chronic and Subchronic Toxicity The toxic effects were mainly neurological and could last from several days to years (58, 59).

3.4.2.3.5 Carcinogenisis The IARC (58) could not find data by which to classify dichloroacetylene for its carcinogenicity to humans.
3.5 Standards, Regulations, or Guidelines of Exposure
OSHA has no PEL for dichloroacetylene, whereas NIOSH recommends treating it as a carcinogen that has a ceiling REL of 0.1 ppm (0.4 mg/m^3) (61). The TLV for dichloroacetylene recommended by the ACGIH is a ceiling of 0.1 ppm (0.39 mg/m^3) with an A3 notation (35). The ILO (75) indicates that the standards and guidelines are similar for other countries, and no international drinking water standard exists (37).

Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

4.0 Allyl Chloride
4.0.1 CAS Number:
[*107-05-1*]
4.0.2 Synonyms:
3-chloropropene; 3-chloropropene-1; 3-chloro-1-propene; 1-chloro-2-propene; chloroallylene,; chloropropene; 3-chloropropylene; alpha-chloroproplylene; 3-chloroprene; 1-chloro propene-2; 3-chloro-1-propylene; 2-propenyl chloride
4.0.3 Trade Names:
NA
4.0.4 Molecular Weight:
76.526
4.0.5 Molecular Formula:
C_3H_5Cl
4.0.6 Molecular Structure:

4.1 Chemical and Physical Properties (76)

Physical State	colorless yellow, or purple liquid

Specific Gravity	0.9376 at 20/4°C
Melting Point	–134.5°C
Boiling Point	44.6°C
Vapor Pressure	39.3 kPa at 20°C
Relative Vapor Density	2.6 (air = !)
Refractive Index	1.4155 (20°C)
Percent in “Saturated” Air	48 at 25°C
Solubility	0.337 g/100 mL in water at 20°C; miscible with ethanol, ethyl ether, and chloroform
Flash Point	–31.7°C (c.c.)
Explosive Limits	3.3 to 11.1% in air
Autoignition Temperature	390°C

4.1.2 Odor and Warning Properties Allyl chloride can be a yellow or purple liquid that has an unpleasant and pungent odor. Shell Chemical Company published the following information in its bulletin (77). The odor threshold for half of the people was 0.47 ppm in air. The odor threshold for essentially all people was 25 ppm. Eye irritation occurs between 50 and 100 ppm. Nasal irritation and pulmonary discomfort may be observed at levels below 25 ppm.

Another study reports a 50% response to 0.21 ppm and a 100% response to 0.5 ppm. A third study reports that a definite odor was detected by 10 to 13 volunteers exposed to 3 ppm (78).

Odor may be considered a warning of levels hazardous from acute exposure, but allyl chloride is not detected at low enough concentrations to warn of levels hazardous from chronic exposure.

4.2 Production and Use

The major use of allyl chloride is as a chemical intermediate for resins and polymers. About 90% is used to make epichlorohydrin, the basic building block for epoxy resins, and in glycerol synthesis (79). Allyl chloride is flammable. World production in 1989–1990 was estimated at 500–600 thousand tons per year, and production facilities were located in South America, China, Europe, and the United States (79).

4.3 Exposure Assessment

4.3.1 Air Few data are available for allyl chloride in the environment (79).

4.3.3 Workplace Methods Allyl chloride can be measured in the workplace by using a solid sorbent tube (coconut shell charcoal, 100 mg/50 mg) and using the gas chromatography, FID technique. The working range is 0.16 to 3 ppm (0.5 to 10 mg/m^3) for a 100-L sample. The method is applicable to short-term samples taken at 1 L/min (80).

4.3.5 Biomonitoring/Biomarkers No data were found that would indicate the utility of biological monitoring, and it appears doubtful if it would be useful at the exposure level acceptable to workers.

4.4 Toxic Effects

4.4.1 Experimental Studies Although older data indicate that allyl chloride is moderate in acute toxicity and high in chronic toxicity, data recently derived for rats and mice indicate considerably lower liver and kidney toxicity. The effects are primarily due to inhalation, which can produce respiratory irritation, as well as liver and kidney injury. Effects on the pancreas have been alleged, but this has not been confirmed. Skin contact can produce irritation and a deep-seated pain referred to as “deep-bone ache.”

There are reports of polyneuropathies in exposed workers and experimental animals, changes that

have not been seen in laboratory animals exposed to higher concentrations of vapor in other studies. These claims obviously need confirmation.

Literature was reviewed by NIOSH (81) and IARC (79, 82).

4.4.1.1 Acute Toxicity Smyth and Carpenter (83) reported an oral LD_{50} of 700 mg/kg of body weight as determined in rats. Karmazin (84) also reported moderate oral toxicity; LD_{50}s of 450, 500, and 300 mg/kg were determined for rats, mice, and rabbits, respectively. Mild degenerative changes were observed in the myocardium, livers, and kidneys. Lu et al. (85) reported 425 and 460 mg/kg LD_{50}s for mice and rats, respectively.

Unless confined on the skin, allyl chloride is only mildly irritating. It may be absorbed through the skin in amounts sufficient to cause systemic intoxication in animals. Smyth and Carpenter reported an LD_{50} of 2.2 g/kg for 24 h skin absorption on rabbits. The Shell Chemical Corporation's Industrial Hygiene Bulletin (77) states, “The absorption of the liquid through the skin of human beings is attended by deep-seated pain in the contact area.”

Vapor concentrations of 50 or 100 ppm allyl chloride are irritating to the eyes. Higher concentrations of vapor may cause very severe irritation and pain. Liquid splashed in the eyes would be expected to cause severe irritation and should be washed out immediately with water.

There are contradictory reports of the toxicity of allyl chloride vapors in animals. Acute vapor studies of animals were reported by Adams et al. (86). Maximum exposure time–concentrations in air for a single exposure survived by rats were as follows: 3 h at 290 ppm, 1 h at 2900 ppm, and 15 min at 29,300 ppm. Comparable figures for guinea pigs were 8 h at 290 ppm, 3 h at 2900 ppm, and 1/2 h at 29,300 ppm.

The primary lesions were in the kidneys and the lungs. The kidney injury was severe, and there was congestion, hemorrhage, and marked parenchymatous degeneration. The pulmonary injury was also severe, particularly at higher concentrations. It consisted of marked congestion and frequent hemorrhages in the alveolar spaces.

A similar high acute and subacute toxicity has been shown by Shamilov and Abasov (87), who determined 4 h and 2 h LC_{50}s of 2100 and 2600 ppm (6.6 and 8.2 mg/L) for rats and mice. Four hour daily exposures to 0.4 mg/L (130 ppm) for a month affected the central nervous system and kidney function of rats, as shown by increased excretion of chlorides and protein.

However, a later study indicates significantly less acute effects on rats and mice (Dow Chemical Company, Midland, MI, unpublished data). The reason for the difference in response is not clear but may be due to changes in sample purity, the method of handling the sample, the strains of animals, changes in diets, or combinations of these and other factors. Groups of 10 male and female Fischer 344 rats and $B6C3F_1$ mice were exposed to various concentrations (range 200 to 2000 ppm) for 6 h. Parameters monitored included appearance and demeanor, body weights, clinical chemistry values, organ weights, and gross and histopathological examination. Significant findings included mortality, body weight loss, increased blood urea nitrogen and serum glutamic pyruvic transaminase values, and liver and kidney pathology. Although both liver and kidneys were target organs, the primary effect of allyl chloride exposure in both rats and mice was renal toxicity. Rats were more susceptible to allyl chloride vapor than mice on the basis of mortality data, renal pathology, and associated clinical laboratory findings. Female rats were affected to a greater degree than male rats, whereas male mice were affected to a greater degree than female mice. Minimal effect levels for renal toxicity were 300 ppm for rats and 800 ppm for mice. No significant effects were seen in rats or mice exposed to 200 ppm allyl chloride. Previous studies reported mortality in rats at 300 ppm; hence these results are quite different because the first mortality did not occur until rats were exposed to

concentrations of 1000 ppm.

Lu et al. (85) reported 2 h LC_{50}s of 11.5, 11.0, 11.4, and 5.8 mg/L (3680, 3520, 3660, and 1856 ppm) for female mice, male rats, female rats, and male guinea pigs, respectively. They also reported 2 h "lethal concentrations" of 22.5 and 10.5 mg/L for male rabbits and cats. Another report by these investigators (88) describes the exposures as static with gas chromatographic analysis. Lethal concentrations caused signs of irritation, such as closed eyes, pawing and scratching of the nose and mouth, lacrimation, and salivation, which were most prominent in guinea pigs and cats. Diarrhea occurred within 24 h. Initial signs included hypoactivity, unconsciousness, breath holding, and paralysis of rear legs in mice. Later drowsiness, unconsciousness, tremors, convulsions, and death due to apnea occurred in the various species but were most severe in guinea pigs. Unsteady gait and ataxia in cats were also observed following exposure. Marked injury to the lungs and histopathological changes in the kidneys were reported. Injury to the liver and alveolar space were observed at higher levels. Conditioned reflex was reportedly affected in cats by exposure to 745 mg/m^3 but not to 650 mg/m^3. Duration of exposure was not given.

4.4.1.2 Chronic and Subchronic Toxicity Almeev and Karmazin (89) stated that repeated oral doses of 0.015 mg/kg/day in the course of an 8 month study did not lead to morphological changes or other effects in rats. Karmazin (90) reported changes in conditioned reflexes after 6 months at this same dosage, which was the only dose level in these studies.

Data on repeated exposure of animals are also contradictory. The effects of repeated inhalation of allyl chloride vapors by four species were reported by Torkelson et al. (78). They reported that

animals were exposed repeatedly to either eight or three ppm of allyl chloride in air to establish conditions safe for repeated exposure. Rats, guinea pigs and rabbits had definite liver and kidney pathology after one month of repeated seven-hour exposures to eight ppm.

Histopathological examination showed

significant evidence of ill effect of a severe degree in the liver and kidneys of essentially all the animals. These were characterized by dilation of the sinusoids, cloudy swelling and focal necrosis in the liver; and by changes in the glomeruli, necrosis of the epithelium of the convoluted tubules and proliferation of the interstitial tissues in the kidney.

These species and dogs tolerated similar exposures to 3 ppm for 6 months, and only slight reversible liver pathology was seen in female rats.

The report by Torkelson et al. varies considerably from more recent data from the same laboratory. In 90 day studies, rats and mice have shown no effect from repeated 7 h exposures to 100 ppm or less (Dow Chemical Company, Midland, MI, unpublished data). Groups of 25 rats and mice of each sex were exposed to 0, 50, 100, or 250 ppm for 6 h/day, 5 days/week for 3 months. Ten animals of each sex and species from each concentration were sacrificed after 30 days, and the balance was necropsied at the end of the exposure period. The parameters evaluated included in-life observations, body weight, hematology, clinical chemistry, urinalysis, organ weights, gross necropsy, and light microscopic examination of tissues from major organs. The kidneys of male rats exposed to 250 ppm had increased cytoplasmic granularity and eosinophilic staining of the cortical epithelial cells. There was also an increased incidence and degree of focal tubular collagen and atrophy in the kidneys of the 250-ppm rats. No adverse effects were observed in any group of mice or in rats exposed to 100 ppm or lower after 90 days.

Because of outbreaks of polyneuropathy in workers, limited studies were conducted in animals by Lu et al. (85). Six male rabbits and two female cats were reportedly exposed to a nominal concentration of 206 mg/m^3 (66 ppm) for 6 h/day, 6 days/week for 3 months. Muscle weakness in the extremities, lurching motion, and unsteady gait were evident in all rabbits by the second month, but there was considerable difference in the time of onset in individual rabbits. Paralysis and unsteady gait, muscle atrophy, and emaciation were seen in rabbits but only muscle weakness and unsteady gait in rats. EMG changes, degeneration of peripheral nerve fibers only in distal nerves, and liver kidney and lung pathology were observed. Such marked peripheral nerve injury or paralysis has not been observed in other studies at higher concentrations in rats and mice.

Ten male and one female rabbit and 20 male rats were also exposed for 6 h/day, 6 days/week for 5 months to 17.5 mg/m^3 (5.6 ppm) without apparent ill effects. EMG studies showed occasional sharp waves in three rabbits at the end of the exposure, but the investigators did not attach significance to them.

In a follow-up study, He et al. (91) treated 10 albino mice three times per week with gavage doses of 300 or 500 mg/kg for 2 to 17 weeks. They reported that 70% of the animals had focal kidney change and that central-peripheral distal type axonopathy was commonly seen. Tolerance developed from continued dosing.

Omura et al. (92) found that male ICR mice died within 24 hours after a single subcutaneous injection of 496–1037 mg/kg body weight and had severe haemorrhage and edema of the lung and inconsistent, non-dose-related damage to the liver and kidney. When the surviving mice were sacrificed one week later, the only histopathological changes were found in the testes.

4.4.1.4 Reproduction and Developmental Intraperitoneal injections of 80 mg/kg given from day 1 to day 15 of gestation caused severe toxicity in rat fetuses. The sample used may not have been pure, and the route of treatment is most unnatural (93).

Allyl chloride was not teratogenic in rats or rabbits following exposure to 30 or 300 ppm for 7 h/day during the period of major organogenesis (94).

Decreases in body weight gain and increased liver weight were observed among both rats and rabbits exposed to 300 ppm of AC, and an increase in kidney weights was observed in maternal rats. The incidence of fetal resorptions was not significantly increased in either test species.

Ossification of vertebral centra and sternebrae was delayed at 300 ppm.

This slight delay in fetal development may be associated with the observed effects in the maternal animals at this level. Fetal body weights and measurements were not adversely affected in rats, thus the effects on the offspring were minimal and were observed only at an exposure level which also produced effects in the maternal animal. Low incidences of malformed fetuses were observed in all test groups, including controls, for both rats and rabbits and there was no indication of a teratogenic response in either species following inhalation exposure.

Mutagenic data were summarized by the IARC (82), which concluded that allyl chloride was positive in many test systems. Redistilled allyl chloride was studied for mutagenic structure–activity relationships in a large series of compounds (95) and then compared to chemical alkylating capacity using 4-(*p*-nitrobenzyl) pyridine. Mutagenicity in *S. typhimurium* TA 1535, 1537, 1538, 98, and 100

bacteria with and without liver homogenate (S-9) activation was determined. Allyl chloride was mutagenic even without liver homogenate. It was positive in a chemical alkylating test, and the authors considered that it was a direct-acting mutagen, particularly because adding of the S-9 fraction greatly decreased mutagenic activity.

4.4.1.5 Carcinogenesis Allyl chloride was included in the NCI gavage bioassay program and reportedly showed no evidence of carcinogenicity in Osborne–Mendel rats of either sex. There was a higher than background incidence only of squamous cell carcinomas and papillomas in the forestomachs of both sexes of mice and squamous cell papillomas in the forestomachs of female mice. The incidence in other organs did not increase.

The doses fed by gavage were as follows: male rats, 77 and 57; female rats, 73 and 55; male mice, 199 and 172; and female mice, 258 and 129 mg/kg/day. Survival of high-dose male mice, male rats, and female rats was poor. As in many of these old studies, histopathological examinations were inadequate. Gastric irritation was evident.

Groups of 30 Ha:ICR Swiss mice received 31 or 90 mg technical grade allyl chloride in acetone on their skin three times per week for 440 to 594 days without evidence of tumors. Equivocal results were observed in a two-stage mouse-skin assay, that involved a single 94 mg application followed by 3 days/week treatment with phorbol myristyl acetate (20).

Allyl mercapturic acid was isolated from the urine of rats dosed with allyl chloride (96). These investigators also reported that 3-hydroxypropylmercapturic acid was identified as a metabolite. A study of the pharmacokinetics and metabolism following single administration of ^{14}C-allyl chloride to CDF-Fischer 344 rats by oral, inhalation, and intravenous exposure was reported (97).

Following oral and inhalation exposure, the fate was dose- and route-dependent. Most of the radioactivity was excreted as polar metabolites in urine or as CO_2 and parent compound in expired air. Epichlorohydrin was not a major metabolite. A one-compartment bimodal absorption model adequately described the parent compound blood level following oral treatment, and a two-compartment model better described the blood levels following intravenous dosing and inhalation exposure. The terminal half-life in blood depended on the inhaled concentration at high concentrations, but at 100 ppm or less, the half-lives were less than 30 min. A single 6 h exposure to 1000 or 2000 ppm caused marked depletion of nonprotein sulfhydryl (NPSH) in the liver, kidneys, and lungs, but a 100 ppm exposure caused only a slight although statistically significant decrease. NPSH was not changed in kidneys, liver, lung, or blood after a 6 h exposure to 100 ppm. Cytotoxicity was apparent in rats' kidneys 24 h after a 6 h exposure to 1000 or 2000 ppm.

IARC (79) has found inadequate evidence of carcinogenicity in experimental animals.

4.4.2 Human Experience Because of its recognized toxicity, allyl chloride has generally been handled carefully during its manufacture. Eye irritation resulting from overexposure to the vapors has been the most frequent complaint (77, 81). The onset of orbital pain may be delayed several hours after exposure. More intense vapor exposure produces conjunctivitis, reddening of the eyelids, and corneal burn.

One unique feature of dermal exposure is a so-called deep-bone ache, which has been reported following dermal contact.

A report available only as an abstract indicates kidney dysfunction in workers exposed above the 3 mg/m^3 standard. Although kidney injury is consistent with the response in animals, not enough data are given in the abstract to determine the significance of the report in terms of dosage (98).

Another report by Hausler and Lenich (99) also inadequately describes the employees' exposure

levels but indicates many adverse effects in a population of 60 people. An odor of garlic on the breath and body was a common complaint. The skin and respiratory tracts appear normal, but there were alterations in liver function tests. These effects disappeared following better industrial hygiene control measures.

Neurological effects attributed to allyl chloride in the absence of liver and kidney injury have been reported in Chinese workers (91). Although the peripheral neuropathies were ascribed by the investigators to inhaled allyl chloride, absorption through the skin was not considered. Furthermore, their results were not confirmed in other countries. No explanation is readily apparent, and the issue merits further study.

Enterline et al. (100) found limited evidence for elevated heart disease in a Texas plant where workers were exposed to allyl chloride and high, moderate, low, or no exposure to epichlorohydrin. It was suggested by the senior author that further research on this apparent association is needed (101), and Ross (102) suggested that the study lacked data on confounders and adequate exposure data.

Olsen et al. (103) reported on a cohort of 1064 men employed at a Texas plant in epoxy resin, glycerine, and allyl chloride/epichlorohydrin production between 1957 and 1986 and followed-up through 1989. There were 66 total deaths (SMR = 0.8; 95% CI 0.6–1.0) and 10 cancers (SMR = 0.5; CI 0.2–0.9). However, the authors noted that the cohort was limited due to sample size, duration of follow-up, small numbers of deaths both expected and found, and the limited exposure potential.

The IARC found that it could not classify allyl chloride as a human carcinogen on the basis of available data (79).

4.5 Standards, Regulations, or Guidelines of Exposure

The TLV for allyl chloride recommended by the ACGIH is 1 ppm (3 mg/m^3), and the STEL is 2 ppm (6 mg/m^3) with an A3 notation. The OSHA PEL is 1 ppm (3 mg/m^3) as is the NIOSH REL (80). Skin contact must be prevented because allyl chloride may be absorbed (76). The ILO (104) indicates that similar standards or guidelines are used in other countries (104). No international guidelines for drinking water have been suggested (37).

Unsaturated Halogenated Hydrocarbons

R. A. Lemen, Ph.D., MSPH

5.0 Hexachlorobutadiene

5.0.1 CAS Number:

[*87-68-3*]

5.0.2 Synonyms:

HCBD; perchlorobutadiene; hexachloro-1,3-butadiene; 1,1,2,3,4,4-hexachloro-1,3-hexachlorobutadiene; dolen-pur; gp-40-66:120; hexachlorobuta-1,3-diene; hexachlorobutadiene 13-

5.0.3 Trade Names:

NA

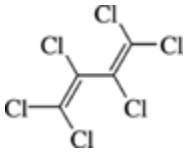
5.0.4 Molecular Weight:

206.76

5.0.5 Molecular Formula:

C_4Cl_6

5.0.6 Molecular Structure:



5.1 Chemical and Physical Properties
5.1.1 General The physical properties listed for hexachlorobutadiene are somewhat uncertain (105, 106).

Physical State	colorless liquid
Specific Gravity	1.68 (25/4°C)
Melting Point	–21°C
Boiling Point	212°C
Vapor Pressure	20 Pa at 20°C
Relative Vapor Density	9.0 (Air = 1)
Refractive Index	1.5535 (25°C)
Percent in "Saturated" Air	0.037 at 25°C
Solubility	insoluble in water at 20°C (0.00032 g/100 mL)
Flammability	not flammable by standard tests in air
Flash Point	90°C

5.1.2 Odor and Warning Properties Old data on an inadequately characterized sample indicate that 1 ppm was detectable by only about half of those who attempted to smell it. The odor of hexachlorobutadiene should be considered inadequate to warn against excessive repeated exposures. It reportedly has a turpentine-like odor.
5.2 Production and Use
Although hexachlorobutadiene (HCBD) has been used as a pesticide in other countries, exposure in the United States has mostly been as an unwanted by-product of certain processes associated with chlorination of hydrocarbons. It is reported to have some use as a chemical intermediate (107). In the United States it was also used for recovering chlorine-containing products and as a fluid for gyroscopes (108).
5.3 Exposure Assessment
5.3.1 Air The air around vineyards where hexachlorobutadiene was used was found contaminated within a radius of ≥100 meters (108). It has also been found near plants that manufacture tetrachloroethylene; trichloroethylene (highest level reported was 463 mg/m^3) at lower levels was found near plants that produce chlorine and triazine herbicide and in landfills where chemical wastes were dumped (109, 110).

5.3.3 Workplace Methods Sampling is done with a solid sorbent tube (XAD-2; 100 mg/50 mg) and then measured by the gas chromatography/ECD technique (NIOSH Method 2543). The working range is 0.01 to 2.0 mg/m^3 for a 100-L sample. The estimated limit of detection (LOD) is 0.02 mg per sample (111).

5.3.4 Community Methods Many methods have been suggested for measuring hexachlorobutadiene in air, water, food and drink, biological tissues, and soil. A good summary can be found in IARC Monograph 71 (108).

5.3.5 Biomonitoring/Biomarkers Currently there are no useful biological monitors for hexachlorobutadiene, particularly at the low levels recommended for occupational exposure. Kociba et al. (112) suggested that urinary excretion of coproporphyrins be included as part of a medical

surveillance program for employees.

5.4 Toxic Effects

5.4.1 Experimental Studies Kociba et al. cite literature values for acute oral LD_{50}s of 90 mg/kg for guinea pigs, 87 to 116 mg/kg for mice, and 200 to 350 mg/kg for rats. They also determined an LD_{50} of 580 mg/kg for adult male rats and a range of 200 to 400 mg/kg for adult female rats. Weanling rats have LD_{50}s of 65 and 46 mg/kg for males and females, respectively. Most deaths occurred 2 to 3 days after treatment but some were delayed as long as 17 days. Short-term dietary studies in which rats were fed 0, 50, 150, and 450 ppm in their diet for 2 weeks resulted in growth depression and kidney injury similar to that seen in acute studies (122).

Kociba et al. also reported that no kidney injury was produced by daily doses of 3 mg/kg body weight but that higher levels in a 30-day study did. At 100 mg/kg body weight/day, minimal liver injury was observed.

When groups of five $B6C3F_1$ mice of each sex were fed 0, 30, 100, 300, 1000, or 3000 ppm in their feed for 15 days, very severe effects and deaths occurred at the highest dosages (123). Apparently no attempt was made to relate dietary level to dose per body weight in the published paper, but estimated daily intake was calculated in the NTP report of this study (121). Estimated intakes by male mice were 3, 12, 40, 19, and 24 mg/kg/day for the 30-, 100-, 300-, 1000-, and 3000-ppm diets and 5, 16, 49, 30, and 36 mg/kg, respectively, for female mice. All mice died or were sacrificed in a moribund condition after 7 days at the two top levels. There was no mortality at the three lowest levels. However, retardation of growth was seen at all levels, and clinical signs were apparent at 300 ppm and higher. Histopathology was observed in several organs, particularly the liver but also the kidneys and spleens. The weights of several organs, including the thymus, lungs, kidney, and testes, were affected.

When hexachlorobutadiene was fed to mice for 13 weeks at dietary levels of 0, 1, 3, 10, 30, or 100 ppm, no clinical signs or mortality were observed (124). These dietary levels corresponded to 0, 0.1, 0.4, 1.5, 4.9, and 16.8 mg/kg/day for hexachlorobutadiene for male mice and 0, 0.2, 0.5, 1.8, 4.5, and 19.2 mg/kg/day for female mice based on food consumption. A marked reduction in body weight gain and in kidney weight was seen in male mice at 30 and 100 ppm and in female mice at 100 ppm. Thymus weights were comparable in all groups in contrast to marked changes in the two-week study. No gross lesions were seen at autopsy, and the only microscopic lesion was tubular regeneration in the renal cortex at 30 and 100 ppm and possibly at 10 ppm in male mice, although female mice kidneys were affected at all dosage levels. The mobility of sperm was reduced in dosed mice, though not in a dose-related manner. Female mice were more susceptible than males, and a NOAEL was not achieved for female mice. The NOAEL for male mice in this 13-week study was considered by the investigators to be 10 ppm in the diet.

According to Kociba, “Dermal application of 126 mg/kg hexachlorobutadiene was lethal to half the rabbits in 7 hours and 4 of 4 after 24 hours. All rabbits survived the dermal application of 120 mg/kg for 4 hours or 63 mg/kg for 24 hr.”

According to an available abstract, a single subcutaneous injection of 20 mg/kg into female rats resulted in the deaths of young born 3 months later to these dams (866). This must be confirmed.

Single 4- to 7-h exposures to 133 to 500 ppm hexachlorobutadiene caused the deaths of some or all exposed rats. Exposure for 0.9 h to 160 ppm or 3.5 h to 35 ppm was survived by all rats. Guinea pigs and cats died from similar exposures to 160 ppm or from 7.5 h exposures to 35 ppm (112).

Gage (125) exposed rats to 250 ppm for 4 h and 100, 25, 10, or 5 ppm for 6 h. Fifteen exposures to 5 or 10 ppm resulted in no observed toxic effects, except for retarded weight gain at 10 ppm. Fifteen exposures to 25 ppm, two exposures to 100 ppm, and two exposures to 250 ppm resulted in

respiratory irritation and injury, as well as rather pronounced effects on the renal tubules. The adrenals showed injury at 100 and 250 ppm.

Limited unpublished data of The Dow Chemical Company also indicate a rather high subacute toxicity for hexachlorobutadiene when inhaled. Small groups of rats and guinea pigs were exposed to about 8 or 30 ppm 7 h/day, 5 days/week. The guinea pigs exposed to 30 ppm died after four exposures, whereas 9 of 10 rats survived. However, severe injury was grossly apparent in the lungs, livers, and kidneys of the survivors. Ten of 10 rats and four of five guinea pigs survived 197 h exposures to 8 ppm, but liver and kidney injuries were grossly apparent on necropsy.

5.4.1.1 Acute Toxicity Hexachlorobutadiene has a rather high chronic toxicity and can cause lung, liver, and particularly renal injury in rats, including renal cancer. Much of the data for this section are taken from Kociba et al. (112), who reviewed the literature and published their own chronic toxicity and reproductive studies in rats.

The proximal tubules of the kidneys were the site of most injury in Kociba's studies. Subsequently, there have been a number of studies of metabolism and mode of toxic action, including a large number of reports from the Central Research Laboratory of Imperial Chemical Industries (113–119).

Yang (120) published a useful review. NTP (121) reviewed some of the data as part of the ongoing studies referred to in subsequent sections, ATSDR (107) has issued a draft for comment, and the IARC (108) reviewed the data in 1979 and 1987 (3).

5.4.1.2 Chronic and Subchronic Toxicity Small groups of rats, rabbits, and guinea pigs exposed for 7 h/day, 100 times to 3 ppm in a 143 day period were adversely affected, but those exposed 129 times in 184 days to 1 ppm were not. The livers and kidneys of the animals exposed to 3 ppm were the organs most affected (Dow Chemical Company, Midland, MI, unpublished data).

An available abstract indicated that mice and rats tolerated 0.024 mg/L (22 ppm) of hexachlorobutadiene in air for 7 months. The details of the number of hours per day and the number of exposures are not available (126).

Kociba et al. (112) presented the most complete study to date. Their summary follows: In the chronic dietary study, as in shorter term studies conducted previously with HCBD, the kidney was the primary target organ. Ingestion of 20 mg/kg-day of HCBD for up to 2 years caused multiple toxicological effects, including decreased body weight gain, increased mortality, increased urinary excretion of coproporphyrin, increased weights of kidneys, increased renal tubular epithelial hyperplasia, and renal tubular adenomas and adenocarcinomas, some of which metastasized to the lungs.

Ingestion of the intermediate dose level of 2 mg/kg-day of HCBD for up to 2 years caused lesser degrees of toxicity, including increased urinary coproporphyrin excretion and increased renal tubular epithelial hyperplasia. The fact that urinary excretion of coprophyrin increased at this dose level, which produced no neoplasms, may indicate the usefulness of this parameter as a biological monitor when included in a medical surveillance program for workers exposed to HCBD. Ingestion of the lowest level doses of 0.2 mg/kg-day of HCBD for up to 2 years caused no effects that could be attributed to treatment. Whereas the intermediate dose level of 2.0 mg/kg-day caused a slight degree of renal toxicity, the highest dose level of 20 mg/kg-day for up to 2 years caused multiple and substantial toxicological effects, including renal tubular neoplasms. Thus, these data indicate a clear-cut dose-response relationship for HCBD-induced toxicity that affects primarily the kidney. HCBD-induced renal neoplasms occurred only at a dose level higher than that causing discernible renal injury.

5.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Because the kidneys are the primary site of toxic action in rodents, they have also been a major subject of metabolic study. However, the liver,

biliary excretion, reabsorption, and metabolism are also involved (113–119).

Yang (120) has proposed a metabolic scheme based on a number of references.

Davis et al. (127) used low intraperitoneal doses of ^{14}C-hexachlorobutadiene with and without nonradioactive 300-mg/kg oral doses. The oral dose reportedly decreased urine osmolality, the glomerular filtration rate, and drug excretion and caused necrosis of the proximal tubular cells of the kidneys. At 48 h following dosing with only the tracer, rats excreted 40% in the feces and 30% in the urine but those that also received the nephrotoxic 300-mg/kg oral dose excreted only 7% in the feces and 6% in the urine. Eighty-seven percent of that in the urine was water soluble and polar, as was all the activity in the bile. Reichert (128) gave oral doses of 1 or 50 mg/kg ^{14}C-hexachlorobutadiene and after 72 h found 45 and 67% in the feces, as well as 26 and 11%, respectively, in the urine at the two dosages. There was not as marked a change in the amount of unchanged hexachlorobutadiene exhaled, but [^{14}C]CO_2 was reduced from 3 to 1.2%, and 8 to 10 times as high a proportion was bound covalently in the kidneys and liver. Of five major metabolites found in urine, one was the glucuronide, whereas in the bile the major metabolite reported by Reichert was the glutathione conjugate.

Biliary excretion of an orally administered dose of hexachlorobutadiene is high in rats compared to fecal excretion. Within two days, 17 to 20% of a 200-mg/kg dose was excreted in bile versus less than 5% in feces (117). Both the glutathione conjugate and the probable conjugate metabolite, cysteinyl glycine conjugate, were identified. A bile cannula completely protected the kidneys indicating that metabolism by the liver was necessary. Yang (120) summarizes work that supports increased toxicity due to glutathione conjugation rather than the more common detoxification associated with glutathione conjugation.

Payan et al. (129) drew similar conclusions from studies in rats given oral or intravenous doses.

5.4.1.4 Reproduction and Developmental Several studies of teratogenicity and reproduction of hexachlorobutadiene were reported. Japanese quail kept on diets that contained 30 ppm (about 5 mg/kg body weight per day) for 90 days had no deleterious effect on reproduction. Male and female rats were fed 20, 2, or 0.2 mg/kg/day for 90 days before mating and during gestation and lactation. Both sexes fed the two higher levels were adversely affected, primarily in the kidneys, but reproductive indexes were not. Only slight changes occurred at 2 mg/kg/day, and no effects were observed at 0.2 mg/kg/day. The only reproductive finding was a slight nonsignificant decrease in neonatal weight at 21 days at the top dosage only. No toxicological effects were observed among the adults at a dose level of 0.2 mg/kg/day or among the neonates at dose levels of 0.2 or 2.0 mg/kg/day.

Harleman and Seiner (122) also reported no effect on fertility or progeny except for decreased body weight at birth and weaning in rats born to mothers fed 150 ppm in their diet. Grossly observable malformations were not seen in their small study.

Rats were exposed to 0, 2, 5, 10, or 15 ppm hexachlorobutadiene for 6 h/day during days 6 to 20 of gestation in an inhalation teratology study. A significant reduction in maternal weight gain and in fetal body weight occurred at 15 ppm. The incidences of external, visceral, and skeletal alterations did not significantly increase in any of the hexachlorobutadiene-exposed groups. It was concluded that hexachlorobutadiene was not teratogenic at concentrations high enough to cause maternal toxicity and slight fetal toxicity.

Yang (120) summarized conflicting data on the mutagenic potential of hexachlorobutadiene. Reichert et al. presented evidence that published positive results may be due to impure samples and that larger than normal quantities of drug metabolizing enzymes (S-9 mix) are needed in the test system. Two putative metabolites, pentachloro-3-butenoic acid chloride and pentachloro-3-butenoic acid, were mutagenic in the absence of S-9 mix and were 50 to 100 times as active as

hexachlorobutadiene.

5.4.1.5 Carcinogenesis Schrenk and Dekant reported that considerably more binding to DNA occurred in the kidney compared to the liver and concluded that a genotoxic mechanism of carcinogenesis was “operative” in initiating hexachlorobutadiene nephrocarcinogenesis. However, there is strong evidence of such severe proximal tubular injury that the relationship of this injury to subsequent cancer is a likely possibility. In rats given oral administration, it produced benign and malignant tumors in the kidneys in both sexes (108). IARC (108) then concluded that there is limited evidence that hexachlorobutadiene is carcinogenic in rats.

Nakagawa et al. (130) reported that hexachlorobutadiene is a potent nephrotoxicant that selectively damaged the straight portion (pars recta) of the proximal tubule in the rat. They also reported administering 0.1% hexachlorobutadiene for 30 weeks to male Wistar rats previously given 0.1% *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN) in their drinking water for 2 weeks and that the combined treatment resulted in a significantly higher incidence of renal cell tumors than when EHEN was administered alone.

5.4.2 Human Experience In 1979 (108), the IARC cited only one study of human effects. The draft ATSDR profile cited no references to human data. The WHO (105) indicated that hexachlorobutadiene can be absorbed through the skin causing pain, redness, blisters, and skin burns. They also indicated that if it is in the eyes, it can cause pain, redness, severe deep burns, and even loss of vision. If ingested, it can cause a burning sensation, abdominal pain, shock and/or collapse. When inhaled, it can result in a burning sensation, cough, sore throat; the symptoms can be delayed, and coma may occur in severe cases (105). WHO (105) further stated that harmful contamination can be reached in the air rather quickly at 20°C.

5.4.2.2.1 Acute Toxicity Acute or short-term exposures can result in irritation of the eyes, skin, and respiratory tract. The liquid is known to be corrosive and may affect the kidneys (105).

5.4.2.2.2 Chronic and Subchronic Toxicity Chronic, long-term, or repeated exposures can result in skin sensitization and may cause genetic damage in humans (105).

5.4.2.2.5 Carcinogenesis The IARC (108) concluded that there were no data on which to evaluate its human carcinogenicity.

5.4.2.2.6 Genetic and Related Cellular Effects Studies Chronic exposure may cause genetic damage in humans (105).
5.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH recommended TLV is 0.02 ppm (0.21 mg/m^3) and an A3 carcinogen designation (35). OSHA has no PEL and NIOSH recommends treating it as a carcinogen at a REL of 0.02 ppm (0.24 mg/m^3), and both ACGIH and NIOSH note a skin designation (131).

Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

6.0 b-Chloroprene
6.0.1 CAS Number:
[*126-99-8*]
6.0.2 Synonyms:
Chloroprene, 2-chlorobutadiene; chlorobutadiene; beta-chlorobutadiene; alpha-chloroprene;

neoprene; 2-chloroprene; 2-chlorobutadiene; 2-chlorobuta-1,3-diene; 2-chloro-1,3-butadiene
6.0.3 Trade Names:
NA
6.0.4 Molecular Weight:
88.54
6.0.5 Molecular Formula:
C_4H_5Cl
6.0.6 Molecular Structure:

6.1 Chemical and Physical Properties
6.1.1 General (132)

Physical State	colorless liquid
Specific Gravity	0.9583 (20/20°C)
Boiling Point	59.4°C
Melting Point	–130°C
Vapor Pressure	23.2 kPa at 20°C (188 torr at 20°C)
Relative Vapor Density	3.0 (Air = 1)
Refractive Index	1.4583 (20°C)
Percent in "Saturated" Air	28 (25°C) (25.000 ppm at 20°C)
Solubility	0.21152/100 mL at 20°C in water; soluble in alcohol, diethyl ether
Flash Point	–40°C
Explosive Limits	4 to 20% in air

6.1.2 Odor and Warning Properties b-Chloroprene has a pungent, ether-like odor (133) and is a lacrimator.
6.2 Production and Use
Chloroprene is used as a chemical intermediate, largely as a monomer for manufacturing rubber. At room temperature, it reacts with oxygen to form peroxides and polymerizes to produce cyclic dimers or open-chain, high molecular weight products (134).
6.3 Exposure Assessment
Chloroprene is not found as a natural product (135).

6.3.1 Air Chloroprene emissions into the air have been reported in the United States from 838 tons in 1987 down to 446 tons in 1995 (136).

6.3.2 Background Levels Chloroprene has been found in industrial waste water and nearby groundwater and in waste gas from industrial sources (137–139).

6.3.3 Workplace Methods b-Chloroprene in the workplace is sampled with a solid sorbent tube (coconut shell charcoal, 100 mg/50 mg) and then measured using the gas chromatography, FID technique, NIOSH Method 1002. The working range is 10 to 60 ppm (40 to 200 mg/m^3 for a 3-L air sample and the method is sensitive enough to determine concentrations as low as 12 ppm in 15-min samples taken at 0.2 L/min. The estimated limit of detection (LOD) is 0.03 mg per sample (3.8 mg/m^3) assuming a maximum sampling volume of 8 L (140).

6.3.4 Community Methods Methods have been described for sampling b-chloroprene in water using gas extraction, thermal desorption, and gas chromatography/mass spectrometry and the detection limit is thought to be around 0.02 mg/L (135).

6.4 Toxic Effects

6.4.1 Experimental Studies Old reviews of the toxicity of b-chloroprene are available (141, 142), but surprisingly few new references were found since the Third Revised Edition of this publication. What is available tends to support the conclusions of that edition. At high concentrations b-chloroprene has an anesthetic action, but this is not as important as eye and respiratory tract irritation and liver injury, which result from excessive exposures. Hair loss has also been reported in humans and animals exposed to b-chloroprene.

The available literature is extremely contradictory as to the type of injury that has resulted from exposure to b-chloroprene and to the exposure levels that cause them. Russian literature claims considerably different and/or greater effects than have been observed in studies from other places that have tried to confirm these claims. No clear explanation is available, but at least two possible explanations appear reasonable. b-Chloroprene is a very unstable compound, which, unless handled with extreme care, expoxidizes and polymerizes to toxic compounds (143, 144). This might explain the alleged effects in animals. Alleged effects in humans may be due to this same cause or to the use of different chemical processes that produce different types of impurities. Many other causes can be postulated, but in our opinion more credence must be given to animal studies in which the sample is known to have been handled with extreme care and to the results of experience in U.S. industry where the method of handling has been reported.

6.4.1.1 Acute Toxicity b-Chloroprene is an irritant when intubated into the stomach of laboratory animals. It also produces CNS depression, generalized congestion, and edema. Von Oettingen et al. (145) reported that the LD_{100} for rats is 670 mg/kg of body weight. Death occurred from 5 h to 4 days after administration. LD_{50}s of 251 mg/kg for rats and 260 mg/kg for mice were reported by Asmangulian and Badalian (146).

Conjunctivitis and necrosis of the cornea were reported. Von Oettingen (42) quoted Roubal to this effect. Apparently, nervousness and irritability are typical responses to exposure. A more thorough discussion of the clinical picture can be found in reports by Nystrom (143) and Ritter and Carter (147).

The vapors reportedly cause irritation and evidence of pain in the eyes at 625 ppm but not at 160 or 40 ppm in rats exposed for 6 h/day for 4 weeks (147).

Von Oettingen (145) indicated that some systemic toxicity results from repeated topical application of chloroprene to the skin of rats. Ritter and Carter (147) indicated that systemic poisoning results from the topical application of chloroprene to guinea pigs. It is uncertain how completely the animals were prevented from breathing the vapors when it was applied to the skin.

Perhaps the most surprising effect from topical application is the loss of hair. Because hair grows readily when the individual is removed from contact, the action may be directly on the hair. Apparently, this is observed both in humans in industrial operations and in animals exposed in the laboratory. Ritter and Carter question whether this action is of chloroprene itself or an intermediate in the polymerization of chloroprene, but it is agreed that the depilatory action does occur in workers who handle chloroprene in the polymerization process.

Von Oettingen (145) indicated that a 1 h exposure of mice to chloroprene vapor at a concentration of 3 mg/L of air (829.2 ppm) was fatal to all animals exposed. A concentration of 1 mg/L (277 ppm) did not kill any of the animals. They also reported that the LC_{100} is 7.5 mg/L for an 8 h exposure of rabbits of air and is 2.5 mg/L for cats.

Clary et al. (148), using fresh, purified b-chloroprene, determined an approximate lethal concentration of 2280 ppm (8.42 mg/L) for a 4 h exposure of rats. All six rats exposed to 1690 ppm (6.24 mg/L) survived. Injury to the respiratory tract was apparent in a few rats sacrificed 1 or 2 days after exposure. Some liver changes were reported.

They also exposed rats and hamsters to 625, 160, or 40 ppm for 6 h/day, 5 days/week for 4 weeks. The authors concluded that toxic effects were observed at all levels.

The primary effects seen at the low level were skin and eye irritation and weight loss in rats. At higher levels, tissue damage, especially to the lung and liver, and mortality were observed. Hair loss was observed, primarily at the two highest levels in female rats. The range-finding studies indicate that repeated exposure of rats at approximately 625 ppm resulted in mortality, as well as growth retardation. In hamsters, one exposure at 630 ppm was lethal. Midzonal liver degeneration and necrosis, as well as increased liver and kidney weights in both species, were also noted at both the high exposure and midexposure levels. The lower exposure level (40 ppm) was irritating in both species, and significant growth retardation was also noted in the rats. The alopecia observed in the present studies is consistent with earlier reports (144).

Thirteen-week exposures of rats and mice to chloroprene were conducted by NTP as part of their procedure for selecting doses for lifetime studies (134). The exposure concentrations were 0, 5, 12, 32, 80, and 200 ppm for rats and 0, 5, 12, 32, and 80 ppm for mice. Exposures were for 6 h/day. The Pathology Working Group (PWG) draft report (149) indicates

administration of chloroprene to male and female rats via inhalation 5 days per week for 13 weeks resulted in minimal to moderate lesions of the nasal mucosa in those exposed to 80 and 200 ppm. Degeneration and respiratory metaplasia of the olfactory epithelium and suppurative inflammation of the turbinates were observed in 10/10 males and 8/10 females dosed at 200 ppm and 10/10 males and 9/10 females dosed at 80 ppm. Lesions in the liver considered to be compound-related included randomly distributed necrosis in 2/10 males and 6/10 females; hemosiderosis in 5/10 males and 10/10 female rats; and minimal inflammation in 3/10 male and 8/10 females rats limited to the 200 ppm dose level. The PWG considered the 32 ppm dose as the no-effect level for both male and female rats.

Nasal and occular discharge were observed at 200 ppm, and the feet were bloodstained. Growth and final body weight were not affected. Other data in the consulting laboratory report to NTP indicate an increase in kidney weight in both sexes of rats exposed to 80 and 200 ppm but no effect on male reproductive parameters or on cyclicity or length of estrus in female rats. Neurobehavioral test were unaffected. Moderate coagulopathy was also reported at 200 ppm, and the nonprotein sulfhydryl was reduced in the liver and lungs of rats, suggesting conjugation with glutathione. A possible exposure-related minimal suppurative gastritis was observed in the forestomach submucosa of 2/20 rats exposed to 200 ppm.

The draft PWG report summary states.

Administration of chloroprene to male and female B6C3F_1 mice via inhalation 5 days per week for 13 weeks resulted in a minimal or slight epithelial hyperplasia in the forestomach. The incidence was 3/10 male and 7/10 female mice dosed at 80 ppm. The no-effect level was 32 ppm.

At terminal necropsy, gross lesions of firm white nodules or raised pale foci were observed in a few stomachs of the 80-ppm group. In addition, the consulting laboratory report indicated no clinical signs but a slight reduction in body weight gain at 80 ppm. Neither male nor female mice reproductive parameters were altered. No hematologic or clinical chemical parameters were altered,

but nonprotein sulfhydryl content of liver and lungs was reduced at 80 ppm at week 12.

6.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Bartsch et al. (150) reported isolating a metabolite capable of alkylation when they added human liver enzymes to *S. typhimurium* in their mutagenicity test system, but few data have been added since. The most likely route of metabolism is epoxidation and subsquent glutathione conjagation with mercapturic adic formation (151).

6.4.1.4 Reproduction and Developmental Numerous Soviet reports describe teratological and reproductive effects in animals. These effects may have been due to improper handling of the samples and resulting toxic reaction products.

When the purity of the sample was carefully controlled, repeated exposures to 25 ppm or less of the vapor caused no reproductive, teratological, or embryo toxic effects in rats (152). Despite frank clinical toxicity in exposed pregnant rats, fetuses showed no teratogenic effects at b-chloroprene levels as high as 175 ppm (E. I. du Pont de Nemours & Co., Wilmington, DE, unpublished data). Reproductive parameters were unaffected in the NCI study reported in the previous section.

b-Chloroprene, like many other compounds was mutagenic in some but not all test systems. Several reports summarized by NIOSH (141) indicate mutagenic activity in *Drosophila*, mice, and rats in addition to microorganisms. Whether this is due to impurities in the samples is not clear. Bartsch et al. (150) reported that liver enzymes were needed to produce mutations in *S. typhimurium*. They were able to trap an alkylating metabolite and considered the mutagenic activity as the likely result of an oxirane metabolite. An unpublished study (E. I. du Pont de Nemours & Co., Wilmington, DE, unpublished data) found no dominant lethal effects in rats and mice exposed to 100 ppm.

Using NTP genetic test procedures, negative results were obtained in *S. typhimurium* TA98, TA100, TA535, and TA1537 with and without Arochlor-induced rat and hamster liver S-9 homogenate. Dosages were 0, 3, 10, 33, 100, 333, 1000, or 3330 mg/plate. The top dosage inhibited growth. No effect on cytogenetic end points occurred in bone marrow cells of B6C3F1 mice exposed to 0, 12, 32, 80, or 200 ppm (153). A lack of genetic effect has also been demonstrated in groups of 10 to 15 male B6C3F1 mice exposed for 6 h/day for 10 days to ambient air, or 12, 32, 80, or 200 ppm b-chloroprene (154). Butadiene and isoprene that were run concurrently caused several mutagenic effects correlated with exposure concentration. All mice exposed to 200 ppm b-chloroprene died. At 80 ppm and less, there was

no increase in CA (chromosomal aberrations), SCE (sister chromatid exchange) or micronucleated erythrocytes nor did it significantly alter the rate of erythropoiesis or bone marrow cellular proliferation kinetics. However the MI (mitotic index) in the bone marrow of chloroprene exposed mice was significantly increased.

6.4.1.5 Carcinogenesis The IARC (135) determined that there is sufficient evidence for the carcinogenicity of chloroprene in experimental animals. This evaluation is based on production of tumors of the lung, circulatory system, Harderian gland, mammary gland, liver, kidney, skin, mesentery, forestomach, and the Zymbal gland in mice (135). In rats, the IARC found that tumors of the mammary gland increased only at high-doses and when all types were combined (135). No tumors were reported in the hamster studies (135).

A large number of Soviet studies reportedly produced cancer in animals (141). b-Chloroprene dissolved in corn oil (150 mg/kg) was administered to pregnant rats on the 17th day of gestation, and the offspring were treated from weaning with weekly doses of 50 mg/kg for their life spans (155). According to the abstract of this somewhat unusual experimental design, the total incidence of tumors was similar in treated and controls.

Kumming albino mice inhaled 0, 2, 19, or 189 mg/m^3 (0.5, 5, or 50 ppm) for 4 h/day, 6 days/week for 7 months (156). All survivors were killed at the end of the eighth month or when moribund. No lung tumors were found before the sixth month. The reports indicate an increase in lung papilloadenomas and to a lesser extent adenomas occurred in a dose-related manner but it is not clear at what levels of exposure.

The NTP reported significantly increased incidences of neoplasms of the lung, circulatory system, Harderian gland, and mammary gland (females only) and that tumors of the forestomach, liver (females only), kidney (males only), skin and mesentery (females only), and Zymbal gland (females only) also increased after mice inhaled chloroprene that was more than 99% pure at concentrations of 0, 12.8, 32, and 80 ppm (0, 46, 116, and 290 mg/m^3) (157). The IARC (135) noted that the livers of both exposed and control male mice contained lesions consistent with *Helicobacter hepaticus* infection, but the females did not, which may have compromised the detection of neoplastic effects in this organ among the male mice.

The NTP (157) also found increases in neoplasms of the oral cavity, thyroid gland, kidney, lung (males only), and mammary gland (females only) in rats exposed to chloroprene more than 99% pure at inhalation concentrations of 0, 12.8, 32 and 80 ppm (the same as the mice above). Melnick et al. (158) reported that the cancer potency of chloroprene was greater in mouse lungs than in the lungs of rats whereas it was greater in the rat kidney than in the mouse kidney but nearly equivalent in the mammary gland of both rats and mice.

In another study that exposed rats to inhalation concentrations of 0, 10 or 50 ppm (0, 36 or 180 mg/m^3) chloroprene for 6 hours, five days a week for 24 months, mammary tumors significantly increased in exposed female rats, and if skin tumors in the male had originated from the epidermis, then the total number of squamous-cell carcinomas of the skin (5/100) in high-dosed rats would have been significantly different (p<.05) from the control group (159). In a similar study of hamsters, no increase in tumors was found comparing the control group and those exposed (159).

6.4.2 Human Experience

6.4.2.2 Clinical Cases Even more so than other chemicals, the extreme instability of b-chloroprene and the resulting products make it difficult to ascribe effects in humans to the chemical itself. Numerous reports of injury in production and use of b-chloroprene have been published and presented by NIOSH (141) and WHO (132). Symptoms include hair loss, chest pain, fatigue, nausea, personality changes, conjunctivitis, dermatitis and chemical burns, unconsciousness, decreased spermatogenesis and other reproductive effects, sexual impotency, cough, dizziness, and sore throat.

A group of 336 currently exposed and 227 previously exposed b-chloroprene workers was compared to 283 workers never exposed to b-chloroprene (160). No biochemical or hematologic alterations were indicated or suggested for a wide array of tests, including many that were positive in earlier studies.

6.4.2.2.5 Carcinogenesis NIOSH (141) reported skin cancer, lung cancer, and liver and kidney injury.

Careful study of two U.S. plants (161) did not find lung cancer. In this study, no other cause of death was related to exposure to b-chloroprene, and overall mortality was equal to the experience throughout the rest of the company.

Mortality from cancer that accounted for 16 deaths among 1258 workers was reported in a Chinese study resulting in an SMR of 2.4. A significant excess of liver cancer was reported in employees in the monomer workshop, and the SMR was 4.8 (4 observed when only 0.83 would have been

expected) (162). The IARC (135) reported that the selection criteria were not entirely clear and that a bias could have occurred because only reference rates during a three-year period were used.

In a Russian study of Moscow shoe-manufacturing workers, there was an excess of cancer mortality, and 265 deaths had an SMR of 1.2 (95% CI 1.0–1.3). Overall 10 deaths occurred from liver cancer giving an SMR of 2.4 (95% CI 1.1–4.3); leukemia accounted for 13 deaths giving an SMR of 1.9 (95% CI 1.0–3.3). When workers exposed to chloroprene were compared to those unexposed workers, the relative risk of liver cancer increased to 4.2 (95% CI 0.5–33), accounting for 9 deaths; 9 deaths from kidney cancer were also reported giving a relative risk of 3.8 (95% CI 0.5–31); and a slight increase of nine leukemia deaths occurred at a relative risk of 1.1 (95% CI 0.3–3.7). The authors suggested that the leukemia excess may be due to concomitant exposure with benzene, whereas the liver cancer excesses point to the carcinogenic effect of chloroprene (163). A study of chloroprene workers from Armenia evaluated the cancer risk among 1897 men and 417 women at a production plant in Yerevan between 1940 and 1988 and found that the overall cancer mortality was less than expected, but increased incidence (SMR 3.27; 95% CI 1.47–7.27) and mortality (SMR 3.39; 95% CI 1.09–10.5) from liver cancer was found. This increase, it was suggested, had a dose-response relationship through duration of employment, duration of high exposures, and cumulative exposure (164).

The IARC (135) concluded that there was inadequate evidence for the carcinogenicity of chloroprene in humans but given the sufficient evidence from experimental animal studies, gave its overall evaluation that chloroprene is possibly carcinogenic to humans and placed it in its 2B Group.
6.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV of b-chloroprene is 10 ppm with a skin designation (36 mg/m^3). Thus skin contact should be prevented. OSHA has a 25 ppm PEL (90 mg/m^3) also with a skin designation, and NIOSH considers b-chloroprene a carcinogen and recommends a REL ceiling value of 1 ppm for 15 minutes (3.6 mg/m^3) (165). The exposure limits and guidelines of other countries range from 0 mg/m^3 in Germany, because it is considered a carcinogen, to 50 mg/m^3 in Czechoslovakia (135).

Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

7.0 Vinylidene Chloride
7.0.1 CAS Number:
[*75-35-4*]
7.0.2 Synonyms:
1,1-Dichloroethylene, VDC, 1,1-DCE
7.0.3 Trade Names:
NA
7.0.4 Molecular Weight:
96.94
7.0.5 Molecular Formula:
$C_2H_2Cl_2$ or $CH_2{=}CCl_2$
7.0.6 Molecular Structure:

7.1 Physical and Chemical Properties

7.1.1 General (166)

Physical State	volatile, colorless liquid*
Specific Gravity	1.213 (20°C)
Freezing Point	–122.5°C
Boiling Point	31.7°C
Melting Point	–122°C
Vapor Pressure	66.5 kPa at 20°C; (495 torr at 20°C)
Relative Vapor Density	3.3 (air = 1)
Relative Density of the Vapor–Air Mixture at 20°C	2.5 (air = 1)
Refractive Index	1.427 (20°C)
Percent in "Saturated" Air	78
Solubility	0.225 g/100 mL by weight in water at 25°C; soluble in most organic solvents
Flash Point	–19°C (c.c.); –15°C (o.c.)
Autoignition Temperature	570°C
Flammability Limits	5.6 to 16% by volume in air Octanol/water Partition Coefficient as Log P_{OW} 1.32

*In the presence of air or oxygen, and particularly with the inhibitor removed, vinylidene chloride forms a complex peroxide compound at temperatures as low as –40°C. The peroxide is shock-sensitive and explosive. Reaction products formed with ozone may be particularly dangerous.

7.1.2 Odor and Warning Properties Vinylidene chloride has a characteristic sweet smell that resembles carbon tetrachloride or chloroform. Most persons can detect a mild but definite odor at 1000 ppm in air. Some people can detect it at 500 ppm. Vapors that contain decomposition products have a disagreeable odor and can be detected at concentrations considerably less than 500 ppm. Neither the odor nor the irritating properties of vinylidene chloride are adequate to warn of excessive exposure.

7.2 Production and Use

Vinylidene chloride is used as a chemical intermediate, particularly as a copolymer in the production of plastics. Production in 1990 was 290 thousand tons (167).

7.3 Exposure Assessment

7.3.1 Air It is estimated that 2–5% of the vinylidene chloride manufactured is emitted to the air in the United States (168). EPA estimates that the median ambient air level in suburban/urban areas is 20 ng/m^3 (169, 170). The levels found around industrial sources were higher, and the median was 14 mg/m^3.

7.3.2 Workplace Methods Analytical sampling can be done with a solid sorbent tube (coconut shell charcoal, 100 mg/50 mg) and measured by gas chromatography, FID. The working range is 0.5 to 5 ppm (2 to 20 mg/m^3) for a 5-L air sample (NIOSH Method 1015) (171).

7.4 Toxic Effects

Little information is available from studies in humans, and most conclusions are based on animal studies. This may be partly the result of early recognition of the rather high chronic toxicity of vinylidene chloride and the need to control exposures in a manner quantitatively similar to carbon tetrachloride. Exposures to high concentrations result primarily in CNS depression and the associated symptoms of drunkenness, which may proceed to unconsciousness and even death. Liver and kidney injury may result but are more likely the result of repeated exposures. Species, strain,

sex, and nutritional state have a significant impact on the observed responses of laboratory animals to vinylidene chloride. Reviews are available (42, 172–175).

7.4.1 Experimental Studies When VDC was fed in a corn oil solution to male rats, an acute oral LD_{50} of 1500 mg/kg was determined (176). These workers and Jaeger et al. (177) showed that numerous changes in liver and plasma enzymes occur, consistent with the histological changes observed in the livers of treated animals.

Forkert and Reynolds (178) reported unusual histological changes in the Clara cells and ciliated cells of the bronchiolar epithelium of the lungs of rats fed vinylidene chloride at doses of 10 or 200 mg/kg body weight as a solution in mineral oil. Despite serious injury, recovery appeared to be complete 7 days after treatment. Similar changes occurred in mice (179). These investigators examined biochemical changes following 125 mg/kg intraperitoneal doses and noted marked changes in the lung in the absence of liver and kidney effects. Recovery took 3 to 6 weeks. The unusual susceptibility of mice is consistent with data from other studies. As described in the section on carcinogenicity, the mouse kidney is the only organ that shows a positive response in animal studies.

Vinylidene chloride is moderately irritating to the eyes of rabbits. It causes pain, conjunctival irritation, and some transient corneal injury. Permanent damage is not likely. However, a high concentration of the phenolic (MEHQ) inhibitor sometimes used in vinylidene chloride may cause eye injury. Contaminated eyes should be flushed immediately with large quantities of flowing water.

Liquid vinylidene chloride is irritating to the skin of rabbits after direct contact for only a few minutes. The inhibitor content of the vinylidene chloride may be partly responsible for this irritation. Where leaks occur, vinylidene chloride will evaporate and the phenolic (MEHQ) inhibitor may accumulate until it reaches a concentration that can cause local burns and possibly depigmentation of the skin. Particular caution should be used with regard to contamination of clothing, which should be removed immediately and thoroughly cleaned before reuse. The volatility of vinylidene chloride probably prevents absorption of significant quantities through the skin unless it is in solution or confined.

Lethality varies considerably with species, sex, strain, and nutritional status, possibly explained in part by the availability of glutathione, which provides a protective effect. ATSDR (174) reported LCT_{50}s for 4 h exposure of male rats of 6000 to 8000 ppm and for female rats of 10,000 ppm. When rats were non-fasting (sex unspecified), 4 h LCT_{50}s of 10,000 ppm to 15,000 ppm were observed; fasting for 16 h before exposure reduced the LCT_{50} almost 30-fold (177).

Mice were much more susceptible to 4 h LC_{50}s of 100 ppm reported for “fed” male mice and 200 ppm (females) versus 40 and 115 ppm, respectively, for fasting mice (180). When rats received 20 repeated 6 h exposures to 200 ppm, only slight nasal irritation was observed; similar exposure of four male and four female rats to 500 ppm also decreased weight gain and produced liver cell degeneration (125). Rabbits, monkeys, rats, and guinea pigs were exposed for 8 h/day, 5 days/week for 6 weeks to 395 mg/m^3 (100 ppm), and there were no deaths, overt signs of toxicity, or histopathological changes (181).

Seven days of essentially continuous exposure (22 to 23 h/day) to 40 ppm was more toxic to male mice than female mice or male rats in terms of SGOT, SGPT, and lethality (182). Seven of 10 male mice died, whereas no female mice or male rats died. This is consistent with the higher rate of metabolism of vinylidene chloride by mice, the carcinogenic effect in that species, and the higher susceptibility of that species to liver and kidney injury.

Although vinylidene chloride sensitizes the heart of rats to epinephrine, only limited data are available on its potency (183).

7.4.1.2 Chronic and Subchronic Toxicity The results of long-term feeding studies are described in the section on carcinogenicity. Quast et al. reported no effect in dogs fed capsules containing daily doses of 25 mg/kg/day in peanut oil for 90 days (184).

Animals exposed for 5 days/week, 8 h/day for 6 months had liver and kidney injuries at concentrations of 100 and 50 ppm. There was minimal injury to the liver and kidney, even at a concentration as low as 25 ppm (Dow Chemical Company, Midland, MI, unpublished data). In a continuous exposure for 90 days to 189 mg/m^3 (about 47 ppm), considerable mortality occurred in guinea pigs and monkeys (7/15 and 3/9, respectively), but surviving animals exhibited no overt signs of toxicity. Mottled livers were evident on gross examination, and considerable injury was seen microscopically in that organ. Dog livers were most affected, but kidneys, adrenals, and lungs were also injured. Less effect was observed following continuous exposure to 101, 61, and 20 mg/m^3 (181).

Repeated 6 h daily exposures to 25 or 75 ppm for 5 days/week for 90 days resulted in minimal, apparently reversible changes in the livers of rats (185).

7.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Absorption of vinylidene chloride from the lungs or gastrointestinal tract or after intraperitoneal injection is rapid and is dose-dependent and saturable. Furthermore, it is influenced by the state of nutrition of the animal (fasting versus non-fasting rats) and by feeding other substances, including ethyl alcohol. At relatively high dosages, most ingested or injected vinylidene chloride is excreted unchanged in the expired air of rats (199). Mice metabolize a higher proportion of orally administered vinylidene chloride than other species, consistent with the higher toxicity in mice (200).

The metabolism of vinylidene chloride following inhalation and oral administration has been studied (201, 202). Metabolism is dose-dependent. Following a 6 h exposure to 10 ppm, 98% of the acquired body burden was metabolized by the rat to nonvolatile compounds. At 200 ppm, only 92 to 96% was metabolized. Fasting before exposure significantly reduced the detoxifying pathways for vinylidene chloride and enhanced covalent binding of metabolites to liver and kidney tissue. Fasting rats exposed to 200 ppm sustained liver and kidney damage, whereas nonfasting rats did not; fasting had no effect on rats exposed to 10 ppm vapor. The two major urinary metabolites were *N*-acetyl-*S*-(2-hydroxyethyl)cysteine and thiodiglycolic acid, indicating that the major detoxification pathway in the liver is by conjugation with liver glutathione, possibly through an epoxy intermediate. Jones and Hathway (199) found monochloroacetic acid in the urine of rats treated orally with vinylidene chloride. Short et al. (203) also reported that disulfiram reduced the acute lethal and hepatotoxic effects of vinylidene chloride.

Based on published data, Fielder et al. proposed a rather elaborate metabolic map for vinylidene chloride shown in Figure 38.9.

A physiologically based pharmacokinetic model was proposed for the rat. The authors note the extreme sensitivity of their model to vinylidene chloride kinetics and warn that extrapolation to different conditions or to humans must be done very cautiously.

7.4.1.4 Reproductive and Developmental Rats and rabbits were exposed 7 h/day to 20 (rats only), 80, or 160 ppm of vinylidene chloride vapor during organogenesis (186). Pregnant rats were also fed drinking water that contained 200 ppm (w/w) of vinylidene chloride. No teratogenic effects were observed in either species but toxic effects (decreased weight gain, decreased food consumption, increased water consumption, or increased liver weight) were observed in the dams of rats that inhaled 80 or 160 ppm and rabbits that inhaled 160 ppm. Although a teratogenic effect was not observed, embryo toxic and fetotoxic effects were noted in both rats and rabbits. These included delayed ossification, wavy ribs, and resorption (rabbits). The investigators concluded that

at levels causing little or no maternal toxicity (20 ppm in rats and 80 ppm in rabbits), there was no effect on embryonal or fetal development. Among the rats given drinking water that contained 200 ppm vinylidene chloride there was no evidence of toxicity to the dams or their offspring.

On the basis of their inhalation studies, Short et al. (187) claimed that vinylidene chloride is a weak teratogen in rats and mice.

Sprague–Dawley rats were used to evaluate the effects of parental administration of vinylidene chloride in drinking water on reproduction (188). Rats were fed water containing 0, 50, 100, or 200 ppm for three generations, including six litters. Mild dose-related changes of the livers occurred in the dams but not in the offspring. The investigators concluded that reproductive capacity was not affected by the exposure.

Reproductive organs have not been target organs in long- or short-term studies.

Summaries of the available data on mutagenesis are available (173, 174, 189). Vinylidene chloride *per se* is not mutagenic in an *in vitro* test system but positive results have been observed with metabolic activation in several microbial, yeast, and cellular systems. Because glutathione is often present in lower concentrations in *in vitro* systems than it is in mammalian organs, many of these mutagenic tests may not be representative of expected effects in humans.

Vinylidene chloride was inactive in a mouse dominant lethal mutation study (190) after exposure to 40, 120, 200 mg/m^3 (10, 30, or 50 ppm) for 6 h/day for 5 days. Male CD rats exposed to 55 ppm for 6 h/day, 5 days/week were also unaffected when studied for dominant lethal effects (182).

Although reaction with macromolecules occurs following treatment of rats and mice with vinylidene chloride, available data suggest that reaction is the result of metabolic activity and occurs only at concentrations injurious to rodents (191, 192). The weak activity of vinylidene chloride, the protective effect of glutathione, and the lack of direct alkylation are consistent with the low carcinogenic activity seen only in mice, but not in rats and hamsters, and support a nongenotoxic causation of cancer in mice kidneys.

7.4.1.5 Carcinogenesis Varying results have been obtained in carcinogenic studies in animals (193). Although the carcinogenicity of this material has not been observed in several long-term studies in rats (193–195) or in hamsters (195), kidney tumors were reported in a single study in mice (195). The tumors were observed primarily in the kidneys of male mice and were accompanied by significant injury to the kidney tissue (191, 196, 197) considered that the effects were the result of tissue injury and subsequent repair rather than a genetic mechanism that involves alkylation of DNA.

F344 rats were fed 1 or 5 mg/kg body weight and B6C3F$_1$ mice 2 or 10 mg/kg body weight in a corn oil solution by gavage for 104 weeks. The report concludes that “vinylidene chloride was not carcinogenic for F344 rats or B6C3F$_1$ mice of either sex.” Although high-dose male and female rats showed chronic renal inflammation and high-dose male mice showed necrosis of the liver, NTP concluded that maximum tolerated doses had not been fed (198). Vinylidene chloride inhaled for 6 h/day for 12 months caused two hemangiosarcomas (one of the mesenteric nodes and one of the subcutaneous tissue). Although the authors consider the finding significant, the failure to produce this tumor in other long-term studies, together with the fact that vinyl chloride was being used simultaneously in a parallel study, has prompted questions about the significance of the observation.

Van Duuren et al. (20) applied low doses of vinylidene chloride to ICR/Ha Swiss mice skin by several methods. Repeated dermal application of vinylidene chloride by itself produced no tumors, but when a promoter, phorbol myristate acetate, was used, skin tumors resulted. Vinylidene chloride did not produce tumors when injected subcutaneously at weekly intervals at a dose of 2 mg/mouse per injection.

In the largest available study, no increase in tumors was found in rats that ingested up to 19.3 or 25.6 mg/kg/day (male and female rats, respectively) or in rats that inhaled 25 or 75 ppm (v/v) for 6 h/day for 18 months and then kept for their lifetimes (184, 193).

7.4.2 Human Experience 7.4.2.2.1 Acute Toxicity Inhalation can cause dizziness, drowsiness, and even unconsciousness. Skin exposure can cause redness and burns. Exposure of the eyes can result in redness and pain and ingestion can cause abdominal pain and sore throat (166). Ingestion may also cause aspiration into the lungs and a resulting risk of chemical pneumonitis, and it may also affect the central nervous system (166).

7.4.2.2.2 Chronic and Subchronic Toxicity Long-term or repeated exposures that cause dermatitis may result from contact with the skin. Vinylidene chloride may also have long-term effects on the liver and kidneys (166).

7.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms In the Ames bioassay test, vinylidene chloride is activated by human liver S9 supernatant, thus suggesting the presence of cytochrome enzyme P450 (167). The WHO (167) also reported the formation of dichloroacetaldehyde from two human liver microsomal preparations.

7.4.2.3 Epidemiology Studies Studies of industrial populations that handle vinylidene chloride have been published but all are small and of limited value. The first mortality study has limited value because the major interest was vinyl chloride, and only limited exposure to vinylidene chloride occurred. A second study, also by Ott et al., looked at mortality and the findings of health examinations of 138 employees exposed to measured levels of vinylidene chloride where vinyl chloride was not involved. Measured concentrations ranged from 5 to 20 ppm time-weighted average. No effects on mortality or health parameters were found. Studies by Thiess et al. (204) and by Waxweiler et al. (205, 206) were also negative.

The IARC has concluded that there is inadequate evidence in humans and limited evidence in experimental animals for the carcinogenicity of vinylidene chloride and has placed it in its Group 3 category as not classifiable as to its carcinogenicity to humans (207).
7.5 Standards, Regulations, or Guidelines of Exposure
OSHA has no PEL for vinylidene chloride, and NIOSH recommends treating it as a carcinogen based on animal studies (171). The ACGIH recommends a TLV of 5 ppm (20 mg/m^3) with an A4 notation (208). The International Labour Office (209) reports similar values for standards and guidelines in other countries. The World Health Organization has a guideline for drinking water at 30 mg/L (210).

Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

8.0 Vinyl Chloride
8.0.1 CAS Number:
[*75-01-4*]

8.0.2 Synonyms:
Monochloroethylene; chloroethene; chloroethylene; VC; VCM; Vinyl C monomer
8.0.3 Trade Names:
NA
8.0.4 Molecular Weight:
62.5
8.0.5 Molecular Formula:
C_2H_3Cl
8.0.6 Molecular Structure:

8.1 Chemical and Physical Properties
8.1.1 General

Physical State	colorless gas
Specific Gravity	0.9106 (20/4°C)
Melting Point	–153.8°C
Boiling Point	–13.4°C
Vapor Pressure	2530 torr at 20°C
Solubility	0.11 g/100 mL at 25°C; soluble in ethanol, ethyl ether, carbon tetrachloride, and benzene
Stability	may produce peroxides; on combustion degrades to hydrogen chloride, carbon monoxide, carbon dioxide, and traces of phosgene
Flash Point	–77.8°C (open cup)
Autoignition Temperature	472.22°C
Explosive Limits	4 to 22% by volume in air

8.1.2 Odor and Warning Properties Although vinyl chloride has a faintly sweet odor at high concentrations, the odor is of no value in preventing excessive exposure. The actual vapor concentrations that can be detected have never been adequately determined and vary from one individual to another, in impurities in the sample, and probably in duration of exposure.
8.2 Production and Use
Vinyl chloride was first synthesized around 1935 (211). Vinyl chloride has been used in the United States for more than 65 years. Production of vinyl chloride monomer is based on cracking ethylene dichloride (212). The demand for vinyl chloride was 13.7 billion pounds in 1996, 14.5 billion pounds in 1997, and is expected to be 16.8 billion pounds by 2001 (212). The historical growth of the industry has been around 3.7% per year from 1988–1997 and is expected to continue at around 3% through 2001 (212). Ninety-eight percent is used for polyvinyl chloride (PVC) production and the remaining 2% for polyvinylidene chloride and chlorinated solvents (212). More than 70% of the PVC manufactured is used in construction (212).
8.3 Exposure Assessment
8.3.1 Air The air concentrations of VC around PVC plants averages around 44 mg/m^3 (17 ppb), and some measurements in U.S. cities were from 8 mg/m^3–3.2 mg/m^3 (3.1–1250 ppb) in Houston, Texas, an area where large production facilities are located, and in Delaware City, Delaware, with maximum concentrations were 3.9 mg/m^3 91.5 ppm (213–215).

8.3.3 Workplace Methods NIOSH analytical method 1007, has been a method of choice that uses a solid sorbent tube and then the gas chromatography, FID technique. The working range is 0.4 to

40 mg/m^3 (216).

8.3.5 Biomonitoring/Biomarkers Biological monitoring is of little practical value at exposures considered acceptable by today's standards.
8.4 Toxic Effects
8.4.1.1 Acute Toxicity The primary acute physiological effect of vinyl chloride is depression of the central nervous system, which begins to occur at concentrations of 8000 to 10,000 ppm (217). Early studies as a surgical anesthetic were discouraged by its high flammability and by cardiac and circulatory disturbances noted in animals and patients at the 10 to 20% concentration necessary to produce surgical anesthesia (218–220).

Acute liver toxicity even at these high concentrations appeared to be low, but there have since been suggestions of a delayed carcinogenic response following massive subacute exposures in animals (221).

8.4.1.2 Chronic and Subchronic Toxicity Essentially no investigations were published before 1961 on the response to chronic vapor exposure. Schaumann exposed mice and rats and found that they tolerated a level sufficient for "light narcosis" for periods of 4 h/day for five to eight consecutive days or for 1 h/day for 4 weeks without showing kidney or liver injury [as cited by Lehmann and Flury (50)].

Torkelson et al. (222) reported on repeated exposures of animals for 7 h/day, 5 days/week. At 500 ppm, rats showed increased liver weight and histopathology. At 200 and 100 ppm, rats showed increased liver weight, but no changes could be observed in dogs or guinea pigs. All species tolerated 50 ppm for 6 months without adverse effects. Repeated exposures of rats for 1 h/day at 200 or 100 ppm were tolerated without observable effect. The effects on the liver were mild and apparently reversible, and they were not observed in rats kept 6 to 8 weeks after the 6 month exposures ceased. This was the longest period for which any animals were observed in this study.

Noncarcinogenic effects in the liver were also reported in later onconological studies.

8.4.1.4 Reproductive and Developmental At least two studies have shown no teratological response in laboratory animals that inhaled vinyl chloride during pregnancy; however, fetotoxic effects were observed, particularly when ethanol was administered simultaneously in drinking water.

John et al. (223) evaluated the effects on mice, rats, and rabbits. Groups of pregnant CF-1 mice, Sprague–Dawley rats, and New Zealand white rabbits were exposed to 500 ppm vinyl chloride for 7 h daily during organogenesis. Mice were also exposed to 50 ppm and rats and rabbits to 2500 ppm. Maternal toxicity was observed, most prominently in the mice, but the exposures did not cause significant embryonal or fetal toxicity or teratological effects. Simultaneous administration of 15% ethanol in drinking water produced toxic effects greater than those of vinyl chloride alone. Maternal toxicity was increased more than embryo toxicity.

Ungvary et al. (224) showed that vinyl chloride crosses the placenta and is found in the amniotic fluid and fetal blood, as well as in the maternal blood of rats. Pregnant rats were exposed continuously to 1500 ppm (4000 mg/m^3) during the first, second, or third trimester of pregnancy without teratological effects. No embryo toxicity was noted when vinyl chloride was administered during the second or third trimester, but during the first trimester, it increased fetal mortality and caused other fetotoxic effects. Fetal losses and induction of CNS malformation due to trypan blue administration were not potentiated by a combined exposure of pregnant rats to vinyl chloride and the dye. The reproductive organs were target organs in lifetime animal studies, although Bi et al. claim to have produced testicular injury in male Wistar rats in 12 months at 100 ppm (225).

Numerous references attest to the mutagenic effect of vinyl chloride or its metabolites in *in vitro*

systems using bacteria, yeast, and hamster cells (226, 227). *Drosophila* males treated with 1 to 20% vinyl chloride vapors had an increased frequency of complete and mosaic recessive lethals. Muratov and Guskova (228) reported that continuous exposures of rats to 0.15, 0.4, or 10 mg/m^3 (60, 160, or 3900 ppm) for 3.5 months increased the incidence of chromosomal fragmentation, agglutination, and bridging. The incidence reportedly increased when the rats were housed at 35°C rather than at 22°C. No mutagenic effects were observed at 0.07 mg/m^3 (28 ppm).

Inhalation of 2500 or 5000 ppm for 4 h/day for 5 days or intraperitoneal injection of 300 or 600 mg vinyl chloride/kg/day resulted in chromosomal changes in the marrow cells of Chinese hamsters (229). However, Anderson et al. (230) reported the lack of a dominant lethal effect in a study in which mice were exposed to 3000, 10,000, or 30,000 ppm for 5 days. Similarly Short et al. (231) found no evidence of pre- or postimplantation loss in female rats mated with males that had been exposed for 11 weeks to 0, 250, or 1000 ppm. Exposures were for 6 h/day, 5 days/week.

The available mutagenic data are consistent with a genotoxic causation of cancer.

8.4.2 Human Experience 8.4.2.2 Clinical Cases Because vinyl chloride is a gas, the only significant route of toxic industrial exposure is inhalation. Ingesting low levels for a long period of time has also produced adverse effects, including cancer in animals. If vinyl chloride is confined on the skin in a liquid, some might be expected to be absorbed, but the relative amount is small. The likelihood of acute toxic effects is not nearly as significant as are liver injury, angiosarcoma of the liver, liver and biliary cancer, and possibly acroosteolysis. It appears that metabolism of vinyl chloride is necessary before many of its toxic effects occur. Numerous reviews, bibliographies, and key references are available (42, 232–234), and many regulations apply to handling vinyl chloride.

8.4.2.2.1 Acute Toxicity Limited human studies by Mastromatteo et al. (217) showed that concentrations must approach 1% (10,000 ppm) before humans notice the anesthetic effects of vinyl chloride gas. Surgical anesthesia requires concentrations greater than 10%. Baretta et al. (235) studied the expired air of subjects exposed to 50, 250, or 500 ppm for 7.5 h with a half-hour lunch break. Although they concluded that expired air sampling might have utility in monitoring exposure at the occupational standards then in use, expired air can be expected to be of little value at currently accepted levels of exposure.

8.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Numerous studies indicate that a reactive metabolite, not vinyl chloride *per se*, is probably responsible for its toxicity. Although most inhaled vinyl chloride is excreted unchanged, depending on the dose, a varying amount is metabolized in a saturable process (235). Vinyl chloride is metabolized by epoxidation and subsequent production of chloroacetaldehyde. Further oxidation and conjugation with glutathione are responsible for the metabolites in urine.

Gehring et al. (234, 236) analyzed the metabolic and carcinogenic data from humans and laboratory animals. Using several models to predict the incidence in humans from animal data, they found that all models overpredicted, unless corrections were made for rates of metabolism and for the surface areas of the different species.

8.4.2.2.5 Carcinogenesis Because it was one of the first large-scale industrial chemicals clearly demonstrated to cause cancer in humans, it has been the subject of much research and regulation. Only a small portion of the available references have been cited.

The early industrial history of vinyl chloride is remarkably free of adverse reports except for problems of fire and explosion. The earliest reports of adverse effect on industrial workers related to vinyl chloride were of anesthesia and anesthetic deaths. Danziger (237) reported two fatal cases, only one of which was definitely ascribed to a massive exposure to vinyl chloride. Other reports indicate that exposures were poorly controlled, and probably amounted to thousands of parts per millions in

many situations before 1974.

Cutaneous lesions (scleroderma), collagen disease, and Raynaud's syndrome were reportedly observed by Suciu et al. (238) in a PVC plant, but contrary to some reports these authors did not ascribe the effects to vinyl chloride *per se*; rather they considered that they were related to other materials used in the factory. Subsequently, numerous authors reported acroosteolysis in PVC workers in Europe and the United States. This was accompanied by scleroderma and Raynaud's syndrome.

The association of vinyl chloride exposure with human cancer occurred when three case reports of angiosarcoma of the liver were discussed in a report of Creech and Johnson in 1974 (239). This finding led to many studies of the effects of exposure to vinyl chloride. There is no question that angiosarcoma of the liver was caused by exposure to vinyl chloride primarily while cleaning reactor vessels. As of February 1991, a total of 153 vinyl chloride-related deaths due to angiosarcoma of the liver were recorded in non-Soviet bloc countries some cases apparently still living (240). The incidence of death reached a maximum of 10 cases per year during 1973–1984 and subsequently decreased to about four per year. Latency since the year of first exposure averages about 24 years worldwide.

Angiosarcoma of the liver and combined liver-biliary tumors in humans are certainly consistent with the results of studies in animals because they have been produced in several epidemiological studies.

Mutagenic effects reported in workmen exposed to vinyl chloride include increased frequency of chromosomal aberrations, sister chromatid exchange, and micronuclei (241). Several of the studies cited by Sinus et al. (241) indicated that there is a dose response and that no-effect levels for mutagenesis may exist.

A U.S. study covering 1942–1982 identified a population of 10,173 men who satisfied the definition of the study cohort (242). A total of 1536 deaths occurred, and the standardized mortality ratio (SMR) was of 90.07. A total of 359 cancer deaths were observed versus 341.73 expected (SMR 105.1) which was not statistically significant. Angiosarcomas of the liver and combined liver-biliary cancers were significantly elevated.

The investigators also claimed an excess of brain and CNS cancers as a result of exposure to vinyl chloride. There were 23 deaths observed and 12.76 expected (SMR, 180.2). The authors stated,

Our analysis did not demonstrate any dependence of brain cancer mortality on latency. Contrary to our observation on liver cancer, a higher brain cancer mortality risk was found among those who were exposed after age 35 and who were exposed during or after 1960 than those who were exposed before 1960 and at a younger age. Based on the limited exposure information available in this mortality study, the implication of this difference in risk profile is not clear at this point.

Pneumonia as a cause of death was significantly low, but in PVC plants, emphysema (including chronic respiratory disease) was elevated (SMR 163). Earlier English studies suggest that the respiratory effects may have been due to PVC dust.

Cancers of the buccal cavity and pharynx, digestive tract, lung cancer, brain cancer, and lymphatic cancers were reported among workers who were employed at least one year in plants that produced and/or polymerized vinyl chloride (243). Brain and liver cancer were observed among 161 workers who died and were employed in two plants that produced and polymerized vinyl chloride. An 11-fold excess of liver and biliary tract cancer and a fourfold excess of brain cancer occurred. Digestive tract and lung cancer were also elevated (244). Cancer mortality among 257 workers exposed to

vinyl chloride for at least 5 years consisted of a 2.3-fold excess in cancer deaths from all sites and three deaths due to hemangiosarcoma of the liver (245).

A report from the United Kingdom reported an increased risk of digestive system cancers among workers who had 15 years of latency or more from exposures to vinyl chloride or poly(vinyl chloride) (246). The National Institute for Occupational Safety and Health (NIOSH) study by Waxweiler et al. (247) found two causes of death in excess: nonneoplastic respiratory disease (6 obs.vs. 3.4 exp.) and all malignant neoplasms combined (35 obs. vs. 23.4 exp., $p = .05$). When specific cancer sites were evaluated, excess cancers were found for CNS, respiratory system, and hepatic systems in workers who had 15 or more years of latency since first exposure. Pathological analysis of the 14 liver cancer cases, showed that 11 were angiosarcoma, and nine of the ten cases of brain cancer were glioblastoma multiforme. All of the lung cancers were large cell undifferentiated or adenocarcinomas. In Sweden, statistically significant excesses of liver-pancreatic and brain cancer were reported among 771 workers of a vinyl chloride/polyvinyl chloride production plant (248). In Germany vinyl chloride-polyvinyl chloride exposed workers had excesses of cancer of the liver, lung, brain, and the lymphatic and hematopoietic systems (249). In the United Kingdom, excess liver cancer mortality was found at all exposure levels (high, medium, or low) among 7561 males employed at one of four plants that produced poly(vinyl chloride) between 1940 and 1974 (250).

A large multicentric study of European experience combined 12,706 subjects from 19 factories in Italy, Norway, Sweden, and the United Kingdom (241). A total of 1438 deaths were observed versus 1636.4 expected (SMR 88.95). The SMR for all malignant neoplasms was 104, for cancer of the liver-biliary 286 (24 versus 8.4), and for cancer from unspecified sites 187 (24 versus 12.9 expected). Three of the cancers of unspecified site were liver cancers; no other site was in excess.

Another area of interest is the question of what, if any association, did vinyl chloride have in the etiology of lymphoma and hemopoietic cancers? In an industry-sponsored study published in 1974, there was a pattern of increased exposure and lymphoma among 8384 men who had worked at least one year with exposures to vinyl chloride before December 31, 1972. Though not statistically significant, the authors indicated that the findings " ... are particularly interesting." They observed 5 cases when 7.54 would have been expected (243). This paper probably suffered from lack of power to really detect a true increase, so this finding was of great interest. At a conference in New York, the next year, another study, this one conducted by the National Institute for Occupational Safety and Health (NIOSH), looked at four plants and 1,294 workers who had at least 5 years of exposure and also reported a nonstatistically significant excess for lymphatic and haematopoietic system cancers (4 obs. vs. 2.5 exp.—SMR 159). The SMR increased with latency to 176 after a 15 year latency period (247).

Additional studies continued and reported increased mortality from lymphoma. One study of nine different countries found nonstatistical increases in malignant lymphomas in conjunction with exposure to vinyl chloride (251). Such increases were also observed in studies in Germany and Russia in the early 1980s (252–254). In a further report from Russia, some of the same authors of the earlier study, found that a significant increase in deaths from malignancies of the lymphatic and hemopoietic tissues in the absence of liver angiosarcomas occurred among workers employed between 1939 and 1977 in producing vinyl chloride and polyvinyl chloride. They suggest that this finding probably reflected the specific carcinogenic action of different doses of vinyl chloride. The risk of cancer was highest among the workers exposed to concentrations of vinyl chloride of 300 mg/m^3 and also greater in those who had worked at the plant for 15 to 19 years (255).

In a mortality study of 88,000 Union Carbide Corporation personnel employed from 1974 to 1983 using a population-based surveillance system, the overall population exhibited a 30% lower mortality and a 10% lower cancer mortality compared to the general United States population. The mortality rates for both lymphosarcoma and reticulosarcoma were significantly elevated, and according to the authors, these higher rates were found among hourly male employees who were

clustered in one company location. They point out that this same location showed an excess of liver cancer associated with vinyl chloride operations (256).

Briefly, another study found chromosomal breaks induced by vinyl chloride and lymphocytosis (257) in which the authors conclude that G-banding showed that sites of chromosomal break points caused by vinyl chloride can be related to lymphatic tissue disorders. The authors also conclude that lymphomas and leukemias can be expected from vinyl chloride exposure at concentrations as low as 1 ppm. Finally, a study of Danish men found that a probable exposure to vinyl chloride was associated with increased risk of myeloma (a tumor composed of cells derived from hematopoietic tissues of the bone marrow) that rose fivefold from longer exposures (258).

There are epidemiological studies that have not shown such associations with exposure to vinyl chloride, but the studies cited above do point to a general pattern that leads to a conclusion that vinyl chloride exposures can result in malignancies of the lymphatic and hematopoietic system. This is also the conclusion of the International Agency for Research on Cancer, and its conclusion was based on fewer studies than are now available (259). Animal bioassay's have also supported these epidemiological findings (260–262).

Almost 30 years since the first reports of angiosarcomas in the liver of animals and humans, it is clear that, in addition to liver angiosarcoma and combined liver-biliary cancer which have consistently increased, brain and lymphatic cancers are also attributable to exposures to vinyl chloride. Mutagenic effects have been found and have reversed as exposures were better controlled. Liver injury has resulted from vinyl chloride *per se*, as have such well established conditions as acroosteolysis, scleroderma, and Raynaud's syndrome, which have been clearly related to the PVC production process. The International Agency for Research on Cancer has concluded that the evidence for cancer in humans shows that exposure to vinyl chloride causes tumors of the liver, brain, lung, and hematolymphopoietic system (259). The IARC has also concluded that evidence for cancer in animals shows that VC produces tumors of the mammary gland, lung, Zymbal gland, and skin and angiosarcomas of the liver. Oral administration of ethanol and inhalation of vinyl chloride resulted in more liver tumors than from vinyl chloride alone (259).

Tamburro (263) has concluded that current clinical, biochemical, and hematologic tests are of limited value in predicting angiosarcoma but may be of value in other hepatotoxic effects.

8.4.2.2.6 Genetic and Related Cellular Effects Studies Despite efforts to corroborate reported reproductive effects in human studies (264), they have not been confirmed in properly conducted epidemiological studies. In fact the early “positive” report (264) has been severely criticized for bias and defective methodology and, according to independent reviews, should not continue to be cited as evidence for reproductive effects in humans (265–267).

8.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH recommends a TLV of 1 ppm (2 mg/m^3) vinyl chloride. The U.S. Department of Labor (OSHA) PEL is 1 ppm and the 15 min ceiling is 5 ppm; standards in other countries vary, but generally require limiting exposures to 5 ppm or less. It appears reasonable to assume that these levels established to protect against angiosarcoma of the liver will prevent other adverse effects as well. NIOSH recommends treating vinyl chloride as a carcinogen.

8.6 Studies on Environmental Impact

Cases of hepatic angiosarcoma have been reported in persons who had no occupational exposure but lived in the area near vinyl chloride polymerizing or fabricating poly(vinyl chloride) facilities in the United States and Great Britain. This indicates an environmental etiology (268–270).

Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

9.0 Vinyl Bromide
9.0.1 CAS Number:
[*593-60-2*]
9.0.2 Synonyms:
Bromoethylene; bromoethene; monobromoethylene: Vinyl-13C2 bromide (gas)
9.0.3 Trade Names:
NA
9.0.4 Molecular Weight:
106.96
9.0.5 Molecular Formula:
C_2H_3Br
9.0.6 Molecular Structure:

9.1 Chemical and Physical Properties
9.1.1 General

Physical State	colorless gas
Specific Gravity	1.4933
Melting Point	–139.5°C (271)
Boiling Point	15.8°C (271)
Vapor Pressure	119 kPa at 20°C 1033 torr at 20°C
Solubility	soluble in acetone, benzene, diethyl ether, chloroform, and ethanol; insoluble in water (271)
Stability	polymerizes rapidly in sunlight and, can react vigorously in the presence of oxidizing materials (271)
Flash Point	5°C
Explosive Limits	upper, 15%; lower 9% by volume (272)

9.1.2 Odor and Warning Properties Pungent odor. No published data were found but, based on its high chronic toxicity, it can be assumed that vinyl bromide has inadequate warning properties to prevent excessive chronic exposure.
9.2 Production and Use
Vinyl bromide is used as a copolymer primarily in the production of flame resistant acrylic polymers and to a limited extent as a chemical intermediate. Vinyl bromide is produced in Germany, Japan, and the United States (273).
9.3 Exposure Assessment
9.3.1 Air Sampling for vinyl bromide was conducted in two communities in the United States where production facilities were located, but no concentrations were reported in the air. However, the authors did report that vinyl bromide was in the air. More recently, vinyl bromide has been measured in ambient air samples (272).

9.3.2 Background Levels No information on whether vinyl bromide occurs naturally was found. Vinyl bromide may be found in the air as a result of degradation from 1,2-dibromoethane as well as from facilities that use or manufacture it (274).

9.3.3 Workplace Methods NIOSH recommends gas chromatography/flame ionization detection for analysis, Method 1009 a method that is valid over the range of 1.3–56 mg/m^3 (0.3–33 ppm) for a 6-L air sample (80).

9.3.4 Community Methods The method for environmental monitoring using gas chromatography/mass spectrometric has a lower limit of detection of between 10^3–10^5, but no range was given.

9.3.5 Biomonitoring/Biomarkers Vinyl bromide is metabolized and bromide ion is found in the blood of exposed animals. Determination of blood bromide was considered useful for biological monitoring at the then current industrial hygienic levels, but blood bromide is of very limited value at current standards of 1 to 5 ppm.

9.4 Toxic Effects

9.4.1.1 Acute Toxicity Vinyl bromide is a gas and the only significant route of toxic industrial exposure is inhalation. Limited data have been published. According to Leong and Torkelson (275),

Preliminary evaluation of the toxicity of vinyl bromide showed that the compound had an acute oral LD_{50} of approximately 500 mg/kg when a chilled 50% solution in corn oil was fed to male rats. It was found to be slightly to moderately irritating to the eyes, to be essentially nonirritating to the intact or abraded skin or rabbits, and to produce no frostbite from evaporation of the liquid.

Abreu (276) reported that 7 mmol/L (1700 ppm) was the highest tolerable concentration for mice exposed for 10 min and that half that concentration produced pronounced anesthesia. Leong and Torkelson (275) published very limited acute data indicating much lower toxicity than Abreu. They reported that

acute inhalation toxicity studies showed that exposure of rats to a nominal concentration of 100,000 ppm (437,636 mg/m^3) resulted in deep anesthesia and death within 15 minutes, but if the exposure was terminated before death, all animals recovered and survived. Exposure to a nominal concentration of 50,000 ppm (218,818 mg/m^3) resulted in unconsciousness within 25 minutes. All animals survived a 1½-hour exposure, but not a 7-hour exposure. At 25,000 ppm (109,409 mg/m^3) rats were anesthetized, but they recovered rapidly when removed from the atmosphere even after 7 hours of exposure. Necropsy of survivors of the 50,000 ppm groups 2 weeks after exposure revealed slight to moderate liver and kidney damage. However, no abnormality was observed grossly in the survivors of the 25,000-ppm group.

9.4.1.2 Chronic and Subchronic Toxicity Male and female rats, rabbits, and monkeys were repeatedly exposed for 6 h/day to either 250 or 500 ppm for 6 months without apparent effect, except for an increase in blood bromide ion concentration (275). There were no compound-related effects with respect to demeanor, body and organ weights, food consumption, a number of hematologic parameters, or mortality. Gross and microscopic examination of the major organs and tissues at the end of the exposure period revealed no remarkable abnormal changes. This study was not long enough to evaluate carcinogenicity.

9.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Based on bromide release, Gargas and Andersen concluded that vinyl bromide had two distinct saturable components (277). Metabolism is

expected to be similar to that of vinyl chloride, probably proceeding through epoxidation, and subsequent conjugation to macromolecules and other biological compounds (278) Vinyl metabolites to alkylate liver nucleic acids.

9.4.1.3.1 Absorption Vinyl bromide inhaled by rats was readily absorbed by the lung and showed an 11-fold accumulation in the entire organism compared to equilibrium (274).

9.4.1.4 Reproductive and Developmental No data were found, even by the IARC working group (59, 274).

9.4.1.5 Carcinogenesis Sprague–Dawley rats were exposed to nominal concentrations of 10, 50, 250, or 1250 ppm vinyl bromide gas for 6 h/day, 5 days/week (279). Groups were scheduled for sacrifices after 9, 12, 18, or 24 months; however, the 1250-ppm group had to be sacrificed after 72 weeks because of severe effects. In general, the results were quite similar to those seen from exposure to vinyl chloride. The investigators concluded that a decline in body weights was evident among all exposure levels. Microcytic anemia, elevated serum bromide levels, decreased BUN, elevated alkaline phosphatase, elevated LDH, and hematuria were observed. Angiosarcomas, primarily of the liver, were induced in both male and female rats in all four exposure groups. An increase in the number of Zymbal's gland neoplasms was found in both male and female rats at exposure levels of 52, 247, and 1235 ppm. An increased incidence of primary hepatocellular neoplasms was seen in males exposed to 247 ppm and in females exposed to 9.75, 52, and 247 ppm. The increase in primary hepatocellular neoplasms was detected primarily in animals that survived the 24-month exposure or died following 18 months of exposure. No exposure-related pathology was observed in the brains of the rats.

Similarly, results were seen in groups of six rats exposed to 50, 250, or 1250 ppm for 6 months as part of a carcinogenic study and killed as part of an interim sacrifice (279). After 1 year, however, tumors of the liver and Zymbal glands of the ears were observed. Liver angiosarcomas and Zymbal gland tumors that were dose-response related were observed after inhalation by rats (274).

The carcinogenic potency of vinyl bromide compared to vinyl chloride has not been established; however, Bolt et al. (280) studied the formation of preneoplastic hepatocellular foci in newborn rats and concluded that vinyl bromide had only one-tenth the potency of vinyl chloride. The investigators speculated that the lower potency may be associated with the lower rate of metabolism reported for vinyl bromide (281).

9.4.1.6 Genetic and Related Cellular Effects Studies Vinyl bromide vapors were mutagenic in *Salmonella typhimurium* TA1530 and TA100. Addition of rat and human liver enzymes enhanced activity in the *in vitro* test system (282) and also induced somatic mutations in *Drosophila melanogaster* (274). It is thought that vinyl bromide reacts with DNA and form etheno adducts, the same as those formed by vinyl chloride (283).

9.4.2 Human Experience Human experience has been limited, but it should also be assumed that vinyl bromide, like vinyl chloride, can cause certain cancers in humans. Toxicological reviews are available (173, 279).

9.4.2.2.1 Acute Toxicity Vinyl bromide can cause loss of consciousness and is a skin and eye irritant with that results in a frostbite type of burn (173).

9.4.2.2.5 Carcinogenesis No data for the effects of vinyl bromide on humans were available (274). However, the IARC (274) has classified vinyl bromide as probably carcinogenic to humans (2A) based on the consistently parallel response between vinyl bromide and vinyl chloride. Both vinyl chloride and vinyl bromide are activated to their corresponding epoxides via a P450-dependent pathway (274).

9.5 Standards, Regulations, or Guidelines of Exposure

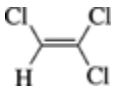
The ACGIH recommends a TLV of 0.5 ppm (2.2 mg/m^3) for vinyl chloride. OSHA has no standard and the standards in other countries require limiting exposures to 5 ppm or less. The National Institute for Occupational Safety and Health (NIOSH) recommends treating vinyl bromide as a carcinogen limited to 0.2 ppm, the limit of quantification (LOQ) (284).
9.6 Studies on Environmental Impact
Vinyl bromide as a degradation product of 1,2-dibromoethane may form in the air (274).

Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

10.0 Trichloroethylene
10.0.1 CAS Number:
[*79-01-6*]
10.0.2/10.0.3 Synonyms & Trade Names:

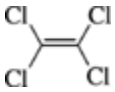
Acetylene Trichloride	Fluate	TCE	Tri-Clene
Algylen	Germalgene	Threthylen	Trielene
Anamenth	Lanadin	Threthylene	Trielin
Blacosolv	Lethurin	Tri	Trilene
Chlorilen	Narcogen	Triad	Triline
Chlorylen	Narkosoid	Trial	Trimar
Densinfluat	Nialk	Triasol	Vestrol
Dow-Tri	Perm-A-Clor	Trichloran	Vitran
Ethinyl Trichloride	Petzinol	Trichloren	Westrosol
Fleck-Flip	Philex	Triclene	

(285, 286).
10.0.4 Molecular Weight:
131.39
10.0.5 Molecular Formula:
C_2HCl_3
10.0.6 Molecular Structure:



Unsaturated Halogenated Hydrocarbons
R. A. Lemen, Ph.D., MSPH

11.0 Tetrachloroethylene
11.0.1 CAS Number:
[*127-18-4*]
11.0.2 Synonyms:
tetrachloroethylene; 1,1,2,2-tetrachloroethylene; tetrachloroethene; PERK;PERC; Dowper; Perclene; Nema; Tetracap; Tetropil; Ankilostin; Didakene; carbon dichloride; perchlor; antisol1; fedal-un; PER; Perawin; Perclene d; Percosolve; perklone; persec; tetlen; tetraleno; tetralex; tetravec; tetrochloroethane; tetroguer; perchloroethylene
11.0.3 Trade Name:
NA
11.0.4 Molecular Weight:
165.83
11.0.5 Molecular Formula:
C_2Cl_4
11.0.6 Molecular Structure:



11.1 Chemical and Physical Properties

Physical State	colorless liquid
Specific Gravity	1.625
Melting Point	–22°C
Boiling Point	121°C
Vapor Pressure	1.9 kPa at 20°C (20 torr at 26.3°C)
Relative Vapor Pressure	5.8 (air = 1)
Solubility	almost insoluble in water (0.015 g/100 mL at 25°C); soluble in ethanol, and ethyl ether, chloroform, and benzene

11.1.2 Odor and Warning Properties Perchloroethylene has a not unpleasant ethereal or aromatic odor. In addition to clinical evaluation of perchloroethylene as an anesthetic, several other studies in human subjects are available. Hake and Stewart (428) summarized their extensive studies on humans. The analysis of expired air and urine were discussed in the preceding section and dermal absorption of perchloroethylene in the section on skin absorption. Based on detailed studies of neurological, psychological, and behavioral effects and the volunteers' subjective response, the authors concluded that 100 ppm of perchloroethylene was probably without effect but the margin of safety is small. Perchloroethylene plus alcohol or Valium (Diazepam) had no more effect on performance than alcohol or Valium alone. At 200 ppm some subjects objected to the odor and eye irritation, and higher concentrations were unacceptable. Light-headedness began at 200 ppm or slightly above.

Carpenter (429) exposed himself and three other subjects to perchloroethylene and determined that the odor was detectable at 50 ppm; that 500 ppm produced salivation, a metallic taste, eye irritation, and other objectionable reactions; and that 1000 and 2000 ppm produced the beginnings of narcosis and discomfort. This is consistent with data by Rowe et al. (430), who found that 280 ppm was

objectionable to test subjects and 216 ppm was marginal.

11.2 Production and Use

Perchloroethylene is used as an industrial solvent, particularly in dry cleaning and degreasing. It has been used as an anti helmintic in humans and animals. It also finds limited use as a chemical intermediate.

11.3 Exposure Assessment

Sampling in the workplace is done by air bag using gas chromatography (portable/photoionization detector (PDI) (431). The working range for this method is from 0.1 to 100 ppm for both air and exhaled breath samples by direct on-site analysis or by collection into inert sampling bags.

11.3.3 Workplace Methods NIOSH Method 1003 is recommended for determining workplace exposures to tetrachloroethylene (80).

11.3.5 Biomonitoring/Biomarkers Hake and Stewart (428) summarized much of their own and others' data on the use of expired air for monitoring industrial exposures. This included the results of an extensive study (432) in which male and female human subjects were exposed singly or repeatedly for various periods of time to several concentrations of perchloroethylene. Graphs are presented that are useful in estimating worker's exposure on the basis of expired air samples. It appears that analysis of expired air is useful for monitoring occupational exposure to perchloroethylene but that analysis of urinary metabolites is of less value (433).

11.4 Toxic Effects

The major response to perchloroethylene at high concentrations is CNS depression. It is not, however, sufficiently effective to be considered a useful anesthetic. Irritation of the eyes, nose, and throat may also be observed at high concentrations. There are some indications of nausea and gastrointestinal upset at high concentrations, and changes in the liver and kidneys may be seen following excessive exposure; however, the effects are not as severe or striking as they are from a material such as carbon tetrachloride. Relatively few incidences of industrial problems due to exposure to perchloroethylene have been reported, probably because of a number of circumstances, including low vapor pressure and toxicity.

Case reports relate a rather consistent set of symptoms. Certainly anesthesia and, in cases of higher exposure, liver injury are related to perchloroethylene. Nausea, headache, anorexia, vertigo, dizziness, and other symptoms may be related to the CNS and hepatic effects. Sensitization of the heart to epinephrine does not occur with this compound. As for many compounds, massive doses of perchloroethylene given by gavage produced liver cancer in mice but not rats. Kidney tumors occurred only in male rats and a possible increase in mononuclear cell leukemia was also observed in both sexes of rats. Numerous reviews are available (6, 42, 142, 434, 435).

11.4.1.1 Acute Toxicity Perchloroethylene has moderate to low toxicity by single-dose ingestion. When fed to laboratory mice, an LD_{50} of 8850 mg/kg was reported. Animals survived at 4000 (dog and cat) and 5000 (rabbit) mg/kg. A dose of 500 mg/kg reportedly does not cause death in humans (436). Pozzani et al. (437) reported an acute oral LD_{50} of 2600 mg/kg for rats, and Hayes et al. (438) reported 3835 and 3005 mg/kg for male and female rats, respectively.

Liquid perchloroethylene may cause pain, lacrimation, and burning; however, permanent injury is unlikely. High concentrations of the vapors are uncomfortable to the eyes.

If perchloroethylene is allowed to evaporate, no significant effect on the skin is likely. However, if it is confined on the skin or if exposures are prolonged and frequently repeated, the solvent causes dermatitis by defatting the skin. Absorption of liquid through the skin is not likely to be a significant route of toxic exposure (439, 440), although some absorption does take place. Riihimaki and Pfaffli (441) determined that absorption of the vapors through the skin of human subjects was not significant at 600 ppm.

The response of rats to single exposures was reported by Rowe et al. (430). They stated that 2000 ppm was tolerated for up to 14 h and 3000 ppm was tolerated for 4 h with no deaths. Unconsciousness was observed in the rats within a few minutes at concentrations of 6000 ppm or more, and after several hours at 3000 ppm, but unconsciousness was not observed at 2000 ppm. At these high-level single exposures, the predominant response was one of depression of the nervous system. Deaths occurred during or immediately after exposure. There were slight changes in the liver, characterized by a slight increase in weight, slight increase in total lipids, and slight cloudy swelling.

Pozzani et al. (437) reported an 8 h LC_{50} of 34.2 mg/L (5040 ppm) for rats.

Several other investigations studied the effect of perchloroethylene on the liver and confirmed the observation of Rowe et al. (430). Kylin et al. (442) exposed mice for 4 h to 200, 400, 800, or 1600 ppm. No liver necrosis was observed, but fatty infiltration consistent with dose was observed at all levels.

Drew et al. (443) exposed rats to 500, 1000, or 2000 ppm perchloroethylene vapors for 4 h and measured serum enzymes. Four liver enzymes (SGOT, SGPT, glucose-6-phosphatase, and ornithine carbamyl transferase) were markedly increased by exposure to 2000 ppm and moderately increased by exposure to 1000 ppm, but were affected very little by exposure to 500 ppm.

Gehring (444) exposed mice to 3700 ppm and determined an anesthetic ED_{50} of about 234 min, a SGPT ED_{50} of 470 min, and an LT_{50} of 730 min. He concluded that liver toxicity was of relatively low importance compared to anesthesia.

The hepatotoxicity and renal toxicity of perchloroethylene were studied following subcutaneous injection. Plaa et al. (445) determined an LD_{50} of 390 mg/kg when perchloroethylene was injected in male mice. The hepatoxicity was low (rated 3 versus 1 for 1,1,1-trichloroethane and 190 for carbon tetrachloride). Plaa and Larson (48) measured nephrotoxicity following intraperitoneal injection and concluded that perchloroethylene was only weakly nephrotoxic.

Other references reported LD_{50} values of 4600 to 5700 mg/kg for mice (444, 446) and 3400 mg/kg for dogs given intraperitoneal injections.

11.4.1.2 Chronic and Subchronic Toxicity The NCI included perchloroethylene in their bioassay program, but unfortunately their experimental design did not call for adequate histological examinations of noncancerous lesions. They did report toxic nephropathy as discussed later under carcinogenesis (447).

When perchloroethylene was administered in drinking water for 90 days, body weight decreased and there were suggestions of liver effects but no clear evidence of injury at 1400 mg/k/day, the highest dosage fed (438).

The first chronic study of tetrachloroethylene vapors was carried out by Carpenter (429). He exposed rats to concentrations of 70, 230, and 470 ppm for 8 h/day, 5 days/week for periods up to 7 months. All of his animals survived and had growth comparable to his controls. No pathological effects were observed at 70 ppm. At 230 ppm, he observed some pathological changes in both the liver and kidneys. At 470 ppm, the pathological indications of injury to the liver and kidneys were more striking.

Rowe et al. (430) reported the results of chronic vapor exposures of several species of animals. At 1600 ppm in air, rats showed a drowsy, depressed condition for the first week and later a definite “irritation.” Enlargement of the liver and kidneys was noticeable. Guinea pigs showed a loss in body

weight, an increase in liver weight, and moderate histological changes. At 400 ppm, after 130 exposures of 7 h/day over a period of 183 days, rats showed no evidence of adverse effect. Guinea pigs showed definite increases in liver and kidney weights and slight fatty degeneration of the liver. Rabbits and monkeys showed no evidence of injury. At 200 ppm, guinea pigs showed an increase in liver weight, an increase in total liver lipids, and slight to moderate histopathological changes in the liver. At 100 ppm, female guinea pigs showed an increase in liver weight. Histologically, the liver appeared normal.

Guinea pigs in these studies displayed a particular susceptibility and showed changes even at 100 ppm. However, because human experience had been favorable, these authors were inclined to accept the previously used maximum allowable concentration of 200 ppm as satisfactory. They suggested, however, that this should be considered a ceiling and fluctuations should be around an average of 100 ppm.

In a similar study, rats, mice, guinea pigs, rabbits, and dogs were exposed to a 4:1 mixture of 1,1,1-trichloroethane and perchloroethylene vapors (448). Animals exposed to 800 ppm 1,1,1-trichloroethane plus 200 ppm perchloroethylene for 7 h/day for 6 months exhibited mild and reversible liver and kidney changes consistent with the effect expected from 200 ppm of perchloroethylene alone. Repeated exposures to 400 ppm 1,1,1-trichloroethane plus 100 ppm perchloroethylene had no effect in all species.

Kylin et al. (449) exposed mice to 200 ppm for 4 h/day, 6 days/week for 1, 2, 4, or 8 weeks. Fatty degeneration was observed, but no liver cell necrosis or effects on the kidneys were observed.

NTP exposed rats and mice for 6 h/day, 5 days/week for 13 weeks to establish a dose for the lifetime study reported in the section on carcinogenesis (450). The targeted concentrations were 0, 100, 200, 400, 800, and 1600 ppm. The highest concentration was lethal to 20 to 70% of the rats and mice. Exposures to 200 to 800 ppm caused minimal to mild hepatic congestion in rats.

In dosed male and female mice, minimal to mild hepatic leukocytic infiltration, centrilobular necrosis, bile stasis (400–1600 ppm) and mitotic alteration (200–1600 ppm) were produced. Tetrachloroethylene exposure also caused minimal renal tubular cell karyomegaly in mice at concentrations as low as 200 ppm.

11.4.1.3 Pharmacokinetics Metabolism, and Mechanisms Perchloroethylene is metabolized by a microsomal cytochrome P450 mixed-function oxidase system. Metabolism is dose-dependent in the rat, first-order at low concentrations and zero-order (metabolic saturation) at higher concentrations (281). Mice metabolize perchloroethylene faster than rats, which do so faster than humans. Mice and probably humans also have saturable metabolisms (464).

When given to rats by gavage or inhalation, much of the administered perchloroethylene was recovered unchanged in expired air (465). These investigators reported that 72 and 90% of the body burden were expired unchanged after oral doses of 1 and 500 mg/kg in rats and 68 and 88% after a 6-h exposure to 10 or 600 ppm vapor. The balance was primarily nonvolatile metabolites.

In mice there was a shift in metabolism at high doses (458), and much more was excreted unchanged above 500 mg/kg given orally.

By far the major urinary metabolite in rats and mice is trichloroacetic acid; more than half appears as the acid and its conjugate. Much smaller amounts of oxalic acid, trichloroethanol, dichloroacetic acid, and *N*- trichloroacetylaminoethanol or its conjugate (466) are excreted. Ethylene glycol,

chlorine, and CO_2 have been reported by others as metabolites. Conjugation with glutathione is not as significant as with some other chlorinated solvents, but at high doses, a mercapturic acid conjugate has been found in bile and urine. More is found in the rat than in the mouse. Gehring et al. (6) commented on the carcinogenic significance of this metabolite, and noted that although it appears to be a "spill-over" metabolite, it has mutagenic activity in bacterial assays (Ames test), suggesting that care be taken to avoid kidney and liver injury by limiting human exposure.

11.4.1.4 Reproduction and Developmental Early studies of reproduction by Carpenter (429) showed no effect at 420 ppm. Schwetz et al. (451) evaluated the teratogenic potential of perchloroethylene in rats and mice. Pregnant rats and mice were exposed to 300 ppm perchloroethylene for 7 h/day on days 6 to 15 of gestation. They reported a significant decrease in the fetal body weight of mice and a slight, but statistically significant, increase in the incidence or resorptions among the rat fetal population. Soft tissue examination of fetuses from exposed mice revealed a significant increase in the incidence of subcutaneous edema. The incidence of skeletal anomalies was not different from the controls, but among litters of mice the incidence of delayed ossification of skull bones and the incidence of split sternebrae increased slightly compared to those of the controls. A teratogenic effect was not observed. Negative teratological studies have also been reported in rats and rabbits by Beliles et al. (452) and John et al. (453).

Perchloroethylene was inactive when tested in *E. coli* and *S. typhimurium*, even when mouse liver enzymes were added (54).

NIOSH (454) and Bartsch et al. (455) also reported no mutagenic effects in tests with *Salmonella* but Cerna and Kyperova (456) claimed that it was positive even without metabolic activation. The available abstract also indicated that perchloroethylene was positive in a host-mediated assay in ICR mice, but the response was at high dosages (LD_{50} and 1/ 2 LD_{50}) and was not dose-related.

Cerna and Kyperova (456) reported no cytogenetic changes in female ICR mice given half the LD_{50} once or one-sixth the LD_{50} five times by intraperitoneal injection.

Rampy et al. (457) reported no mutagenic effects in lymphocytes of rats after 12 months of 6 h daily exposures 5 days/week to either 300 or 600 ppm of the vapor.

NTP conducted its battery of mutagenic tests as part of the cancer bioassay (450). It had negative results in all categories including the *S. typhimurium* Ames test with and without activation, mouse lymphoma with and without activation, sex-linked recessive mutations in Drosophila, and sister chromatid exchange in Chinese hamster ovary cells. Schumann et al. (458) did not find evidence of significant binding to hepatic DNA.

Other references cited by ATSDR (435) in its 1992 review give conflicting results, possibly due to impure samples or samples inhibited with epoxides. It is clear, however, that perchloroethylene is at most a weak mutagen.

11.4.1.5 Carcinogenesis Several studies of different types have been conducted on perchloroethylene, indicating that it has a low carcinogenic potential in mice, but not a definite effect in rats.

When perchloroethylene was fed by gavage at doses of approximately 1000 and 500 mg/kg/day to Osborne-Mendel rats and $B6C3F_1$ mice in the NCI bioassay program, hepatocellular carcinomas increased in mice but not in rats (447, 459). Toxic nephropathy was seen in both rats and mice.

Perchloroethylene was not active when tested for lung adenomas in Strain A cancer-susceptible mice (460). The mice were injected intraperitoneally with 80 mg/kg (14 injections), 200 mg/kg (24

injections), and 400 mg/kg (24 injections).

Van Duuren et al. (20) treated the skin of mice in different manners and did not produce cancer of the skin or of distant sites. Doses of 54 and 18 mg/kg were applied three times per week to the dorsal skin of mice. A dose of 163 mg/kg was applied in conjunction with a promoter (phorbal myristate acetate).

In a toxicological and carcinogenic study in which rats were exposed for 6 h/day for 12 months to 600 or 300 ppm perchloroethylene vapor and then kept for their lifetimes, there was no evidence of a tumorigenic response in either sex (457). Other criteria examined included body weights, mortality, hematologic data, urinalyses, clinical chemistry determinations, lymphocyte cytogenetics, terminal organ weights, and gross and histopathological changes, especially tumor incidence. An increase in mortality from the 5th to the 24th month of the study in male rats exposed to 600 ppm was the only deviation from controls that was considered related to exposure. The mortality increase was associated with an earlier onset of spontaneous advanced chronic renal disease.

Studies have been conducted to explain mechanistically the sensitivity of the $B6C3F_1$ mouse and the resistance of the rat to perchloroethylene-induced hepatocellular carcinoma (458). On the basis of body weight, mice activated perchloroethylene to a greater extent than rats, resulting in a greater degree of hepatic injury in the mouse. The authors suggested that the predominant mechanisms of tumorigenicity of perchloroethylene in the mouse was by recurrent hepatic cytotoxicity which enhanced the spontaneous incidence of hepatocellular carcinoma normally found in $B6C3F_1$ mice and not by direct interaction of perchloroethylene with hepatic DNA. They also suggested that the levels of perchloroethylene that protect against organ toxicity should be effective in preventing any tumorigenic risk of perchloroethylene to humans.

NTP (450) exposed rats to 0, 200, or 400 ppm and mice to 0, 100, or 200 ppm for 6 h/day, 5 days/week for 103 weeks. They concluded that

under the conditions of these 2-year inhalation studies, there was clear evidence of carcinogenicity of tetrachloroethylene for male F344/N rats as shown by an increased incidence of mononuclear cell leukemia. There was clear evidence of carcinogenicity for $B6C3F_1$ mice as shown by increased incidence of both hepatocellular adenomas and carcinomas in males and of hepatocellular carcinomas in females.

Because there was considerable tissue injury in the mouse liver and rat kidney and because the mononuclear cell leukemia is very common in the Fischer rat, there has been a considerable question about the significance of these data. The lack of or weak mutagenic activity in most test systems also supports a nongenetic mechanism for the production of tumors.

When exposed for only 10 consecutive days to 0, 100, 200, or 400 ppm (the same as the NTP study), rats were unaffected, but mice showed considerable evidence of liver injury, including peroxisomal proliferation (461). Likewise, Goldworthy et al. (462, 463) reported hyalin droplet formation in male rat kidneys, a finding often related to specific organ toxicity and carcinogenicity in male rats.

11.4.2 Human Experience Oral doses of about 60 to 86 mg/kg were given when perchloroethylene was used as an anthelmintic (434). Metabolism in humans is consistent with that found in rats and mice, but is slower. Most of the inhaled perchloroethylene is excreted unchanged over a relatively long period of time (432).

The older data on human exposure to perchloroethylene were summarized by von Oettingen (42) and

more recent data by NIOSH (454). As expected, numerous case reports give conflicting data.

Deaths probably due to anesthesia have occurred, but there is little documentation of the concentrations inhaled. In other cases, victims have been unconscious for hours and survived with no sequelae. In general, it appears that the following responses are possible: anesthesia ranging from slight inebriation to death, nausea, although less pronounced than carbon tetrachloride or ethylene dichloride; and headache, anorexia, and eye and nasal irritation. Liver injury following excessive subacute and chronic exposure has been reported in a few but not all subjects.

11.4.2.2.5 Carcinogenesis Perchloroethylene is considered a carcinogen in the latest annual report of the National Toxicology Program (467). The International Agency for Research on Cancer (IARC) considers perchloroethylene *probably carcinogenic to humans*, which they base on *sufficient evidence* in experimental animals and *limited evidence* in humans (286). NIOSH recommends treating perchloroethylene in the workplace as a *potential occupational carcinogen* (323, 397).

Two cohort studies have reported excesses of cancer of the esophagus, and relative risks were 2.1 and 2.6, respectively (409, 411). However, caution should be used in interpreting these results because of the lack of smoking and alcohol histories. Cervical cancers increased in two cohort studies, and relative risks were 1.7 and 3.2, respectively (409, 412). Blair et al. (409), Spirtas et al. (410), and Anttila et al. (412) found excesses of non-Hodgkin's lymphoma, and relative risks were 1.7, 3.2, and 3.8, respectively in three different cohort studies of workers exposed to perchloroethylene. One study found a significant excess of leukemia which appeared to be dose-related whether or not the latent period was considered (468). Hepatocellular adenomas and carcinomas in mice significantly increased in both sexes as did mononuclear-cell leukemia in rats of both sexes (450, 469).

Overall, perchloroethylene causes peripheral nervous system damage, liver injury, defects in memory, various CNS effects, esophageal cancer, non-Hodgkin's lymphoma, leukemia, and cervical cancer in humans. In animals, it has caused kidney and liver injury, as well as liver cancer and leukemia. Toxic effects from animal studies of perchloroethylene have been known since the early 1950s (430, 470), and since the early 1940s the ingestion of PCE by humans has been known to cause psychosis, vertigo, intoxication, giddiness, nausea, sleepiness, and unconsciousness (471–473).
11.5 Standards, Regulations, or Guidelines of Exposure
OSHA has a PEL of 100 ppm and a ceiling of 200 ppm, and a 300 ppm 5-min max peak in any 3 hours (474). NIOSH recommends treating tetrachloroethylene as a carcinogen (474).

The TLV recommended by the ACGIH is 25 ppm (170 mg/m^3). Perchloroethylene is classified as A3 (animal carcinogen).

The Biological Exposure Indices Committee of the ACGIH recommends a limit of 10 ppm perchloroethylene is end-exhaled air (1 ppm = 6-8 mg/m^3 at NTP).

Care should be taken to use these TLVs and BEIs only in the manner recommended by the committees. It is also desirable not to depend only on the BEIs but also to use air monitoring because brief, high exposures may produce unacceptable incoordination and yet result in acceptable BEIs. In view of the carcinogenic response in animals, human exposure should be carefully controlled to prevent possible liver and kidney injury.

Dibenzo-*p*-Dioxins: 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin

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Introduction

Dibenzo-*p*-dioxins are a class of compounds of which there are 75 possible isomers as shown in the following structure and Table 65.1. A recent IARC Monograph (1) summarizes much of the information on these compounds (Table 65.2) (2–4). By far, the majority of the information is for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic of the isomers. Most of the material in this chapter relates to this compound.

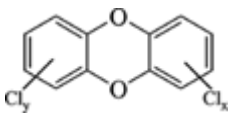

Table 65.1. Isomers of Dibenzo-*p*-Dioxins

Number of Cl Atoms	Number of Isomers
1	2
2	10
3	14
4[a]	22
5	14
6	10
7	2
8	1
Total	75

[a] The most important isomer is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

Dibenzo-*p*-Dioxins: 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin

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Halogenated Biphenyls

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1.0 Introduction

Polyhalogenated biphenyls are a family of compounds based on biphenyl as the parent compound. Chlorinated and brominated biphenyls have been manufactured for commercial purposes. There are 209 possible structural congeners of polychlorinated biphenyl (PCB) (1) and for polybrominated biphenyls (PBBs) the same number of congeners (2) can exist.

1.0.1 CAS Numbers

A listing of all PCB congeners is given in Table 66.1 along with their Chemical Abstract Services (CAS) Registry numbers an identifying numbering system (3). Table 66.2 contains synonyms and molecular structures of PCB congeners.

Table 66.1. Numbering of PCB Isomers and their CAS Numbers

Ballschmiter No.[a]	Structure[b]	CAS No.
Monochlorobiphenyls		
Molecular weight: 188.66		
Molecular formula: $C_{12}H_9Cl$		
1	2	[*2051-60-7*]
2	3	[*2051-61-8*]
3	4	[*2051-62-9*]
Dichlorobiphenyls		
Molecular weight: 223.10		
Molecular formula: $C_{12}H_8Cl_2$		
4	2,2'	[*13029-08-8*]
5	2,3	[*16605-91-7*]
6	2,3'	[*25569-80-6*]
7	2,4	[*33284-50-3*]
8	2,4'	[*34883-43-7*]
9	2,5	[*34882-39-1*]

10	2,6	[*33146-45-1*]
11	3,3'	[*2050-67-1*]
12	3,4	[*2974-92-7*]
13	3,4'	[*2974-90-5*]
14	3,5	[*34883-41-5*]
15	4,4'	[*2050-68-2*]

Trichlorobiphenyls

Molecular weight: 257.55

Molecular formula: $C_{12}H_7Cl_3$

16	2,2',3	[*38444-78-9*]
17	2,2',4	[*37680-66-3*]
18	2,2',5	[*37680-65-2*]
19	2,2',6	[*38444-73-4*]
20	2,3,3'	[*38444-84-7*]
21	2,3,4	[*55702-46-0*]
22	2,3,4'	[*38444-85-8*]
23	2,3,5	[*55720-44-0*]
24	2,3,6	[*55702-45-9*]
25	2,3',4	[*55712-37-3*]
26	2,3',5	[*38444-81-4*]
27	2,3',6	[*38444-76-7*]
28	2,4,4'	[*7012-37-5*]
29	2,4,5	[*15862-07-4*]
30	2,4,6	[*35693-92-6*]
31	2,4',5	[*16606-02-3*]
32	2,4',6	[*38444-77-8*]
33	2',3,4	[*38444-86-9*]
34	2',3,5	[*76708-77-5*]
35	3,3',4	[*55712-37-3*]
36	3,3',5	[*38444-87-0*]
37	3,4,4'	[*38444-90-5*]
38	3,4,5	[*53555-66-1*]
39	3,4',5	[*38444-88-1*]

Tetrachlorobiphenyls

Molecular weight: 291.99

Molecular formula: $C_{12}H_6Cl_4$

40	2,2',3,3'	[*38444-93-8*]
41	2,2',3,4	[*52663-59-9*]
42	2,2',3,4'	[*36559-22-5*]
43	2,2',3,5	[*70362-46-8*]
44	2,2',3,5'	[*41464-39-5*]
45	2,2',3,6	[*70362-45-7*]
46	2,2',3,6'	[*41464-47-5*]
47	2,2',4,4'	[*2437-79-8*]

48	2,2',4,5	[*70362-47-9*]
49	2,2',4,5'	[*41464-40-8*]
50	2,2',4,6	[*62796-65-0*]
51	2,2',4,6'	[*68194-04-7*]
52	2,2',5,5'	[*35693-99-3*]
53	2,2',5,6'	[*41464-41-9*]
54	2,2',6,6'	[*15968-05-5*]
55	2,3,3',4	[*74338-24-2*]
56	2,3,3',4'	[*41464-43-1*]
57	2,3,3',5	[*70424-67-8*]
58	2,3,3',5'	[*41464-49-7*]
59	2,3,3',6	[*74472-33-6*]
60	2,3,4,4'	[*33025-41-1*]
61	2,3,4,5	[*33284-53-6*]
62	2,3,4,6	[*54230-22-7*]
63	2,3,4',5	[*74472-34-7*]
64	2,3,4',6	[*52663-58-8*]
65	2,3,5,6	[*33284-54-7*]
66	2,3',4,4'	[*32598-10-0*]
67	2,3',4,5	[*73575-53-8*]
68	2,3',4,5'	[*73575-52-7*]
69	2,3',4,6	[*60233-24-1*]
70	2,3',4',5	[*32598-11-1*]
71	2,3',4',6	[*41464-46-4*]
72	2,3',5,5'	[*41464-42-0*]
73	2,3',5',6	[*74338-23-1*]
74	2,4,4',5	[*32690-93-0*]
75	2,4,4',6	[*32598-12-2*]
76	2',3,4,5	[*70362-48-0*]
77	3,3',4,4'	[*32598-13-3*]
78	3,3',4,5	[*70362-40-1*]
79	3,3',4,5'	[*41464-48-6*]
80	3,3',5,5'	[*33284-52-5*]
81	3,4,4',5	[*70362-50-4*]

Pentachlorobiphenyls

Molecular weight: 326.44

Molecular formula: $C_{12}H_5Cl_5$

82	2,2',3,3',4	[*52663-62-4*]
83	2,2',3,3',5	[*60145-20-2*]
84	2,2',3,3',6	[*52663-60-2*]
85	2,2',3,4,4'	[*65510-45-4*]
86	2,2',3,4,5	[*55312-69-1*]
87	2,2',3,4,5'	[*38380-02-8*]
88	2,2',3,4,6	[*55215-17-3*]

89	2,2',3,4,6'	[*73575-57-2*]
90	2,2',3,4',5	[*68194-07-0*]
91	2,2',3,4',6	[*68194-05-8*]
92	2,2',3,5,5'	[*52663-61-3*]
93	2,2',3,5,6	[*73575-56-1*]
94	2,2',3,5,6'	[*73575-55-0*]
95	2,2',3,5',6	[*38379-99-6*]
96	2,2',3,6,6'	[*73575-54-9*]
97	2,2',3',4,5	[*41464-51-1*]
98	2,2',3',4,6	[*60233-25-2*]
99	2,2',4,4',5	[*38380-01-7*]
100	2,2',4,4',6	[*39485-83-1*]
101	2,2',4,5,5'	[*37680-73-2*]
102	2,2',4,5,6'	[*68194-06-9*]
103	2,2',4,5',6	[*60145-21-3*]
104	2,2',4,6,6'	[*56558-16-8*]
105	2,3,3',4,4'	[*32598-14-4*]
106	2,3,3',4,5	[*70424-69-0*]
107	2,3,3',4',5	[*70424-68-9*]
108	2,3,3',4,5'	[*70362-41-3*]
109	2,3,3',4,6	[*74472-35-8*]
110	2,3,3',4',6	[*38300-03-9*]
111	2,3,3',5,5'	[*39635-32-0*]
112	2,3,3',5,6	[*74472-36-9*]
113	2,3,3',5',6	[*68194-10-5*]
114	2,3,4,4',5	[*74472-37-0*]
115	2,3,4,4',6	[*74472-38-1*]
116	2,3,4,5,6	[*18259-05-7*]
117	2,3,4',5,6	[*68194-11-6*]
118	2,3',4,4',5	[*31508-00-6*]
119	2,3',4,4',6	[*56558-17-9*]
120	2,3',4,5,5'	[*68194-12-7*]
121	2,3',4,5',6	[*56558-18-0*]
122	2',3,3',4,5	[*76842-07-4*]
123	2',3,4,4',5	[*65510-44-3*]
124	2',3,4,5,5'	[*70424-70-3*]
125	2',3,4,5,6'	[*74472-39-2*]
126	3,3',4,4',5	[*57465-28-8*]
127	3,3',4,5,5'	[*39635-33-1*]

Hexachlorobiphenyls

Molecular weight: 360.88

Molecular formula: $C_{12}H_4Cl_6$

128	2,2',3,3',4,4'	[*38380-07-3*]
129	2,2',3,3',4,5	[*55215-18-4*]

130	2,2',3,3',4,5'	[*52663-66-8*]
131	2,2',3,3',4,6	[*61798-70-7*]
132	2,2',3,3',4,6'	[*38380-05-1*]
133	2,2',3,3',5,5'	[*35694-04-3*]
134	2,2',3,3',5,6	[*52704-70-8*]
135	2,2',3,3',5,6'	[*52744-13-5*]
136	2,2',3,3',6,6'	[*38411-22-2*]
137	2,2',3,4,4',5	[*35694-06-5*]
138	2,2',3,4,4',5'	[*35065-28-2*]
139	2,2',3,4,4',6	[*56030-56-9*]
140	2,2',3,4,4',6'	[*59291-64-4*]
141	2,2',3,4,5,5'	[*52712-04-6*]
142	2,2',3,4,5,6	[*41411-61-4*]
143	2,2',3,4,5,6'	[*68194-15-0*]
144	2,2',3,4,5',6	[*68194-14-9*]
145	2,2',3,4,6,6'	[*74472-40-5*]
146	2,2',3,4',5,5'	[*51908-16-8*]
147	2,2',3,4',5,6	[*68194-13-8*]
148	2,2',3,4',5,6'	[*74472-41-6*]
149	2,2',3,4',5',6	[*38380-04-0*]
150	2,2',3,4',6,6'	[*68194-08-1*]
151	2,2',3,5,5',6	[*52663-63-5*]
152	2,2',3,5,6,6'	[*68194-09-2*]
153	2,2',4,4',5,5'	[*35065-27-1*]
154	2,2',4,4',5,6'	[*60145-22-4*]
155	2,2',4,4',6,6'	[*33979-03-2*]
156	2,3,3',4,4',5	[*38380-08-4*]
157	2,3,3',4,4',5'	[*69782-90-7*]
158	2,3,3',4,4',6	[*74472-42-7*]
159	2,3,3',4,5,5'	[*39635-35-3*]
160	2,3,3',4,5,6	[*41441-62-5*]
161	2,3,3',4,5',6	[*74472-43-8*]
162	2,3,3',4',5,5'	[*39635-34-2*]
163	2,3,3',4',5,6	[*74472-44-9*]
164	2,3,3',4',5',6	[*74472-45-0*]
165	2,3,3',5,5',6	[*74472-46-1*]
166	2,3,4,4',5,6	[*41411-63-6*]
167	2,3',4,4',5,5'	[*52663-72-6*]
168	2,3',4,4',5',6	[*59291-65-5*]
169	3,3',4,4',5,5'	[*32774-16-6*]

Heptachlorobiphenyls

Molecular weight: 395.33

Molecular formula: $C_{12}H_3Cl_7$

170	2,2',3,3',4,4',5	[*35065-30-6*]

171	2,2',3,3',4,4',6	[*52663-71-5*]
172	2,2',3,3',4,5,5'	[*52663-74-8*]
173	2,2',3,3',4,5,6	[*68194-16-1*]
174	2,2',3,3',4,5,6'	[*38411-25-5*]
175	2,2',3,3',4,5',6	[*40186-70-7*]
176	2,2',3,3',4,6,6'	[*52663-65-7*]
177	2,2',3,3',4',5,6	[*52663-70-4*]
178	2,2',3,3',5,5',6	[*52663-67-9*]
179	2,2',3,3',5,6,6'	[*52663-64-6*]
180	2,2',3,4,4',5,5'	[*35065-29-3*]
181	2,2',3,4,4',5,6	[*74472-47-2*]
182	2,2',3,4,4',5,6'	[*60145-23-5*]
183	2,2',3,4,4',5',6	[*52663-69-1*]
184	2,2',3,4,4',6,6',4',6	[*74472-48-3*]
185	2,2',3,4,5,5',6	[*52712-05-7*]
186	2,2',3,4,5,6,6'	[*74472-49-4*]
187	2,2',3,4',5,5',6	[*52663-68-0*]
188	2,2',3,4',5,6,6'	[*74487-85-7*]
189	2,3,3',4,4',5,5'	[*39635-31-9*]
190	2,3,3',4,4',5,6	[*41411-64-7*]
191	2,3,3',4,4',5',6	[*74472-50-7*]
192	2,3,3',4,5,5',6	[*69782-91-8*]
193	2,3,3',4',5,5',6	[*69782-91-8*]

Octachlorobiphenyls

Molecular weight: 429.77

Molecular formula: $C_{12}H_2Cl_8$

194	2,2',3,3',4,4',5,5'	[*35694-08-7*]
195	2,2',3,3',4,4',5,6	[*52663-78-2*]
196	2,2',3,3',4,4',5,6'	[*42740-50-1*]
197	2,2',3,3',4,4',6,6'	[*33091-17-7*]
198	2,2',3,3',4,5,5',6	[*68194-17-2*]
199	2,2',3,3',4,5,6,6'	[*52663-73-7*]
200	2,2',3,3',4,5',6,6'	[*40186-71-8*]
201	2,2',3,3',4,5,5',6'	[*52663-75-9*]
202	2,2',3,3',5,5',6,6'	[*2136-99-4*]
203	2,2',3,4,4',5,5',6	[*52663-76-0*]
204	2,2',3,4,4',5,6,6'	[*74472-52-9*]
205	2,3,3',4,4',5,5',6	[*74472-53-0*]

Nonachlorobiphenyls

Molecular weight: 464.22

Molecular formula: $C_{12}HC_9$

206	2,2',3,3',4,4',5,5',6	[*40186-72-9*]
207	2,2',3,3',4,4',5,6,6'	[*52663-79-3*]
208	2,2',3,3',4,5,5',6,6'	[*5121-88-0*]

	Decachlorobiphenyl	
209		2,2',3,3',4,4',5,5',6,6' [*2015-24-3*]

[a] From Ref. 3.
[b] See Table 66.2 for synonyms and molecular structure. Compounds identified by Ballschmiter number.

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Halogenated Benzenes

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A. Introduction

This group of chemicals is derived through substitutions of chlorine for hydrogen atoms on the benzene ring. The toxicological properties of chlorinated benzenes differ substantially from benzene in that they lack the hematological toxicity and leukemogenic activity that have been associated with benzene. The compounds have an aromatic odor with lower volatilities, higher densities, and lower flammabilities than the parent compound benzene. Some of the settings in which exposures may be encountered are in manufacturing sites, home and public areas where deodorants or disinfectants are present, and in the applications of the materials as fumigants, insecticides, lacquers, paints, and seed disinfection products.

Because a substantial number of studies have focused on comparative evaluations of compounds in this chemical group, the results of these investigations are presented below prior to detailed discussions of individual compounds. In addition, a summary of various regulatory classifications of these compounds is provided.

Comparative Toxicological Properties of Chlorobenzenes

According to a Chemical Manufacturers Association (CMA) Technical Report (1), consistently observed signs of acute intoxication vary with the route of administration and the degree of exposure. Varshavskaya (2) reported the following effects for chlorobenzene and *o*- and *p*-dichlorobenzenes (DCB) in mice, rats, and guinea pigs: hyperemia of the visible mucous membranes, increased salivation and lacrimation, and initial excitation followed by drowsiness, adynamia, ataxia, paraparesis, paraplegia, and dyspnea. Induced mortality, which usually occurs within 3 days, results from respiratory paralysis. Changes revealed by gross postmortem examination may include hypertrophy and necrosis of the liver and submucosal hemorrhages in the stomach. Histologically disclosed changes are edema of the brain and necrosis of the centrobular region of the liver, the proximal convoluted tubules of the kidneys, the bronchial and bronchiolar epithelium of the lungs, and the stomach mucosa. The liver generally showed the most severe damage.

Table 67.1 (3) presents data on the acute oral toxicity of mono- and dichlorobenzenes in rodents. This information suggests greater toxicity for *o*-DCB relative to the other compounds in three of four animal species tested. The basis for this observation may lie within the differences seen for the metabolism of these compounds, and the formation of a more reactive metabolite for the *ortho*-substituted chemical (discussed further below).

Table 67.1. Oral LD_{50} for Chlorobenzenes (3)

	LD_{50} (Mg/kg body weight)		
Species	**Chlorobenzene**	***o*-Dichlorobenzene**	***p*-Dichlorobenzene**
White mice	1145	2000	3220
White rats	2390	2138	2512
Rabbits	2250	1875	2812
Guinea pigs	5060	3375	7595

The acute effects of intraperitoneal dosing of a series of chlorinated benzenes (mono-, di-, tri-, tetra-, and penta-substituted) were assessed in rats (4). Following single doses at levels in excess of 100 mg/kg, animals were monitored for evidence of liver, kidney, and thyroid effects. The 1,2-di-, 1,2,4-tri-, and 1,2,4,5-tetrachlorobenzenes were most toxic in terms of body weight losses over 3 days. Liver function enzyme levels [alanine aminotransferase (ALT)] were significantly elevated, as were microscopic signs of cellular damage following treatments with 225 and 450 mg/kg of the monochloro compound, ≥150 mg/kg of 1,2-dichlorobenzene, and ≥185 mg/kg and above of 1,2,4-trichlorobenzene. Kidney changes included protein droplet nephropathy for the 1,4 dichloro and the more highly substituted compounds. Serum thyroxine (T4) levels were suppressed at the lowest doses administered (1 mmol/kg) for the 1,2-dichloro and the higher-substituted benzenes. The greatest activity was seen for the tri and penta compounds. This activity appears to depend on formation of phenolic metabolites, which were shown to have the capacity to displace T4 from serum binding proteins in the rat. Alternatively, enhanced metabolic deiodination of T4 may result from induction of hepatic enzymes by the chlorinated benzene compounds. The precise mechanism for this phenomenon has not yet been established.

Hepatotoxicity evaluations of the three dichlorobenzene isomers (*ortho*, *meta*, *para*) were made following intraperitoneal injection into Sprague–Dawley and F344 male rats (5). Liver effects were monitored using plasma ALT levels, microscopic observations, liver nonprotein sulfhydryl (NPSH) concentration, and ^{14}C-DCB binding to liver proteins. One day following a dose of 132 mg/kg of each isomer, ALT levels were increased for *o*-DCB only. As dose levels were increased up to 5 times, *p*-DCB exhibited no activity in this assay, whereas *m*-DCB induced a weak response beginning at 264 mg/kg. Test chemical binding to proteins paralleled this liver response. Results for phenobarbital-pretreated rats indicated that liver enzyme induction was associated with the hepatotoxity of the *ortho* and *meta* isomers but not the *para* isomer. Further evidence of enzyme mediation in the hepatotoxic mechanism was found when SKF-525A (a cytochrome P450 enzyme inhibiter) blocked the response of the *ortho* and *meta* isomers. NPSH levels were depressed relative to controls following dosing of *ortho* and *meta* isomer dosing, but the para isomer did not cause any change in this parameter. The authors concluded that the relative hepatotoxicity of dichlorobenzene isomers is *o*- > *m*- ≫ *p*-, and that oxidative biotransformation plays an important role in this activities of these chemicals.

Carcinogenicity of Chlorinated Benzenes

The carcinogenic potentials of many of the chlorobenzenes have been assessed in animal studies. Table 67.2 (6–13) summarizes these findings.

Table 67.2. Results of Carcinogenesis Bioassays in Rodents Following Administration and Chlorinated Benzenes

	Tumors In

Compound	Mice	Rats	Dose (mg/kg)	Ref.
MCB	None	Liver nodules (males)	60, 120 oral 30, 60 (male mice)	6
o-DCB	None	None	60, 120 (gavage)	7
p-DCB	Liver	Males—kidney	150, 300—male rats 300, 600—others oral	8
	None	None	75,500 ppm inhaln. 5 hr/day, 5 days/week, 57 weeks—mice; 78 weeks—rat	9
HCB	Liver	Liver, males—kidney	6–24 mg/kg daily (diet)	10, 11
	Liver, thyroid, angiosarcomas	(Hamsters)	4–16 mg/kg daily	12, 13

The findings for monochlorobenzene (MCB) were negative in mice whereas benign liver tumors were induced in rats. *o*-DCB did not induce rodent tumors in this bioassay. *p*-DCB was shown to be carcinogenic in both rodent species in oral gavage studies, but the results were negative in inhalation tests. Owing to the relatively short periods of exposure in the latter study compared to the conventional 100+ weeks, the results may be considered equivocal. Hexachlorobenzene (HCB) has been demonstrated to induce tumors in multiple species in multiple organs. These results have contributed to the higher suspicion of carcinogenic potential for HCB compared to other chlorinated benzenes (see Table 67.3).

Table 67.3. Cancer Classifications for Chlorobenzenes

Chemical	USEPA (26)	IARC (27)	NTP (28)	ACGIH (29)
Chlorobenzene	D[a]	—	—	—
o-Dichlorobenzene	—	3[a]	—	—
p-Dichlorobenzene	C[b]	2B[d]	+[e]	—
Tri-, tetra-, pentachlorobenzenes	—	—	—	—
Hexachlorobenzene	B2[c]	2B[d]	+[e]	—

[a] Not classifiable as to carcinogenicity in humans.
[b] Possible human carcinogen.
[d] Possibly carcinogenic to humans.
[e] Reasonably anticipated to be carcinogenic to humans.
[c] Probable human carcinogen (no human evidence).

The chlorobenzene class of compounds is devoid of significant evidence of genetic toxicity (14). MCB and *o*-DCB are the two members of the class most likely to form expoxides, which renders

suspect genotoxic activities. However, MCB was negative in bacterial and *Aspergillus* gene mutation tests and in rat hepatic DNA repair assays but weakly positive in a mouse micronucleus assessment (15). The mutagenicity literature for *o*-DCB indicates some activity in higher plants but no effects in *Salmonella*, *Escherichia coli*, or yeast (16). *p*-DCB literature (17) indicates that the compound lacks genotoxic activity in bacteria, hepatic DNA repair assays, mouse lymphoma cells, tests for chromosomal aberrations in lymphocytes, Chinese hamster ovary (CHO) cells, and rat and mouse bone marrow cells. This compound did induce chromosomal changes in various higher plant assays, although human health implications have not been established (see further discussion for *p*-DCB below). HCB has been shown to be devoid of genotoxic activities in *Salmonella* gene mutation and rat dominant lethal testing (18). This lack of genetic activity suggests that alternative mechanisms of action (nongenotoxic) for the tumorigenic members of the class need to be considered.

Because of the induction of kidney tumors by *p*-DCB and HCB, these chemicals as well as other chlorobenzenes were investigated for evidence of a protein-mediated mechanism that is known to operate for numerous chemicals, including unleaded gasoline and *d*-limonene. It was discovered that both *p*-DCB (19) and HCB (20) induced a male rat–specific protein that causes increased kidney cell turnover and necrosis (sometimes referred to as *hyalin droplet nephropathy*) with kidney tumor formation a long-term outcome of this chronic injury. The implication of these findings is that kidney tumors formed in this manner have no relevance to human risk assessments because the protein (a_{2u}-globulin) responsible for the adverse effects in the kidney is unique to male rats. This concept is now recognized in certain regulatory agencies (21). Evaluations of other agents have been performed for this protein-induction activity, and results indicate that the 1,3,5 (22) and 1,2,4 (23) trichlorobenzenes, 1,2,4,5-tetrachlorobenzene (24), and pentachlorobenzene (25) are active. However, the actual carcinogenic potentials of these chemicals have not been determined in long-term bioassays.

The U.S. Environmental Protection Agency (USEPA) and Occupational Safety and Health Administration (OSHA) regulate various chlorobenzenes as pesticides, as potential pollutants of air and water, or as workplace contaminants. These agencies as well as other nonregulatory bodies [International Agency for Research in Cancer (IARC), National Toxicology Program (NTP), American Conference of Governmental Industrial Hygienists (ACGIH)] issue classifications that are intended to indicate the level of evidence for carcinogenic potentials in humans (based on animal data) for each of these chemicals. These classifications are presented in Table 67.3 (26–29).

The precise relevance to human health of tumor findings in animal studies is a topic that continues to be actively debated. Although there is no substantive evidence that any of the chlorobenzenes have induced cancer in humans, positive results in animals indicate a need for awareness that exposure to these materials should be kept to a minimum.

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B. Halogenated Benzenes

Table 67.4. Excretion and Distribution of Radioactive Metabolites from Orally Administered [^{14}C]-Chlorobenzene in Rabbits[a] (51)

	% of Dose

Urine	19.6
Feces	
Methanol extract	1.05
Dry burn	1.55
Tissues (one animal)	0.053

[a] Combined total urinary, carcass, and fecal ^{14}C collected during 4 days dosing and 3 subsequent days. Total dose = 8.28 g.

Table 67.5. Distribution of RadioactiveMetabolites in Urine of Rabbits Dosed Orally with ^{14}C-Chlorobenzene (51)

Metabolite	% of Total Urinary Radioactivity
3,4-Dihydro-3,4-dihydroxychlorobenzene	0.57
Monophenols	2.84
Diphenols	4.17
Mercapturic acids	23.80
Ethereal sulfates	33.88
Glucuronides	33.57
Total	98.83

Table 67.6. Subchronic Toxicities of Hexachlorobenzene[a]

Species	Dose	Test Duration	Effects Observed
Rats	2 mg/kg/day	13 days	No toxic effects
	6 mg/kg/day	13 days	Skin twitching and nervousness
	20 mg/kg/day	13 days	Neurotoxic symptoms; increase in liver weight
	60, 200 mg/kg/day	13 days	Neurotoxic symptoms; increase in liver and kidney weights
Rats	10 mg/kg/day	30 days	No toxic effects
	30, 65 mg/kg/day	30 days	Increase in feed consumptions/body weight gains; increased urinary coproporphyrin; increase in liver/body weight ratio
	100 mg/kg/day	30 days	Same as at 30 mg/kg/day plus elevated excretion of uroporphyrin
Rats	100 mg/kg/day	51 days	13/33 deaths in 1 months; neurotoxic symptoms; increased liver weight;

			porphyria
Rats	300 mg/kg/day	10 days	30% mortality
	150 mg/kg/day	30 days	60% mortality
	50 mg/kg/day	30 day	30% mortality
Male rats	0.2%	12 weeks	Retardation in weight gain; prophyria; degenerative changes in liver
Rats	0.025 mg/kg/day[b]	4–8 months	No toxic symptoms; possible effect on conditioned reflexes
Guinea pigs	0.5%	8–10 days	Marked neurological symptoms
Mice	0.5%	8–10 days	Marked neurological symptoms
Rabbits	0.5%	6 weeks	Increase in urinary porphyrins
	0.5%	8–12 weeks	Mortalities
Japanese quail	1 ppm	90 days	No toxic effects
	5 ppm	90 days	Slight increase in liver weight; slight porphyria
	20 ppm	90 days	Increased liver weight, decreased egg production; porphyria; liver/kidney pathological changes
	80 ppm	90 days	5/15 deaths (18- to 62-day period); neurotoxic symptoms; porphyria; increased liver weight; decreased egg production and hatchability; liver/kidney pathological changes.
Japanese quail	500, 2500 ppm	30 days	All 12 died in 30 days
	100 ppm	3 months	Mortality (1/12 on 20th day, 10 within 7 weeks 1 in 10 weeks); one surviving cock showed marked loss of weight; necrosis of liver cells and porphyria
Chickens	120–480 ppm	3 months	No toxic effects

[a] This table was prepared by C. E. Mumma and E. W. Lawless for the EPA (119) and is based on information from a 1975 report by the National Academy of Sciences (120). The route is oral (in diet) unless otherwise indicated.
[b] Administered in water.

9.0 Other Halogenated Benzene Compounds

o-, *m*-, and *p*-dibromobenzene
Tri- and tetrabromobenzenes
1,2-, 1,3-, 1,4-bromochlorobenzene
2,4- and 3,5-dibromochlorobenzene
o-, *m*-, and *p*-bromofluorobenzene
2,4- and 3,4-dibromofluorobenzene
o-, *m*-, and *p*-bromotoluene
o-, *m*-, and *p*-bromophenol

9.1 Chemical and Physical Properties
A potential source of information is the Material Safety Data Sheets from the suppliers of these chemicals. Further data may be available from the chemical literature.
9.2 Production and Use
Many halogenated benzene chemicals are manufactured and sold, but only in small amounts (<1 million lb) relative to those for the lower chlorinated benzenes. These materials are sold for the manufacture of specialty products (e.g., pharmaceuticals, agricultural chemicals, high performance polymers).

Virtually no data have been published on the health effects of these chemicals. Producers may have information that is unpublished.

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Organic Chlorofluoro Hydrocarbons
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A. Introduction

The chlorofluorocarbons (CFCs) were introduced in the 1930s as “safe” replacements for refrigerants such as sulfur dioxide, ammonia, carbon tetrachloride, and chloroform. In World War II, they were used to produce insecticide aerosols to protect the troops in tropical areas against malaria and other insectborne diseases. During the next 40–50 years, the number and type of applications expanded to include foam blowing, precision cleaning, and propellants for medicinal, cosmetic, and general-purpose aerosols, air conditioning, and refrigeration. These uses eventually resulted in emission of the CFCs into the atmosphere. Because of their low chemical reactivity, they typically

have long atmospheric residence times, and as a consequence, they are distributed globally (Table 68.1) (1–12).

Table 68.1. Ozone-Depletion Potential (ODP), Atmospheric Lifetime, years (AL), and Greenhouse Warming Potential (GWP) for Various Chlorofluorocarbons, Hydrochlorofluorocarbons, and Hydrofluorocarbons

			GWP Relative to		
Substance	ODP	AL years	CFC 11	CO_2 (100 yr)	References
CFC 11		65			1, 2
	1.0	60	1.0	4000 (230 yr)	
CFC 12	1.0	102		8100	1, 3, 5
		110	3.1		
	0.82–1.0				
CFC 13	No data				
CFC 112	No data				
CFC 112a	No data				
CFC 113		90			3, 4, 4a
	0.9–0.8	90	1.3–1.4		
CFC 113a	No data				
CFC 114	0.85–1.0	200	3.7–4.1		3, 4a
CFC 114a	No data				
CFC 115	0.30–0.50	380			1, 3, 4a
	0.40–0.60	400	7.4–7.6		
HCFC 21		2			5
HCFC 22	0.05	15	0.1	1500	3, 4, 4a
			0.32–0.37		
HCFC 123	0.012–0.02	1.4	0.02		3, 4a
		1.6	0.017–0.02		
HCFC 124	0.022	6.6	0.10		4, 6
HCFC 132b	0.025	4			7
HCFC 133a	No data				
HCFC 141b	0.10–0.12	10.8	0.12	600	3, 4, 4a, 8, 9
	0.07–0.11	7.8	0.087–0.097		
HCFC 142b	0.05–0.06	18.4	0.34–0.39	1800	5
HFC 32	0	6	0.13	580	10, 11
HFC 125	0	40.7	0.84	3400	4a, 6, 12

		28.1	0.51–0.65		
HFC 134a	0	14	0.3		4a, 9, 10
		15	0.24–0.29		
HFC 152a	0	1.7	0.026–0.033		4a
HFC 245fa	0	8.4		790	Personal communication

In 1974 Molina and Rowland (13) hypothesized that, once the CFCs reach the stratosphere, they will undergo breakdown to release chlorine atoms. The chlorine atoms could then react with the stratospheric ozone breaking it down into oxygen (Fig. 68.1). Since the stratospheric ozone absorbed much of the sun's ultraviolet b radiation (UVB), decreased ozone levels would lead to increases in ground-level UVB (14). This could affect crop growth and lead to increases in cataracts and nonmelanoma skin cancers. Following reports of a marked drop in column ozone over Antarctica (the "ozone hole") during the Antarctic winter, in 1987 most of the nations of the world drafted and signed an agreement calling for the phaseout of CFCs. This agreement is known as the *Montreal Protocol*.

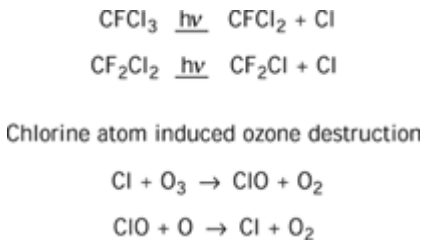


Figure 68.1. Stratospheric breakdown of CFCs 11 and 12.

Development was initiated on two types of "in-kind" replacements (15–17). The first were the hydrochlorofluorocarbons (HCFCs) and the second were the hydrofluorocarbons (HFCs). Both contain hydrogen and are susceptible to attack by hydroxyl radicals present in the atmosphere. Therefore, they have a shorter atmospheric lifetime and either are not transported to the stratosphere or are transported there only in small amounts. The HCFCs contain chlorine and are still capable of causing ozone depletion, although, since their atmospheric lifetimes are short, their ozone-depleting potential (ODP) is lower than those associated with the CFCs. The HFCs do not contain chlorine (or bromine, also associated with ozone depletion). They, therefore, do not cause ozone depletion. A ranking scale has been developed using CFC11 as the reference compound, with an assigned value of 1. These values are also presented in Table 68.1.

A second concern, regarding both CFCs and their replacements, is that they are greenhouse warming gases. They, along with other substances such as carbon dioxide, trap the sun's infrared radiation and convert it to heat. However, they are also good insulating materials, and frequently their use as foam blowing agents in refrigeration equipment can lead to considerable energy savings, reducing carbon dioxide emissions. The greenhouse warming potentials (GWPs) for many of the CFCs, HCFCs, and HFCs are given in Table 68.1.

Many methods have been developed for atmospheric monitoring of these substances. For low level determinations, frequently a preconcentrating step is employed first, then the collected material is eluted into a gas chromatograph using either an electron capture detector or high resolution mass spectrometry (Brunner) (18, 19). Collection materials include cold, activated carbon (20), cold, activated carbon plus Tenax-TA (21), porous glass beads (22), sorption on cold SE-30/glass wool (23), or sorption on cold OV-101 (24, 25) all followed by gas chromatography (GC) with an electron

capture detector. These methods are reported to have a detection level of 1 part per trillion (ppt). Sorption on cold activated charcoal coupled with GC and high resolution mass spectroscopy has a detection limit of 2.6 ppt (26). Sensitivity without precollection is much lower, frequently in the range of 50–100 ppb (27, 28) although with an electron capture detector it reportedly can reach 5–10 ppt (29–31). For higher levels, sorption on silica gel followed by GC with a flame ionization detector has been used (32) or direct chromatography with flame ionization detection (33, 34). Methods have also been developed to measure low levels in water (35).

Because of their widespread use and concerns about their environmental effects and health effects, several reviews have been written on these materials, such as the IPCS monograph on the fully halogenated chlorofluorocarbons (36), the IPCS monograph on the partially hydrogenated chlorofluorocarbons (37), the review of the alternate fluorocarbons by Dekant (15), the detailed discussion on CFC 11 written by Aviado in the last edition of this book (38), and the series of Joint Assessment of Commodity Chemicals monographs published by ECETOC on HCFC 22, HFC 32, HCFC 123, HCFC 124, HFC 125,HCFC 132b, HCFC 133a, HFC 134a, and HCFC 141b.

From the reviews as well as the data presented later in this chapter, it can be seen that many of these chemicals are not highly toxic. Some, in fact, do not show significant signs of toxicity at air exposure levels up to a few percent or even over 5 or 10%. The most typical response seen following overexposure is CNS depression related to the anesthetic properties of many of these chemicals. Also, some have caused hepatotoxicity and occasionally reproductive effects. In the 1960s, it was discovered that inhalation of the vapors of some of the CFCs could produce a “high.” This was a preanesthetic effect associated with central nervous system (CNS) depression. Some individuals, typically teenagers, would spray substances containing CFC propellants into a bag and then take several deep breaths of the vapor. The products associated with this abuse included fry pan vegetable oil sprays, aerosol deodorants and hairsprays, and glass chiller sprays. The propellants most often involved were blends of CFCs 11 and 12, although nonchlorofluorocarbon substances such as toluene, benzene, and gasoline were also implicated (39–41). Occasionally one of the individuals would show a short period of excitement and then collapse and die. Autopsy generally was unremarkable. Death was attributed to cardiac arrhythmia resulting from sensitization of the heart to catechol amines (42). In all, some 65 deaths were attributed to this CFC “sniffing.” Although rare, a few cases of death have been reported for people using metered dose inhalants for asthma (43). In these cases, it could not be determined whether death was due to the propellant or a sympathomimetic agent. It did appear that the inhalant had been overused. Occupationally, there were also reports of a few accidental deaths attributed to overexposure to CFCs, most typically CFC 113. The pattern was similar to that reported in the abusive “sniffing” situations. An individual was working in a confined area where large quantities of CFC 113 were present. In such cases, the individual is overexposed for a fairly short time, collapses, and develops a rapid heartbeat, which can lead to cardiac arrhythmia and possibly death (44). Several approaches using mice (45, 46), monkeys (47), rabbits (48), and dogs (49) have been evaluated; however, the protocol that involves exposure of dogs to test a compound under conditions designed to simulate stress, while monitoring cardiac function, has provided good comparative information. This protocol was developed in the late 1960s and early 1970s (42, 50–52) and has recently been reviewed (399). The protocol involves training a group of dogs to calmly accept the procedure for several days prior to the exposure. On the day of the exposure, each dog is exposed individually. The dog is placed in a sling and the snout-only exposure mask and EKG leads are attached. After 2 min, the dog is given an injection of epinephrine (adrenaline) of 4–12 mg/kg. An amount that has previously been determined to be just below that necessary to produce a spontaneous arrhythmia. The animal is observed for 5 min. If no arrhythmias are produced, the exposure is initiated. After 5 min of exposure, the dog is given a second injection of epinephrine and the exposure is continued for another 5 min with EKG monitoring for ventricular fibrillations or cardiac arrhythmias. The test is concluded at that point. Each dog will receive multiple exposures, each separated by at least one week. The study should be designed to allow for the determination of a no-observed-effect level (NOEL), a threshold, and the EC_{50} as median effect concentration. The two most important values are the NOEL and threshold. The level of epinephrine

used represents approximately 10 times the level seen in people under stress; this makes the test highly sensitive. In fact, the NOEL determined in this test is well below the minimum exposure level required to induce cardiac effects in humans or animals resulting solely from a combination of stress and exposure. This has been demonstrated using CFC 113 as an example. For CFC 113, with injections of epinephrine, the highest NOEL was 2500 ppm and the threshold was 5000 ppm (52). When 12 dogs were exposed to 2000 ppm for 6 h and then given and injection of epinephrine, only one developed an arrhythmia. When dogs were exposed to concentrations of ≤ 12,000 ppm and frightened by electric shock or a loud noise, none developed an arrhythmia. Likewise, when dogs were exercised on a treadmill and exposed to 20,000 ppm of CFC 113, none developed an arrhythmia (50). No arrhythmias were seen in monkeys exposed to 50,000 ppm or in mice exposed to 100,000 ppm of CFC 113 without injections of epinephrine or other stressers (125). All of these studies demonstrate the sensitivity of the protocol design in determining the potential for exposure to a chemical to induce cardiac effect. A comparison of the dogs given an injection of epinephrine to those exercising on the treadmill indicates at least an eightfold difference in thresholds. If the comparison is made to monkeys not under stress, the difference is at least 20-fold. Finally, with HCFC 142b, in conjuction with epinephrine, arrhythmias were seen in all 12 dogs exposed to 100,000 ppm. Without epinephrine, exposures of 800,000 ppm of HCFC 142b caused only a marked response in one of the dogs. When the dogs were exposed to 800,000 ppm of HCFC 142b and startled with a noise, but not given epinephrine, only 42% gave a marked response (42).

On the following pages, each compound is discussed individually. They have been divided into three general areas: chlorofluorocarbons, hydrochlorofluorocarbons, and hydrofluorocarbons.

Organic Chlorofluoro Hydrocarbons
George M. Rusch, Ph.D., DABT, FATS

B. Chlorofluorocarbons
1.0 Trichlorofluoromethane
1.0.1 CAS Number: [*75-69-4*]

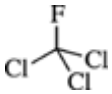
1.0.2 Synonyms: CFC 11, R-11, fluorotrichloromethane, F-11, Halocarbon 11, Fluorocarbon 11, Freon-11, Frigen 11, Fluorocarbon no. 11, FC 11, Halon 11, Propellent 11, Trichlorofluoromethane (Monofluorotrichloromethane)

1.0.3 Trade Names: Algofrene 11, Isceon 11, Forane 11, Arcton 11, AF 11, Genetron 11, Freon® 11, Freon® MF (solvent), Arcton 9, Genetron 11, Isceon 131, Isotron 11, Ledon 11, Aigofrene type 1, Electro-cf 11; Eskimon 11, Kaltron 11, Khaladon 11

1.0.4 Molecular Weight: 137.38

1.0.5 Molecular Formula: CCl_3F

1.0.6 Molecular Structure:



1.1 Chemical and Physical Properties
1.1.1 General (36)

Physical form	Liquid
Color	Colorless
Boiling point at 101.3 kP_a	23.8°C
Freezing point	–111°C
Specific gravity	1.494 @ 17.2°C
Vapor density	5.86 g/L
Vapor pressure	690 torr at 20°C
Solubility in water	0.11 g/L
log P_{ow}	2.53
Limit of flammability	Nonflammable

1.1.2 Odor and Warning Properties CFC 11 has a light ethereal odor with poor warning properties.

Organic Chlorofluoro Hydrocarbons
George M. Rusch, Ph.D., DABT, FATS

C. Hydrochlorofluorocarbons
11.0 Dichlorofluoromethane
11.0.1 CAS Number: [*75-43-4*]

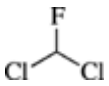
11.0.2 Synonyms: HCFC 21, F-21, R-21, dichloromonofluoromethane, refrigerant R21, freon 21, fluorodichloromethane, R-21

11.0.3 Trade Names: Genetron 21, AF-21, Freon® 21

11.0.4 Molecular Weight: 102.92

11.0.5 Molecular Formula: $CHCl_2F$

11.0.6 Molecular Structure:



11.1 Chemical and Physical Properties
11.1.1 General (7, 117)

Physical form	Gas
Color	Colorless
Boiling point at 101.3 kP_a	8.9°C
Freezing point	–135°C
Specific gravity	1.405 at 9°C
Liquid density at 9°C	1.405
Vapor density (air = 1)	Data not available

Vapor pressure at 25°C	Data not available
Solubility in water at 25°C	9.5 g/L
log P_{ow}	Data not available
Limit of flammability	Not flammable

11.1.2 Odor and Warning Properties Dichlorofluoromethane is almost odorless with poor warning properties.

Organic Chlorofluoro Hydrocarbons
George M. Rusch, Ph.D., DABT, FATS

D. Hydrofluorocarbons
19.0 Difluoromethane
19.0.1 CAS Number: [*75-10-5*]

19.0.2 Synonyms: HFC 32, R-32, HFA 32

19.0.3 Trade Names: Ecoloace 32, Forane 32, Asahiklin 32, Genetron 32; Meforex 32; Klea 32

19.0.4 Molecular Weight: 52.024

19.0.5 Molecular Formula: CH_2F_2

19.0.6 Molecular Structure:

19.1 Chemical and Physical Properties
19.1.1 General (336)

Physical form	Gas
Color	Colorless
Boiling point at 101.3 kP_a	–51.7°C
Freezing point	–136°C
Liquid density at 20°C	1.1 g/mL
Vapor density (air = 1)	1.8
Vapor pressure at 25°C	1670 kP_a
Solubility in water at 25°C	4.4 g/L
log P_{ow}	0.21
Limit of Flammability	lower, % v/v: 13.6
	upper, % v/v: 32.2

19.1.2 Odor and Warning Properties Difluoromethane is odorless or has a light ethereal odor with poor warning properties.

Organic Chlorofluoro Hydrocarbons

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Miscellaneous Chlorinated Hydrocarbon Pesticides
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A. Introduction

This chapter presents information on two structurally and toxicologically different classes of chlorinated pesticides: the organochlorine insecticides and the herbicide 2,4-dichlorophenoxyacetic acid (2,4D). The first group described, the chlorinated hydrocarbon insecticides, belong to a structural class containing only carbon, hydrogen and chlorine. This pesticide group has dramatically decreased in use and fallen into regulatory disfavor because, in general, its structural properties promote both persistence in the environment and bioaccumulation within the food chain. In contrast the herbicide 2,4D contains carbon, hydrogen, chlorine, and oxygen, and is a widely used herbicide with environmental and toxicological properties distinctly different from the organochlorine insecticides.

The organochlorine insecticides represent the first group of synthetic compounds to have a significant impact on the control of infectious diseases transmitted via insect vectors. These insecticides were used extensively in the United States and other Western countries, and are still used in Third World regions as both agricultural insecticides and agents to combat such vectorborne

diseases as malaria, typhus, plague, Chagas' disease, yellow fever, dengue, encephalitis, filariasis, and African trypanosomiasis (sleeping sickness) (1). Of these insecticides, DDT (dichlorodiphenyltrichloroethane) is credited as the primary compound that, for the first time in history, brought epidemics of malaria, typhus, and plague to a complete stop. DDT was introduced in 1943, with related insecticides following shortly thereafter. This chemical is still used extensively in tropical regions to combat malarial mosquitoes, and substitution of this pesticide with others such as malathion would be most expensive.

From 1950 to 1972, the U.S. production of DDT in 1000-kg units equaled 1,204,700. The production of the aldrin–toxaphene group (aldrin, chlordane, dieldrin, endrin, heptachlor, toxaphene) during 1952–1972 totaled $865{,}600 \times 10^3$-kg units; a total of $41{,}500 \times 10^3$-kg units of benzene hexachloride (lindane) was manufactured in the United States from 1950 to 1963. Of these quantities, approximately 50% of the DDT and 80 percent of the aldrin–toxaphene group were used in the United States (2, 3).

One attribute that contributes to the effectiveness of this chemical class is the persistence in the environment, providing not only an immediate impact on insect populations but also a prolonged insecticidal presence extending well beyond the time of application. This persistence is now generally considered an undesirable feature owing to findings suggesting delayed adverse impacts on nontarget populations of insects as well as birds. In addition, increased cancer risks for humans are alleged to result from exposures to these chemicals such as those resulting from pesticide applications and ingestion of contaminated fish and other food species. Although the actual balance of risks versus benefits associated with the use of these insecticides is debated, regulatory action has virtually eliminated their use in the United States and other western countries. Table 69.1 summarizes the regulatory status of these products (4, 5).

Table 69.1. Regulatory Standings of Chlorinated Hydrocarbon Insectides (4, 5)

Chemical	U.S. Registration	Foreign Use
Aldrin/dieldrin	EPA canceled all products	Yes
Chlordane/heptachlor	Voluntarily canceled; use for fire ants in power transformers, existing stocks for termites in homeowners' possession allowed; may reinstate for termite use pending finding of air monitoring tests	Use in termite control, some agricultural applications
DDT	Canceled all products	Yes
Endrin	Voluntary cancellation, all products	Unknown
Kepone	Canceled all products	Unknown
Lindane	Restricted uses (plant nurseries, pet shampoos, livestock sprays, seed treatment, household sprays, flea collars, hardwood logs, etc.); avocados, pecans are only food crop use allowed	Yes
Mirex	Canceled all products; existing stocks used for ants on pineapples in Hawaii	Unknown
Toxaphene	All products canceled; existing stocks use allowed for cattle dip, pineapples	Unknown

	in Puerto Rico, bananas in Virgin Islands, emergency use on corn, cotton, small grains

The persistence of these insecticides in the environment and their prolonged activity against pests following application can be attributed to a combination of their insolubility in water and high solubility in fats, absorption and adsorption onto particulate matter, and resistance to chemical, physical, and microbiological degradation. From target crops and surrounding soil and water, these compounds have entered the food chains of mammals, birds, fishes, and other animal species. DDT in particular was implicated in inducing acute and perhaps chronic insecticide intoxications in fish and birds as a result of bioaccumulation. In 1970, at the height of insecticidal use in the United States, Canada, and European countries, significant decreases in eggshell thickness were found in 15 of 22 species of aquatic birds, particularly in those feeding in fresh and brackish waters near agricultural areas. According to King et al. (6), population declines of the following species were observed, and continued study was proposed: brown pelican, reddish egret, white-faced ibis, laughing gull, and Forster's tern. The acute lethal potencies of these compounds in laboratory rats vary considerably, as shown in Table 69.2 (7).

Table 69.2. Acute Toxicity of Organochlorine Insecticides[a]

Acute Toxicity	Pesticide	CAS Number	Rat Oral LD_{50} (per kg Body Weight) Males and Females Combined (7)
Highly toxic	Endrin	[*72-20-8*]	13 mg
	Dieldrin	[*60-57-1*]	46 mg
	Aldrin	[*309-00-2*]	50 mg
Moderately toxic	Toxaphene	[*8001-35-2*]	85 mg
	Lindane	[*58-89-9*]	90 mg
	Heptachlor	[*76-44-8*]	131 mg
	Kepone	[*143-50-0*]	95 mg
	p,*p*'-DDT	[*50-29-3*]	116 mg
	Chlordane	[*57-74-9*]	283 mg
Slightly toxic	Kelthane	[*115-32-2*]	1.05 g
	p,*p*'-DDE	[*72-55-9*]	1.16 g
	Perthane	[*77-47-4*]	4.0 g
	Hexachloro-pentadiene		(corrosive)

[a] Reproduced with permission by American Medical Association, August 29, 1979.

Smith (8) discusses the fact that the primary acute toxicity noted in animals and humans following excessive exposures to chlorinated insecticides is neurological hyperactivity. With DDT and related compounds, the effects progress gradually from mild tremors to convulsions, whereas convulsions are the first sign of intoxication for compounds such as lindane, aldrin, dieldrin, endrin, toxaphene, and related materials. The latter can produce incoordination, weakness, and an ataxic state that is not associated with tremor, discriminating the intoxication induced by these substances from that of DDT. In general, the acute effects have not been shown to pose significant hazards to exposed

populations, and current concern over the toxicities of these compounds is linked primarily to chronic low-level exposures discussed below.

As mentioned above, because of reported environmental effects of these pesticides plus their classifications in the early 1970s as "potential human carcinogens," the use of most organochlorine pesticides was discontinued or markedly curtailed in the United States, Canada, and most European countries (9–11). The alleged human hazard, cancer, was based on observations of tumor induction in laboratory animals, primarily in mice, in which these compounds produced benign and malignant liver cell tumors. Table 69.3 (12–15) lists carcinogenicity classifications by the U.S. Environmental Protection Agency (USEPA), the National Toxicology Program (NTP), and the International Agency for Cancer Research (IARC); these classifications are intended to reflect human cancer risks related to chemical exposures to the chlorinated pesticides listed.

Table 69.3. Carcinogenicity Classification[a] of Chlorinated Insecticides

Chemical	USEPA (12, 13)	NTP (14)	IARC (15)	Basis
Aldrin	B2	—	3	Mouse liver tumors
Chlordane/heptachlor	B2	—	3	Mouse liver tumors
Chlordecone (Kepone)	—	e	2B	Rat, mouse liver tumors
DDT	B2	e	2B	Mouse liver, lung tumors, lymphomas; rat liver tumors; no tumors in three hamster studies
Dieldrin	B2	—	3	Mouse liver tumors
Endrin	—	—	3	No evidence
Lindane	B2/C	e	—	Mouse liver tumors
Mirex	B2	e	2B	Mouse, rat liver, and thyroid tumors
Toxaphene	B2	e	2B	Mouse, rat liver tumors

[a]

B2 Probable human carcinogen (no human evidence).

2B Possibly carcinogenic to humans.

C Possible human carcinogen.

3 Not classifiable as to carcinogenicity in humans.

e Reasonably anticipated to be carcinogenic to humans.

One reason for this debate is that few chemicals that induce rodent tumors appear to induce activity in humans. In 1975, Kraybill (16) wrote "None of the pesticide chemicals thus far have been shown to be carcinogenic to man." Workers (mostly men) who have been engaged in the manufacture, handling, and spraying of DDT, aldrin, dieldrin, toxaphene, chlordane, and heptachlor have been exposed to considerably higher concentrations and quantities of these insecticides than the general population of the United States. Among the exposed groups, only acute effects such as eye, skin, or respiratory irritation were reported, particularly following exposures to dusty formulations of the compound. High worker exposure occurring during the early years of production of some of these compounds was associated with induction of liver microsomal enzymes and the ability of some highly exposed workers to increase their drug-metabolizing capacity.

However, frank and undisputed injury to the liver or other human organs has not been reported in the United States, Canadian, and Western European literature. To the best of our knowledge the organochlorine insecticides (individually and in combination) that have been ingested with home- and restaurant-prepared food and drink by the U.S. population for more than 35 years (DDT was introduced in 1943), followed by a period of greatly reduced intake, have caused no recognized or clearly defined harmful effects. The significance of rodent liver tumors as indicators of human cancer risks continues to be debated in scientific circles (17–19).

Parenthetically, although the organochlorine insecticides are considered potential human carcinogens, it is noted that there has been a significant, almost constant decrease in the incidence of liver cancer deaths (males and females, classified since 1949 as primary, secondary, and not stated whether primary or secondary) in the continental United States, namely, from 8.8 (per 100,000 population) in 1930 to 8.4 in 1944 (when DDT was introduced for use) and to 5.6 in 1972. In the period 1985 to 1987, the liver cancer death rate in the United States was 4.1. According to U.S. vital statistics for the general U.S. population, this almost steady decline in total liver cancer deaths for a 55-year period is even more significant in light of the constantly increasing lifespan of the people of the United States, which, in turn, has resulted in a constant increasing percentage of the population "at risk" for liver cancer (2, 3).

Although liver cancer death rates have declined, the incidence of human breast cancer has increased (20). This increased incidence of breast cancer was largely attributed to more frequent use of mammography and other screening techniques, as well as other changes in other risk factors such as prevalence of certain reproductive variables e.g., age of first child, diet, alcohol consumption, and long-term use of menopausal estrogens. However, because of the weak estrogenic activity of several organochlorine chemicals, several epidemiology studies have evaluated the association between exposure to organochlorine chemicals such as the polychlorinated biphenyls (PCBs) and DDT and an increased incidence of breast cancer (21, 22). A case-control study reported by Wolff and co-workers (23) demonstrated a positive association between blood *p*,*p*'-DDE (the main tissue metabolite of DDT) concentrations and increased incidence of breast cancer. Subsequent larger case-control studies, however, failed to identify a link between DDT exposure and breast cancer (24, 25). The lack of an association between DDT exposure and an increased incidence of breast cancer was further supported by the observation that the *p*,*p*'-DDE metabolite of DDT is not estrogenic, and that the estrogenic activity of DDT was associated only with *o*,*p*'-DDE, a DDT-family member found at low or nondetectable concentrations in most environmental and human samples (26).

Miscellaneous Chlorinated Hydrocarbon Pesticides
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B. Specific Chlorinated Hydrocarbon Pesticides

Miscellaneous Chlorinated Hydrocarbon Pesticides

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Ethers

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A. General

1.1 Sources

Naturally occurring ethers may be constituents of essential oils and may be extracted from these sources. Although some ethers may appear naturally, they may be prepared synthetically from other chemicals or other ethers (1).

Symmetrical ethers are produced by the catalytic dehydration of their corresponding alcohols, for example, diethyl ether from ethanol (2). They are also obtained as by-products from the formation of their corresponding esters or alcohols. Ethers may also be made by special synthesis procedures (3, 4). Some ethers are obtained through the destructive distillation of selected hardwoods.

1.2 Uses
Ethers have a wide variety of industrial uses. Their commercial value is recognized in the following industries: rubber, plastics, paints and coatings, refrigeration, medicine, dentistry, petroleum, chemical, perfume, cosmetics, toiletries, and food.

The more volatile ethers have been used as liquid refrigerants, general anesthetics, commercial solvents, primers for gasoline engines, fuel additives (5), and rocket propellants. Other ethers have been used as alkylating agents in chemical syntheses of organic chemicals and in the manufacture of polymers. They are also used to denature alcohol (6). Halogenated ethers are used in the preparation of ion-exchange resin (7), which is a modified polystyrene resin that is chloromethylated and then treated with a tertiary amine or with a polyamine. Ethers have wide use as commercial solvents and extractants for esters, gums, hydrocarbons, alkaloids, oils, resins, dyes, plastics, lacquers, and paints. They are used as dewaxing extractants for lubricating oils. Ethers have had limited use as cleaning and spotting agents. They are used as chemical intermediates in the manufacture of textile aids, such as dyes and resins. In the pharmaceutical industry, ethers are used as solvents, suspending agents, flavorings for oral drugs, and dental products. They are used to increase viscosity, as penetrants and wetting agents, and as antioxidants and stabilizers. Ethers are used in foods as flavorings and in perfumes as fragrances. They are used as solvents for elastomers and for regenerating rubber. They have use as antiskinning agents in surface coatings and as weathering agents for paints and plastics. Ethers are also used in soaps. Ethers appear in heat transfer agents. Several industries use specific ethers for thickening, dispersing, suspending, binding, and film forming.
1.3 Physical and Chemical Properties
A summary of physical and chemical properties of ethers is presented in Table 72.1 (8–15).

Aliphatic Carboxylic Acids, Saturated
Steven T. Cragg, Ph.D., DABT

A. Saturated Aliphatic Monocarboxylic Acids
Industrial Applications
Saturated, aliphatic monocarboxylic acids are used in many varied applications, such as in the production of synthetic fiber materials, resins, plastics, and dyestuffs. A number of the acids and their esters are important chemical intermediates or solvents and are used in cosmetics or food applications.
Health Effects
The major physiological effect of the majority of the monocarboxylic acids is primary irritation of the moist surfaces of the body (eye, skin, or mucous membranes). The degree of irritation usually depends on the strength of the acid (dissociation), its water solubility, and its potential to penetrate the skin or, with the more volatile acids, the potential for exposure through vapor contact. The dissociation constants and aqueous solubilities for these acids are given in Table 70.1. The short-chain acids such as formic, acetic, and propionic acids are relatively strong acids and can produce burns similar to those of mineral acids. Higher molecular weight acids such as lauric and stearic acid are not strong irritants probably due mostly to poor skin penetrability, low volatility, and low water solubility. Their dissociation constants are similar to those of many of the shorter chain acids.

Table 70.1. Physical Properties of Saturated Aliphatic Monocarboxylic Ac

Chemical Abstracts Acid	CAS	Mol.	M.P.	B.P. (°	Specifi

Acid	Name	Number	Wt.	(°C)	C)	Solubility[a]			Gravit
Formic	Methanoic	[*64-18-6*]	46.03	8.4	100.8	∞	∞	Ether (∞) Acetone (v) Benzene (s)	1.220 (20/4)
Acetic	Ethanoic	[*64-19-7*]	60.05	16.7	118.0	∞	∞	Ether (∞) Acetone (∞) Benzene (∞)	1.049 (20/4)
Propionic	Propanoic	[*79-09-4*]	74.08	–20.8	141.1	∞	∞	Ether (∞) Chloroform (∞)	0.993 (20/4)
Butyric	Butanoic	[*107-92-6*]	88.12	–7.9	163.5	∞	∞	Ether (∞)	0.958 (20/4)
Isobutyric	2-Methylpropranoic	[*79-31-2*]	88.12	–47	154.7	20%	∞	Ether (∞) Chloroform (∞)	0.949 (20/4)
Valeric	Pentanoic	[*109-52-4*]	102.15	–34/–58	186.4	3.3%	∞	Ether (∞) Chloroform (∞)	0.942 (20/4)
Isovaleric	3-Methylbutanoic	[*503-74-2*]	102.15	–29.3	176.5	4.2%	∞	Ether (∞) Chloroform (∞)	0.925 (20/4)
Caproic	Hexanoic	[*142-62-1*]	116.18	–5	205	1.1%	S	Ether (s)	0.927 (20/4)
Isocaproic	4-Methylpentanoic	[*646-07-1*]	116.18	–33.0	201	SI s	S	Ether (s)	0.923 (20/4)
2-Methylvaleric	2-Methylpentanoic	[*97-61-0*]	116.18		193.5	0.6%	S	Ether (s)	0.927 (16/14)
2-Ethylbutyric	2-Ethylbutanoic	[*88-09-5*]	116.18	–31.8	194	SI s	S	Ether (s)	0.924 (20/4)
Heptanoic	Heptanoic	[*111-14-8*]	130.21	–7.5	223	0.2% (15°)	S	Ether (s) Acetone (v)	0.920 (20/14)
Caprylic	Octanoic	[*124-07-2*]	144.23	16.7	240	V sl s	S	Ether (s) Chloroform (s)	0.910 (20/4)

2-Ethylhexanoic	2-Ethylhexanoic	[*149-57-5*]	144.23		228 (755 mm)	S (hot)	SI s	Ether (s)	0.902 (25/4)
Nonanoic	Nonanoic	[*112-05-0*]	158.24	13	254	Ins	S	Ether (s)	0.906 (20/4)
								Chloroform (s)	
Capric	Decanoic	[*334-48-5*]	172.27	31.6	268	Ins	S	Methanol (s)	0.888 (35/4)
								Benzene (s)	
								Chloroform (s)	
Undecylic	Undecanoic	[*112-37-8*]	186.29	30	284	Ins	S	Ether (s)	0.891 (30/4)
Lauric	Dedecanoic	[*143-07-7*]	200.36	44	225 (100 mm)	Ins	S	Ether (s)	0.868 (50/4)
								Methanol (s)	
								Benzene (s)	
Myristic	Tetradecanoic	[*544-63-8*]	228.40	54.2	250.5 (100 mm)	Ins	S	Ether (s)	0.844 (80/4)
								Chloroform (s)	
								Benzene (s)	
Palmitic	Hexadecanoic	[*57-10-3*]	256.43	64	267 (100 mm)	Ins	S	Ether (∞)	0.836 (91/4)
								Acetone (s)	
								Benzene (s)	
Stearic	Octadecanoic	[*57-11-4*]	284.47	69.4	291 (110 mm)	0.03% (25°)	S	Ether (s)	0.839 (80.4)
								Acetone (v)	
								Chloroform (s)	

[a] ∞, soluble in all proportions; V, very soluble; S, soluble; SL s, slightly soluble; V sl s, very slightly soluble; Ins, insoluble.

Metabolic Fate

Saturated, straight-chain monocarboxylic acids are incorporated into normal intermediary metabolism and are ultimately broken down by the b-oxidation pathway to produce acetate and an acid with two fewer carbons than the original acid. The process is repeated until the end product is acetate, propionate, or butyrate. Acetate and butyrate are utilized for energy via the citric acid cycle or are converted to acetoacetate and subsequently other ketone bodies. Ketone bodies may be oxidized or excreted in the urine, depending on the nutritional state of the organism. Propionate originates from odd-chain acids and is converted to carbohydrate and, unlike acetate, into lipids.

In some cases, medium-chain acids are partly oxidized by  -oxidation. This produces dicarboxylic acids, which may be broken down by b-oxidation from either end.  -Oxidation does not normally occur with straight-chain acids that have more than 12 carbon atoms; it may occur when the capacity for b-oxidation is exceeded because of a large dose or blocked because of substitution in the a or b position on the molecule. Medium- and long-chain fatty acids also may be metabolized via chain elongation, which occurs by the addition of two-carbon (acetate) units to the carboxyl group of the original acid. Short-chain acids, such as butyric, caproic, and caprylic acids, may be converted to long-chain fatty acids, but this occurs largely by cleaving into two-carbon units, which are used as building units for chain elongation.

In general, a-ethyl-substituted acids are not readily metabolized and are eliminated primarily by conjugation with glucuronic acid and excretion in the urine or by dealkylation.

Table 70.2. Acute Toxicity of Saturated Monocarboxylic Acids

Acid	Species	Route	LD_{50} (mg/kg)	Ref.
Formic	Mouse	Oral	1076	4
	Mouse	IV	142	4
	Mouse	IP	940	5, 6
	Rat	Oral	1830	5, 6
	Rabbit	Oral	>4000 (LD_{Lo})	7
	Rabbit	IV	239 (LD_{Lo})	8
Acetic	Mouse	Oral	4960	9
	Mouse	IV	525	10
	Mouse	Inhaln	5620 ppm (LC_{50}/1 hr)	11
	Mouse	Inhaln	5000 ppm (LC_{50}/1 hr)	12
	Rat	Oral	3310	9
	Rat	Oral	3530	13
	Rat	Inhaln	16000 ppm (LC_{Lo}/4 hr)	13
	Rabbit	Oral	1200 (LD_{Lo})	14
	Rabbit	Oral	600 (LD_{Lo})	14
	Rabbit	Skin	1060	15
	Rabbit	SC	1200 (LD_{Lo})	14
	Guinea pig	Inhaln	5000 ppm (LC_{20}/1 hr)	12
Propionic	Mouse	Oral	5100[a]	16
	Mouse	IV	625	10
	Rat	Oral	4260	17
	Rat	Oral	2600	18
	Rat	Oral	5160[b]	16
	Rabbit	Skin	496	17

Butyic	Mouse	Oral	500 (LD_{Lo})	19
	Mouse	IV	800	10
	Mouse	IP	3180	20
	Mouse	SC	3180	20
	Rat	Oral	8790	21
	Rat	Oral	2940	13
	Rat	Oral	2000	22
	Rabbit	Oral	3600 (LD_{Lo})	19
	Rabbit	Skin	6083	21
	Rabbit	Skin	530	23
Isobutyric	Rat	Oral	280	17
	Rabbit	Oral	8000	24
	Rabbit	Skin	500	17
Valeric	Mouse	IV	1290	25
	Mouse	SC	3590	25
	Mouse	Inhaln	4100 mg/m^3 (LC_{50}/2 hr)	22
	Mouse	IP	3590	20
	Rat	Oral	1055	17
	Rat	Oral	1844	22
	Rabbit	Skin	660	17
	Rabbit	Skin	290	26
Isovaleric	Mouse	IV	1120	10
	Rat	Oral	2000	27
	Rat	Oral	<3200	28
	Rabbit	Skin	3560	29
	Rabbit	Skin	310	27
Caproic	Mouse	IP	3180	20
	Mouse	SC	3180	20
	Mouse	IV	1725	10
	Rat	Oral	5970	21
	Rat	Oral	3000 (LD_{Lo})	29
	Rabbit	Skin	630	9
	Guinea pig	Skin	5000 (LD_{Lo})	30
Isocaproic	Mouse	Oral	5000	22
	Mouse	Inhaln	4100 mg/m^3 (LC_{50}/2 hr)	22
	Mouse	IP	3180	20
	Mouse	IV	1725	10
	Mouse	SC	3180	20
	Rat	Oral	2050[c]	31
	Rat	Oral	>3200	28
	Rat	Oral	3000	30
	Rabbit	Skin	630	10

	Rabbit	Skin	1050[c]	32
	Guinea pig	Skin	4635	30
2-Methylvaleric	Rat	Oral	1890	33
	Rat	Oral	1600–3200	34
	Rat	Oral	2040	10
	Rabbit	Skin	2500	35
2-Ethylbutyric	Rat[d]	Oral	2033	10
	Rabbit	Skin	480	10
Heptanoic	Mouse	Oral	6400	36
	Mouse	IV	1200	10
	Rat	Oral	7000	37
Caprylic	Mouse	IV	600	10
	Rat	Oral	1280	17
	Rat	Oral	10080	38
	Rabbit	Skin	650	17
	Rabbit	Skin	>5000	39
2-Ethylhexanoic	Rat	Oral	3000	29
	Rat	Oral	1600	40
	Guinea pig	Skin	5690	30
	Rabbit	Skin	1260	41
Nonanoic	Mouse	Oral	15000	42
	Mouse	IV	224	10
	Rat	Oral	3200 (LD_{Lo})	28
	Rabbit	Skin	>5000	43
Capric	Mouse	IV	129	10
	Rat	Oral	3320[c]	17
	Rabbit	Skin	1575[c]	17
	Rabbit	Skin	>5000	44
Undecylic	Mouse	IV	140	10
Lauric	Mouse	IV	131	10
	Rat	Oral	12000	37
Myristic	Mouse	IV	43	10
Stearic	Mouse	IV	23	10
	Mouse	IV	56	45, 46
	Rat	Oral	4640 (LD_{LO})	47
	Rat	IV	22	10
	Rat	Oral	>5000	48
	Rabbit	Skin	>5000	48

[a] Sodium salt.
[b] Calcium salt.
[c] Experiments using mixed isomers of unspecified composition.
[d] Female.

10% corn oil solution.

Aliphatic Carboxylic Acids, Saturated
Steven T. Cragg, Ph.D., DABT

B. Saturated Polycarboxylic Acids
Introduction
Industrial Applications Saturated, aliphatic polycarboxylic acids are used in applications similar to those of monocarboxylic acids.

Health Effects The physiological effects of saturated, aliphatic polycarboxylic acids are similar to those described for monocarboxylic acids.

The acid dissociation constants and water solubilities of aliphatic dicarboxylic acids are presented in Table 70.3. The short-chain acids, in particular oxalic and malonic acids, are relatively strong acids and can cause local irritation, whereas the longer chain acids (e.g., pimelic and sebacic) are not irritants. The presence of the second carboxyl function in oxalic acid greatly increases its acidity, compared with formic acid. The fact that oxalic acid is a solid and has less water solubility may partly counteract the effect of increased ionization.

Table 70.3. Physical Properties of Saturated Aliphatic Polycarboxylic A

						Solubility[a]			
Acid	**Chemical Abstracts Acid Name**	**CAS Number**	**Mol. Wt.**	**M.P. (°C)**	**B.P. (° C)**	**H_2O**	**Alcohol**	**Other**	**Spe Gra**
Oxalic	Ethanedioic	[*144-62-7*]	90.04	189.5	157 (sublimes)	8.3%	V	Ether (sl s) Chloroform (ins) Benzene (ins)	1. (1
Malonic	Propanedioic	[*141-82-2*]	104.07	135.6 (dec.)	Dec. 140	V	V	Methanol (v) Ether (s) Pyridine (s)	1. (1
Succinic	Butanedioic	[*110-15-6*]	118.10	189.0	235 (dec.)	Sl s (v, hot)	S	Ether (s) Acetone (s) Benzene	1. (2

								(ins)	
Malic (DL)	Hydroxybu-tanedioic	[*6915-15-7*]	134.10	131		S	S	Methanol (s) Ether (sl s) Benzene (ins)	1. (2(
Thiomalic	Mercaptobutane-dioic	[*70-49-5*]	150.15	154		S	S	Ether (sl s) Acetone (s) Benzene (ins)	
Tartaric (L)	2,3-dihydroxybu-tanedioic	[*87-69-4*]	150.10	171		V	V	Ether (sl s) Benzene (ins)	1. (2(
Adipic	Hexanedioic	[*124-04-9*]	146.16	153	338	Sl s	V	Ether (s) Acetone (s) Benzene (ins)	1. (2:
Citric	2-Hydroxy-1-2,3-propanetricar-boxylic	[*77-92-9*]	192.14	153		V	V	Ether (s) Chloroform (ins) Ethyl acetate (s)	1. (1{ (anl
Pimelic	Heptanedioic	[*111-16-0*]	160.19	106	272 (100 mm, subl.)	S	S	Ether (s) Benzene (ins)	1. (1:
Suberic	Octanedioic	[*505-48-6*]	174.22	144	300 (subl.)	Sl s	S	Ether (sl s) Chloroform (ins) Methanol (s)	1. (2:
Azelaic	Nonanedioic	[*123-99-9*]	188-25	106.5	287 (100 mm)	Sl s	V	Ether (sl s) Benzene (sl s)	1. (2(
Sebacic	Decanedioic	[*111-20-6*]	202.28	134.5	295 (100 mm)	Sl s	V	Ether (v) Benzene (ins) Acetone (s)	1. (2(

[a] ∞, soluble in all proportions; V, very soluble; S, soluble; SL s, slightly soluble; V sl s, very

slightly soluble; Ins, insoluble.

Metabolic Fate Dicarboxylic acids are less extensively metabolized than monocarboxylic acids. An exception to this is the succinate, which is rapidly metabolized by incorporation into intermediary metabolic pathways to produce glucose and glycogen.

Appreciable quantities of many of the dicarboxylic acids are excreted in urine; the amount depends on the dose and route of administration. Some metabolism of the longer chain acids does occur by b-oxidation, producing a dicarboxylic acid that has two fewer carbons than the original. This process may continue as far as the succinate. Oxalic acid is excreted unchanged, and malonic acid is only partly degraded, apparently by decarboxylation to acetate.

Table 70.4. Acute Toxicity of Unsaturated Polycarboxylic Acids

Acid	Species	Route	LD_{50} (mg/kg)	Ref.
Oxalic	Rat (male)	Oral	475[a]	28
	Rat (female)	Oral	375[a]	28
	Mouse	Oral	8400 (TD_{Lo})	316
	Mouse	IP	270	317
	Rabbit	Skin	20000[a] (not lethal)	28
	Cat	SC	112 (LD_{Lo})	318
	Dog	Oral	100 (LD_{Lo})	318
Malonic	Mouse	Oral	4000	35
	Mouse	IP	300	319
	Mouse	IP	Approx. 1500	27
	Rat	Oral	1310	320
	Rat	IP	Approx. 1500	27
Succinic	Rat	Oral	2260	321
	Mouse	IP	2702	322
Malic	Mouse	Oral	1600–3200	321
	Mouse	IP	50–100	321
	Rat	Oral	>3200	321
	Rat	IP	100–200	321
Thiomalic	Mouse	IP	500	322
	Rat	Oral	800–1600[b]	27
	Rabbit	IV	>1000	323
	Guinea pig	Skin	>2000	27
Tartaric	Mouse	IV	485	324
	Mouse	Oral	4360[c]	325
	Rabbit	Oral	5000 (LD_{Lo})	326
	Rabbit	Oral		325

			5290[d]	
	Dog	Oral	5000 (LD_{Lo})	327
Adipic	Mouse	IV	680	324
	Mouse	Oral	1900	324
	Mouse	IP	275	328
	Rat	Oral	3600 (LD_{Lo})	329
	Rat	Oral	>11000	330
	Rat	IP	275	324
	Rabbit	Oral	>11000	330
Citric	Mouse	IV	42	331
	Mouse	Oral	5040	332
	Mouse	IP	961	331
	Mouse	IP	903	317
	Mouse	SC	2700	332
	Rat	Oral	11700	332
	Rat	IP	883	331
	Rat	SC	5500	332
	Rabbit	IV	330	331
	Rabbit	Oral	7000 (LD_{Lo})	326
Pimelic	Mouse	Oral	4800	35
	Rat	Oral	>3200	27
	Rat	Oral	7000	333
Sebacic	Mouse	Oral	6000	35
	Mouse	IP	500	331

[a] As a 5% aqueous solution.
[b] As a 10% solution.
[c] Sodium salt.
[d] 3/7.

Aliphatic Carboxylic Acids, Saturated

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Aliphatic Carboxylic Acids, Unsaturated
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Unsaturated Monocarboxylic Acids
Introduction
Industrial Applications The alkenoic series of carboxylic acids are obtained from such natural sources as animal tallows and greases, and vegetable, coconut, palm, and marine oils. Several have also been produced synthetically from petroleum sources. They are frequently referred to as fatty acids (C_6 to C_{24}) and have important commercial applications in plastics, coating materials, fungicides, food preservatives, lubricants, and perfumes. They have been used as softening agents for rubber and as pharmaceuticals in medicine and dentistry. Acids of this type are unstable and polymerize readily, hence offering important chemical and physical properties for use in producing esters, acid halides, acid amides, and acid anhydrides.

As a class, the unsaturated carboxylic acids have been subjected to an extensive battery of studies, including acute, short-term, and chronic toxicity and carcinogenicity tests and reproductive and developmental toxicity and genotoxicity tests. Overall, these acids have a low level of mammalian toxicity, although they are strong skin and eye irritants in animal tests and are irritating to mucosal membranes in humans. For those acids for which adequate studies have been conducted, there is no evidence that they are reproductive or developmental toxicants or carcinogens. Mutagenicity and clastogenicity studies suggest that this group of acids is devoid of genotoxic activity. The biochemistry of many of these acids can be found in general textbooks. Rapid metabolism to other fatty acids may explain their general low degree of toxicity. The physical properties and acute toxicity of saturated monocarboxylic acids are provided in Tables 71.1 and 71.2 (1–35) respectively.

Table 71.1. Physical Properties of Unsaturated Aliphatic Monocarboxylic Acid

Acid	Chemical Abstracts Acid Name	CAS Number	Mol. wt.	M.P. (°C)	B.P. (°C)	Solubility[a]			Sp Gr
						H_2O	Alcohol	Other	
Propiolic	2-Propynoic	[*471-25-0*]	70.05	18	144 (dec)	∞	∞	Ether (∞) $CHCl_3$ (∞) Benzene (∞)	1. (2
Acrylic	2-Propenoic	[*79-10-0*]	72.06	3	141.6	∞	∞	Ether (∞) Acetone (sl s) Benzene (sl s)	1.((2
Crotonic	(*E*)-2-Butenoic	[*107-93-7*]	86.09	71.5–71.7	185	v	v	Ether (sl s) Acetone (sl s)	1. (1
Methacrylic	1-Methyl-2-Propenoic	[*79-41-4*]	86.09	16	162–163	sl s	∞	Acetone (∞)	1.((2

Pentenoic	4-Pentenoic	[*591-80-0*]	100.13	22.5	188–189	sl s	∞	Acetone (∞)	0.9 (2
Hexanoic	2-Hexanoic	[*1191-04-4*]	114.15	94				Benzene (sl s)	
Sorbic	(*E,E*)-2,4-Hexadienoic	[*110-44-1*]	112.14	134.5	228 (dec.)	sl s (hot)	sl s	Ether (v)	1. (1
Heptenoic	2-Heptenoic	[*18999-28-5*]	128.9						
Undecylenic	10-Undecenoic	[*112-38-9*]	184.28	24.5	275	ins	sl s	Ether (sl s) $CHCl_3$ (sl s) Benzene (sl s)	
Linolenic	9,12,15-Octadecatrienoic	[*1955-33-5*]	278.44	–11.3		ins	sl s	Ether (sl s) Benzene (sl s)	0.9 (2
Linoleic	(*Z,Z*)-9,12-Octadecadienoic	[*2197-37-7*]	280.45	–5		ins	∞	Ether (∞) Acetone (∞) $CHCl_3$ (∞) Benzene (∞)	0.9 (2
Linolelaidic	(*E,E*)-9,12-Octadecadienoic	[*506-21-8*]	280.45						
Elaidic	(*E*)-9-Octadecenoic	[*112-79-8*]	282.47	45		ins	sl s	Ether (sl s) $CHCl_3$ (sl s) Benzene (sl s)	0.8 (4
Oleic	(*Z*)-9-Octadecenoic	[*112-80-1*]	282.47	13.2		ins	∞	Ether (∞) Acetone (∞) $CHCl_3$ (sl s) Benzene (∞)	0. (2
Ricinoleic	(*Z*)-12-Hydroxy-9-octadecenoic	[*141-22-0*]	298.47	5.5		ins	sl s	Ether (sl s)	0. (21
Arachidonic	(*Z,Z,Z,Z*)-5,8,11,14 Eicosatetraenoic	[*506-32-1*]	304.48	–49.5	(dec.)	ins	sl s	Ether (sl s) Acetone (sl s)	

[a] ∞, soluble in all proportions; v, very soluble; sl s, slightly soluble; ins, insoluble; dec., decomposes.

Table 71.2. Acute Toxicity of Unsaturated Monocarboxylic Acids

Acid	Species	Route	LD_{50} (mg/kg)	Ref.
Propiolic	Mouse	Oral	100–200	1
	Mouse	i.p.	25–50	1
	Rat	Oral	100–200	1
	Rat	i.p.	25–50	1
	Guinea pig	Skin	0.1–1.0 (mL/kg)	1
Acrylic	Mouse	Inhaln	5300 mg/m^3 (LC_{50}/2 h)	2
	Mouse	Oral	2400	3
	Mouse	i.p.	128 (LD_{Lo})	4
	Mouse	i.p.	0.016 (mL/kg)	5
	Mouse	s.c.	1590	6
	Rat	Oral	340–3200	7–9
	Rat	i.p.	22–24	8, 10
	Rat	Inhaln	3.6 g/m^3 (LC_{50}/4 h)	8
	Rat	Inhaln	19 g/m^3 (LC_{Lo}/5 h)	11
	Rat	Inhaln	Satd. atm. (LC_{50}/3.5 h)	12
	Rat	Inhaln	11.5 g/m^3 (no mort./4 h)	12
	Rat	Inhaln	Satd. atm. (no mort./8 h)	13
	Rabbit	Skin	280	14
Methyl-	Rat	Inhaln	1350 ppm/4 h	15
Ethyl-	Rat	Inhaln	2180 ppm/4 h	15
Butyl-	Rat	Inhaln	2730 ppm/4 h	15
Crotonic	Mouse	Oral	400–4800	4, 16
	Mouse	i.p.	25–50	16
	Mouse	s.c.	3590	6
	Rat	Oral	400–1000	16, 17
	Rat	i.p.	25–100	16, 17
	Guinea pig	i.p.	60	18
	Guinea pig	Skin	200	16
	Rabbit	Skin	600	17
Methacrylic	Mouse	Oral	1600	19
	Mouse	i.p.	48	20
	Rat	Oral	2260, 9400	19, 21
	Guinea pig	Skin	1–5 mL/kg	19
	Rabbit	Skin	500	22

Methyl-	Rat	Inhaln	7093 ppm/4 h	15
Ethyl-	Rat	Inhaln	8300 ppm/4 h	15
Buthyl-	Rat	Inhaln	4910 ppm/4 h	15
4-Pentenoic	Mouse	Oral	610	23
	Mouse	i.p.	315	6
	Mouse	s.c.	315	6
	Rat	Oral	470	23
2-Pentenoic	Mouse	i.p.	1580	6
	Mouse	s.c.	1580	6
Hexenoic	Mouse	i.p.	1840	6
	Mouse	s.c.	1840	6
Sorbic	Mouse	Oral	3200–6400	19, 24
	Mouse	i.p.	1600–3200	6, 24
	Mouse	s.c.	2820	6
	Rat	Oral	3200–7360	6, 24, 25
	Rat	i.p.	800–1600	24
Heptenoic	Mouse	i.p.	1600	6
	Mouse	s.c.	1600	6
Undecylenic	Mouse	Oral	>3200, 8150	19, 26
	Mouse	i.p.	960	26
	Rat	Oral	>2500	19, 27
	Guinea pig	Skin	50–240	19
Linolenic	Mouse	Oral	>3200	19
	Rat	Oral	>3200	19
	Guinea pig	Skin	>20 (mL/kg)	19
Linoleic	Mouse	Oral	>3200	28
	Mouse	i.p.	280	29
	Rat	Oral	>3200	30
	Guinea pig	Skin	>20 (mL/kg)	30
Linolelaidic	No mortality (LD_{50}) Studies were found in the literature			
Elaidic	Mouse	i.p.	512 (LD_{Lo})	31
	Mouse	i.v.	100	32
Oleic	Mouse	i.v.	230	33
	Mouse	i.p.	282	29
	Rat	Oral	64 (mL/kg)	30
Ricinoleic	No mortality (LD_{50}) studies were found in the literature			
Arachidonic	Mouse	i.v.	100 (LD_{Lo})	34
	Mouse	i.v.	33	35
	Rat	i.v.	100 (LD_{Lo})	34
	Rabbit	i.v.	1 (LD_{Lo})	34

Aliphatic Carboxylic Acids, Unsaturated
Steven T. Cragg, Ph.D., DABT

Unsaturated Polycarboxylic Acids
Polycarboxylic acids are used to manufacture a wide variety of products such as resins, textiles, medical products, printing inks, and foods. They are also used in organic syntheses and electropolishing applications. Except for fumaric and maleic acids, there is a paucity of information available for these acids. However, similar to that of the monocarboxylic acids, polycarboxylic acids have a low level of mammalian toxicity, although they, too, are strong skin and eye irritants in animal tests. For those acids for which adequate studies have been conducted, there is no evidence that they are genotoxic or carcinogenic. Fumaric, aconitic, and itaconic acids are normal constituents of human metabolism. Information on human exposure is sparse. The physical properties and acute toxicity of saturated monocarboxylic acids are provided in Tables 71.3 and 71.4, (335–341) respectively.

Table 71.3. Physical Properties of Unsaturated Aliphatic Polycarboxylic Acid

Acid	Chemical Abstracts acid name	CAS Number	Mol. Wt.	M.P. (°C)	B.P. (°C)	Solubility[a]		
						H_2O	Alcohol	Other
Maleic	(*Z*)-2-Butenedioic	[*110-16-7*]	116.07	139–140	135°C (dec.)	v	v	Ether (sl s) Acetone (v) $CHCl_3$ (ins) Benzene (ins)
Fumaric	(*E*)-2-Butenedioic	[*110-17-8*]	116.07	300–302 (sealed tube)	290	v sl	sl s	Ether (v sl) Acetone (v sl) $CHCl_3$ (v sl)
Mesaconic	(*E*)-2-Methyl-2-buteneioic	[*498-24-8*]	130.1	204.5	Subl.	v sl	v	Ether (sl s) $CHCl_3$ (v sl) Benzene

								(v sl)
Citraconic	(*Z*)-2-Methyl-2-butenedioic	[*498-23-7*]	130.1	93-93.8 (dec.)		v		Ether (v sl) $CHCl_3$ (ins) Benzene (v sl)
Itaconic	Methylenebutanedioic	[*97-65-4*]	130.1	175	dec.	sl s	sl s	Ether (v sl) Acetone (sl s) $CHCl_3$ (v sl) Benzene (v sl)
Aconitic	1-Propene-1,2,3-tricarboxylic	[*499-12-7*]	174.11	130	198–205 (dec.)	sl s		Ether (v sl)

[a] ∞, soluble in all proportions; v, very soluble; sl s, sightly soluble; v sl, very slightly soluble; ins, insoluble; dec., decomposes; subl, sublimes.

Table 71.4. Acute Toxicity of Unsaturated Polycarboxylic Acids

Acid	Species	Route	LD_{50} (mg/kg)	Ref.
Maleic	Mouse	Oral	2400	3
	Rat	Oral	708	335
	Rat	Inhaln	>0.72 g/m^3 (LC_{50}/1 h)	335
	Guinea pig	Skin	>1000	335
	Rabbit	Skin	1560	335
Fumaric	Mouse	i.p.	200	336
	Rat	Oral	10,700	337
	Rat	i.p.	587 (LD_{Lo})	338
	Rabbit	Oral	500 (LD_{Lo})	339
Mesaconic	Mouse	i.p.	500 (LD_{Lo})	2
Citraconic	Mouse	Oral	2260	23
	Rat	Oral	1320	23
	Guinea pig	Oral	1350	23
Itaconic	No mortality (LD_{50}) studies were found in the literature			
Aconitic	Mouse	i.v.	180	340
	Mouse	Oral	2000	341

Aliphatic Carboxylic Acids, Unsaturated

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Ethers
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A. General
1.1 Sources
Naturally occurring ethers may be constituents of essential oils and may be extracted from these sources. Although some ethers may appear naturally, they may be prepared synthetically from other chemicals or other ethers (1).

Symmetrical ethers are produced by the catalytic dehydration of their corresponding alcohols, for example, diethyl ether from ethanol (2). They are also obtained as by-products from the formation of their corresponding esters or alcohols. Ethers may also be made by special synthesis procedures (3, 4). Some ethers are obtained through the destructive distillation of selected hardwoods.
1.2 Uses
Ethers have a wide variety of industrial uses. Their commercial value is recognized in the following industries: rubber, plastics, paints and coatings, refrigeration, medicine, dentistry, petroleum, chemical, perfume, cosmetics, toiletries, and food.

The more volatile ethers have been used as liquid refrigerants, general anesthetics, commercial solvents, primers for gasoline engines, fuel additives (5), and rocket propellants. Other ethers have been used as alkylating agents in chemical syntheses of organic chemicals and in the manufacture of polymers. They are also used to denature alcohol (6). Halogenated ethers are used in the preparation of ion-exchange resin (7), which is a modified polystyrene resin that is chloromethylated and then treated with a tertiary amine or with a polyamine. Ethers have wide use as commercial solvents and extractants for esters, gums, hydrocarbons, alkaloids, oils, resins, dyes, plastics, lacquers, and paints. They are used as dewaxing extractants for lubricating oils. Ethers have had limited use as cleaning and spotting agents. They are used as chemical intermediates in the manufacture of textile aids, such as dyes and resins. In the pharmaceutical industry, ethers are used as solvents, suspending agents, flavorings for oral drugs, and dental products. They are used to increase viscosity, as penetrants and wetting agents, and as antioxidants and stabilizers. Ethers are used in foods as flavorings and in perfumes as fragrances. They are used as solvents for elastomers and for regenerating rubber. They

have use as antiskinning agents in surface coatings and as weathering agents for paints and plastics. Ethers are also used in soaps. Ethers appear in heat transfer agents. Several industries use specific ethers for thickening, dispersing, suspending, binding, and film forming.

1.3 Physical and Chemical Properties

A summary of physical and chemical properties of ethers is presented in Table 72.1 (8–15).

B. Alkane Ethers

Physiological data on industrially important saturated, symmetrical and asymmetrical alkyl ethers not specifically discussed in this section are presented in Tables 72.5 and 72.9. Data will be found for dihexyl ether (35), di(2-ethylhexyl) ether (35), methyl isopropyl ether (75), and ethyl butyl ether (37). Physical and chemical properties data are presented in Table 72.1.

Table 72.8. Atmospheric Concentration of Diethyl Ether and Reported Effects

Concentration, ppm	Effect
0.7–1920	Reported range of human odor detection
200	Nasal irritation
19,000 (1.9%)	Lower flammability limit, lowest anesthesia limit
42,000 (4.2%)	LC_{50} in mice
50,000 (5.0%)	Maintenance of surgical anesthesia
64,000 (6.4%)	Lethal concentration for rats
100,000–150,000 (10–15%)	Induction of human anesthesia

Table 72.9. Toxic Effects of Other Saturated Alkyl Ethers

Material and Molecular Formula	Anesthetic, mL/kg: Surgical Anesthesia	Anesthetic, mL/kg: Respiratory Arrest	Odor	Remarks
Methyl propyl ether (73, 74) $CH_3OCH_2CH_2CH_3$	Dog, 0.8	2.1	Ethereal	Caused no deleterious effect in dog, monkey, or rat
Methyl isopropyl ether	Dog, 1.12	2.62	Ethereal	Caused no

(75) $CH_3OCH(CH_3)_2$	deleterious effect in dog, monkey, or rat

Table 72.10. Incidence of Kidney Cancers in Male F344 Rats in Inhalation Study[a] with MTBE

Dose, ppm	Adenomas	Carcinomas	Combined adenomas and carcinomas
0	1/44 (2%)	0/44 (0%)	1/44 (2%)
400	0/46 (0%)	0/46 (0%)	0/46 (0%)
3000[b]	5/44 (11%)	3/44 (7%)	8/44 (18%)
8000[b]	3/39 (8%)	0/39 (0%)	3/39 (8%)

[a] 24-month study (144).
[b] 3000 and 8000 ppm rats were sacrificed at 97 and 82 weeks, respectively, at which point the appearance of cancer would be less likely detected.

Table 72.11. Incidence of Cancers in Sprague–Dawley rats exposed only to MTBE for 2 Years[a]

	Male		Female	
Dose, mg/kg[b]	**Testicular Leydig Cell, %**	**Corrected No., %**	**Lymphomas and Leukemia, %**	**Corrected No., %**
0	3.3	7.7	4.0	3.4
250	3.3	8.0	10.0	11.8
1000	18.3	34.4	20.0	25.5

[a] From Belpoggi et al. (146).
[b] 60 animals per group in each sex. Alive male rats at 96 weeks of age, when the first Leydig cell tumor was observed.

Table 72.12. Regulations and Guidelines Applicable to Methyl tert-Butyl Ether (MTBE)[a]

Agency	Description	Information	Ref.

	International		
WHO		NA	
IARC	Group (cancer ranking)	NA	
	National (Domestic)		
Regulations:			
Air: EPA	CAAA Title III	None	U.S. Congress §112 of CAAA 10/26/90
	Standards of Performance for VOC Emissions from SOCMI, Distillation Operations Chemicals Affected	Yes	40 CFR 60.667
	Standards of Performance for VOC Emissions from SOCIL, Reactor Processes Chemicals Affected	Yes	40 CFR 60.707
	Regulation of Fuels and Fuel Additives—Complex Emission Models	Yes	40 CFR 80.45 (151)
	Measurement of Reformulated Gasoline Fuel Parameters	Yes	40 CFR 80.46 (152)
Water: EPA/OW	Description of Bulk Organic Chemicals Subcategory	Yes	40 CFR 414.70
Other: EPA/OERR	Toxic Chemical Release Reporting: Chemicals and Chemical Categories to Which This Part Applies		40 CFR 372.65 (153)
EPA/OSW	Hazardous Waste from Non-specific Sources	Yes	40 CFR 261.31
	Discarded Commercial Chemical Products, Off-specification Species, Container Residues, and Spill Residues Thereof	Yes	40 CFR 261.33
Guidelines:			
Air	ACGIH (A3-Confirmed animal carcinogen)—8-hour Time-Weighted Average	40 ppm	
	EPA/OAR Reference Concentration	3 mg/m^3	
Water:EPA/OSW	1-day Health Advisory	3 m/L (child)	
	10-day Health Advisory	3 mg/L (child)	
	Lifetime Health Advisory	0.02-0.2 mg/L (adult)	

	Longer Term Health Advisory	0.5 mg/L (child) 2 mg/L (adult)
	Reference Dose	0.03 (mg) (kg)/day
	Drinking Water Equivalent Level	0.2 mg/L
Other:		
EPA	Cancer Classification	C[c]
NTP	Cancer Classification	NA
	State	
Regulations and guidelines		
Water:		
	Water Quality: Human Health	
AZ	Domestic Drinking Water	35 mg/L
CT	Drinking Water Guideline	100 mg/L
MA	Drinking Water Guideline	50 mg/L
ME	Drinking Water Guideline	50 pg/L
MI	Domestic Drinking Water	230 mg/L
NH	Drinking Water Guideline	200 mg/L
NJ	MCL Recommendation	70 m/L
RI	Drinking Water Guideline	50 mg/L
VT	Drinking Water Standard	40 mg/L

[a] Update of drinking water guidelines and other areas in progress. Units in table reflect values and units of measure designated by each agency in its regulations or advisories. *Abbreviations*: ACGIH = American Conference of Governmental Industrial Hygienists; CAAA = Clean Air Act Amendments; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; NA Not available at the present time; OERR = Office of Emergency and Remedial Response; OSW = Office of Solid Waste; OW = Office of Water; VOC = Volatile Organic Compound; WHO = World Health Organization.

The lifetime health advisory is 0.020 mg/L, otherwise, it is 0.20 mg/L.

[c] C = Possible human carcinogen.

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C. Alkene Ethers

Physiological data on several symmetrical and asymmetrical alkene ethers are presented in Table 72.5.

Table 72.13. Toxic Effects of Some Alkene Ethers

Material	Species	Anesthetic: Surgical Anesthesia	Anesthetic: Respiratory Arrest	Reference
Ethyl vinyl ether $CH_3CH_2OCH{=}CH_2$	Mouse	6% (v/v)	16% (v/v)	61, 158
	Rat	—	16% (v/v) for 4 hr killed 2, 3, or 4 of 6	159
	Dog	0.56 mL/kg	1.66 mL/kg	
Isopropyl vinyl ether $(CH_3)_2CHOCH{=}CH_2$	Dog	0.50 mL/kg	3.08 mL/kg	160

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D. Polyoxy Ethers
Physical and chemical data are presented in Table 72.1.

Physiological data of polyoxy ethers are presented in Table 72.5. Acute exposure values are presented for 1-butoxy-2-ethoxyethane, 2-butoxyethyl vinyl ether, 1,2-dibutoxyethane, 2,2'-dibutoxyethyl ether, 2-methoxyethyl vinyl ether, and 1,3-dimethoxybutane.

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E. Halogenated Alkyl Ethers
The halogenated ethers are more potent anesthetics than the alkane and alkene ethers, and also have higher acute toxicity. Three references that describe the anesthetic potential of halogenated ethers, which are too numerous to report here, are those by Poznak and Artusio (164), Terrell et al. (165), and Speers et al. (166). Some industrially important halogenated ethers have been shown to be carcinogenic in animals and humans. See Section 1.6 for discussion of this characteristic of these alkylating agents.
18.0 Other Haloethers
Table 72.5 contains toxic effects data for the haloethers 2-chloro-1,1,2-trifluoroethyl methyl ether

and 2-chloroethyl vinyl ether. Tables 72.6, 72.7 and 72.14 contain toxic effects data for the haloethers dichloromethyl methyl ether (178, 184), bis(a-chloroethyl) ether (178), and octachlorodi-*n*-propyl ether (178, 184, 185). Table 72.14 contains, in addition, toxic effects data for the haloethers 2-fluoroethyl methyl ether (186), 2,2,2-tri-fluoroethyl methyl ether (183), 2,2-dichloro-1,1-difluoroethyl methyl ether (59, 187–189), 2,2-difluoroethyl ethyl ether (190), 2,2,2-trifluoroethyl ethyl ether (190), 2-fluoro-1',2',2',2',-tetrachloro-diethyl ether (186), bis(2,2,2-trifluoroethyl) ether (191, 192), 2,2,2-trifluoroethyl vinyl ether (71, 193, 194), bis-1,2-(chloromethoxy)ethane (195), 5-fluoroamyl methyl ether (184), bis-1,4-(chloromethoxy)butane (195), perfluoroisobutenyl ethyl ether (196), 6-fluorohexyl methyl ether (186), 4,4'-difluorodibutyl ether (186), bis-1,6-(chloromethoxy) hexane (195), 4-fluoro-4'-chlorodibutyl ether (186), and 2-fluoro-2'-*n*-butoxydiethyl ether (186).

Table 72.14. Toxic Effects of Miscellaneous Haloethers

Material and Molecular Formula	Remarks
Dichloromethyl methyl ether $CHCl_2OCH_3$	See Table 72.6. Data originally from VanDuuren et al. (178) exhibiting weak carcinogenicity in mice. When evaluated as an initiator of carcinogenesis with phorbol ester, 3 mice out of 20 developed papillomas and 1 developed carcinoma (184).
2-Fluoroethyl methyl ether $CH_2FCH_2OCH_3$	Intraperitoneal LD_{50} in mice is 15 mg/kg (186).
2,2,2-Trifluoroethyl methyl ether $CF_3CH_2OCH_3$	Using 10 min for the exposure time Robbins (190) found the anesthetic dose (AD_{50}) to be 8% (v/v); the fatal dose (FD_{50}) to be 16% (v/v) using 20 mice. The time necessary for induction of anesthesia of mice exposed to be LC_{50} is 20 s. The time necessary for recovery of pain sensation after exposure to the LC_{50} for 10 min is 2 min. The time necessary to return to normal gait after 10 min exposure to the LC_{50} is 4 min.
2,2-Dichloro-1,1-difluoroethyl methyl ether $CHCl_2CF_2OCH_3$ (methoxyfluorane)	Artusio et al. (187) evaluated the anesthetic effects in 100 patients. Induction was smooth; no delirium, hypotension, or ventricular arrhythmia was noted. EEG changes, associated with anesthesia were noted. Nausea, vomiting, and the need for analgesics were reduced. Desmond (188) exposed 11 patients to this anesthetic in operations lasting 3–4 h at a concentration of 0.16%. Renal dysfunction lasting for days postoperatively was characterized by a large volume of low osmolality urine produced. Other reports of dramatic renal failure with use of this anesthetic are discussed. Swann et al. (59) found that 6.4% (v/v) produced respiratory arrest in 2 of 4 mice in 5.25 min. Rats exposed (189) to a 0.5% (v/v) atmosphere for 2, 4, or 6 h showed decreased food intake, diuresis, and reduced urinary osmolality.

2,2-Difluoroethyl ethyl ether $CHF_2CH_2OCH_2CH_3$	Using 10 min for the exposure time, Robbins (190) found the anesthetic dose (AD_{50}) to be 4% (v/v) and the fatal dose (FD_{50}) to be 9% (v/v) using 24 mice. The time necessary for induction of anesthesia of mice exposed to the LC_{50} is 1 min. The time necesary for recovery of pain sensation after exposure to the LC_{50} for 10 min is 2 min. The time necessary to return to normal gait after a 10-min exposure to the LC_{50} is 5–20 min.
2,2,2-Trifluoroethyl ethyl ether $CF_3CH_2OCH_2CH_3$	Using 10 min for the exposure time Robbins (190) found the anesthetic dose (AD_{50}) to be 4% (v/v) and the fatal dose (FD_{50}) to be 8% (v/v) using 16 mice. The time necessary for induction of anesthesia of mice exposed to the LC_{50} is 30 s. The time necessary for recovery of pain sensation after exposure to the LC_{50} for 10 min is 20 s. The time necessay to return to normal gait after 10 min exposure to the LC_{50} is 1 min.
1-Chloroethyl ether $CH_3CHClOCHClCH_3$	See Table 72.6. Data originally from VanDuuren et al. (178) exhibiting moderate carcinogenicity in mice. When injected subcutaneously at a dose of 300 mg in mice, slight carcinogenicity was noted as sarcomas in 4 of 30 mice. When evaluated as an initiator of carcinogenesis with phorbol myristate acetate 7 out of 9 mice developed papillomas.
2-Fluro-1',2',2',2',-tetrachlorodiethyl ether $CH_2FCH_2OCHClCCl_3$	Pattison et al. (186) reported the intraperitoneal LD_{50} in mice to be 48 mg/kg.
Bis(2,2,2-trifluoroethyl) ether $CF_3CH_2OCH_2CF_3$	The clonic convulsion dose (CD_{50}) reported by Truitt and Ebersberger (191) as intravenous in 30 mice is 26 mg/kg. The intravenous LD_{50} is 46 mg/kg. The intraperitoneal clonic convulsion dose (CD_{50}) in 88 rats is 600 mg/kg. The intraperitoneal LD_{50} is 1260 mg/kg in rats. The mouse clonic convulsion dose (CD_{50}) in an inhalation jar is 0.26 mL as volume of product. The tonic convulsion dose (TD_{50}) as volume in an inhalation jar in mice is 0.9 mL and 0.8 mL observed 30 s and 10 min after onset of convulsion, respectively. The mouse inhalation LD_{50} is 2.75 mL and 0.68 mL of product in a jar for the same time intervals. Krantz et al. (192) found the convulsive threshold in rats to be between 29 ppm and 41 ppm for a 90-s exposure time.

2,2,2-Trifluoroethyl vinyl ether $CF_3CH_2OCH{=}CH_2$ (Fluoromar)	Krantz et al. (193) reported the anesthetic properties. Krantz and Carr (71) later reported it to be an excellent analgesic. It does not produce liver damage or sensitize the myocardium to exogenous catecholamines. It produces minimal cardiovascular and respiratory depression. An anonymous report (194) states that animals metabolize this compound to be more toxic trifluoroethanol, which appears only as a trace in humans.
Bis-1,2-(chloromethyoxy) ethane $ClCH_2OCH_2CH_2OCH_2Cl$	VanDuuren et al. (195) demonstrated that 1 mg/0.1 ml of solvent applied to mouse skin 3 times a week produced a statistically elevated incidence of squamous carcinoma. Subcutaneous injections once weekly of 0.3 mg/0.05 mL vehicle produced a statistically elevated incidence of sarcomas. Intraperitoneal injections once weekly of 0.3 mg/0.05 mL vehicle produced a statistically elevated incidence of sarcomas.
5-Fluoroamyl methyl ether $CH_2F(CH_2)_4OCH_3$	Pattison et al. (186) reported that the intraperitoneal LD_{50} for mice is 90 mg/kg.
Octachloro-di-*n*-propyl ether $CCl_3CH(Cl)CH_2OCH_2CHClCCl_3$	VanDuuren et al. (178, 184) reported that skin application in 20 mice as an initiator evaluation with phorbol ester produced 3 papillomas and 1 carcinoma. Evaluated alone it was noncarcinogenic. VanDuuren (185) reported mouse skin tests were negative for carcinogenicity.
Bis-1,4-(chloromethoxy) butane $CH_2ClO(CH_2)_4OCH_2Cl$	VanDuuren et al. (195) demonstrated that 1.0 mg/0.1 mL of vehicle applied to mouse skin 3 times weekly did not produce a statistically elevated incidence of cancer. Subcutaneous injections once weekly of 0.3 mL/0.05 mL of vehicle produced no evidence of cancer. Intraperitoneal injections once weekly at a dose of 0.1 mg/0.05 mL of vehicle produced no evidence of cancer.
Perfluoroisobutenyl ethyl ether $(CF_3)_2C{=}CFOCF{=}C(CF_3)_2$	Schwartzman (196) presented data identifying the olfactory threshold as a level of 2.8 mg/L. Its LD_{50} in mice is 164 mg/kg. A dose of 6 mg/kg in chronic studies in rats and rabbits produced toxic action. A dose of 0.15 mg/kg produced disturbances and minor reversible morphological changes of the nervous system and internal organs. A dose of 0.015 mg/kg produced no changes in 7 months.
6-Fluorohexyl methyl ether $CH_2F(CH_2)_5OCH_3$	Intraperitoneal LD_{50} in mice is 4.0 mg/kg (186).
4,4'-Difluorodibutyl ether $CH_2F(CH_2)_3O(CH_2)_3CH_2F$	Intraperitoneal LD_{50} in mice is 0.82 mg/kg (186).
Bis-1,6-(chloromethyloxy)	VanDuuren et al. (195) demonstrated that

hexane $CH_2ClO(CH_2)_6OCH_2Cl$	1.0 mg/0.1 mL of vehicle applied to mouse skin 3 times a week produced no evidence of cancer. Subcutaneous injections once weekly of 0.3 mg/0.05 mL of vehicle produced a single sarcoma in 50 mice. Intraperitoneal injections once weekly at a level of 0.3 mg/0.05 mL of vehicle produced no evidence of cancer.
4-Fluoro-4'-chlorodibutyl ether $CH_2F(CH_2)_3O(CH_2)_3CH_2Cl$	Intraperitoneal LD_{50} in mice is 1.32 mg/kg (186).
2-Fluoro-2'-*n*-butoxydiethyl ether $CH_2FCH_2OCH_2CH_2O(CH_2)_3CH_3$	Intraperitoneal LD_{50} in mice is 43 mg/kg (186).

The compounds in Table 72.14 are arranged predominantly by increasing chain length and by increases in halogen substituents. Increased fluorination of diethyl ether progressively diminishes its anesthetic potency so that perfluoroethyl ether is devoid of anesthetic properties. On the other hand, a partially fluorinated compound, bis(2,2,2-trifluoroethyl) ether, in addition to some anesthetic action, is a powerful convulsant (192). This chemical is included in Table 72.14. Buckle and Saunders (197) believe that the toxicity of these compounds can be explained by b-oxidation. Pattison et al. (186) propose that the ether link is ruptured *in vivo*. This latter concept is reinforced by work of Johnston et al. (198), who found that animals biotransform trifluoroethyl vinyl ether to its alcohol, trifluoroethanol.

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F. Aromatic Ethers

Table 72.15. Acute Toxic Effects of Cyclic Ethers

Substance	Oral LD_{50}	Intraperitoneal LD_{50}	Subcutaneous LD_{50}	Intravenous LD_{50}	Dermal LD_{50}
Anisole	—	Rat: 100–900 mg/kg (58)	Rat: 3500–4000 mg/kg (58)	—	—
Phenetole	Guinea pig: 3.0–10 g/kg (174)	—	Rat: 3.5–4.0 g/kg (58)[a]	—	—
Guaiacol	Rat: 1.5 g/kg	—	Pigeon: 0.2 g	Mice:	Human:

	(174) Rabbit: 4 g (199) Cat: 60 drops (199) Mouse: 621 mg/kg (200)		(99) Rabbit: 2.5 g (199) Guinea pig: 0.9 g/kg (199) Rat: 0.9 g/kg (199)	170 mg/kg (211)	2 g/human produces chills, temperture drop, collapse, death due to respiratory failure (199) Rabbit: 4.6 g/kg (211)
Hydroquinine monomethyl ether	Rat: 1.6 g/kg (201)	Mouse: 725 mg/kg (201) Rat: 430 mg/kg (201) Rabbit: 720–970 mg/kg (201)	—	—	—
Hydroquinone dimethyl ether	Rat: 8.5 g/kg (201)	—	—	—	—
Hydroquinone monobenzyl ether (Na salt)	Rat: >3.2 g/kg (202)	—	—	—	—
Eugenol	Rat: 2680 mg/kg (203) Rat: 1930 mg/kg (204) Mouse: 3000 mg/kg (203) Guinea pig: 2130 mg/kg (203)	Mouse: 630 mg/kg (209)[b]	—	—	—
Isoeugenol	Rat: 1.56 g/kg (205) Guinea pig: 1.41 g/kg (205)	Mouse: 600 mg/kg (209)[b] Mouse: 365 mg/kg (205) Mouse: 540 mg/kg (205)	—	—	—
Methyl eugenol	Rat: 1179 mg/kg (206)	Mouse: >640 mg/kg (209)[b] Mouse:	—	Mouse: 112 mg/kg (207)	Rabbit: >2025 mg/kg (206)

		540 mg/kg (210)			
Methyl isoeugenol	—	Mouse: 640 mg/kg (209)[b] Mouse: 570 mg/kg (210)	—	Mouse: 181 mg/kg (207)	—
Butylated hydroxyanisole	Rat: 4–5 g/kg in corn oil (201, 207, 208) Rat: 2.5 g/kg in propylene glycol (201, 207, 208)	—	—	—	—
Vanillin (212)	Rabbit: 3.0 g/kg[a] Rat: 1.58 g/kg Rat: 2.0 g/kg Rat: 2.8 g/kg Guinea pig: 1.40 g/kg	Rat: 1.16 g/kg Mouse: 475 mg/kg Mouse: 0.78 g/kg Guinea pig: 1.19 g/kg	Rat: 1.8 g/kg[c] Rat: 1.5 g/kg	Dog: 1.32 g/kg slow infusion	—
Ethyl vanillin (213)	Rat: >2000 mg/kg Rabbit: 3000 mg/kg	Mouse: 750 mg/kg Guinea pig: 1140 mg/kg	Rat: 1800 mg/kg	Dog: 760 mg/kg	—
Phenyl ether (174)	Rat: 4.0 g/kg[d] Rat: 2.0 g/kg[e] Rat: 3.99 g/kg Guinea pig: 4.0 g/kg[d] Guinea pig: 1.0 g/kg[e]	—	—	—	—
	Eye Irritation	Skin Irritation	Sensitization		Fish LC_{50}
Phenetole	—	Rabbit: slight (174)	—	—	—
Guaiacol	Rabbit: Severe, necrosis (174) Rabbit: 10% in	Rabbit: several exposures produced severe irritation, burning, loss of	—	—	—

	propylene glycol—mild (174)	sensation, dermatitis with vesication (150)			
Hydroquinone monomethyl ether	Rabbit: moderate corneal damage (174)	Guinea pig: 40% solution in olive oil and acetone—slight or moderate	Guinea pig: negative (202)		
Hydroquinone dimethyl ether	—	Guinea pig: 40% solution in olive oil and acetone—slight or moderate	Guinea pig: negative (202)	—	—
Methyl eugenol	Rabbit: slight (206)	Rabbit: slight (206)	—	Rainbow trout: 6 ppm, 96 h (206) Bluegill sunfish: 8.1 ppm, 96 h (206)	

[a] Minimum lethal dose.
[b] Dosed simultaneously with hexobarbital or zoxazolamine.
[c] Lethal dose.
[d] Total mortality.
[e] Total survival.

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G. Hydroquinone Ethers
Repeated exposure to these chemicals may result in depigmentation of skin. Excessive skin contact may cause dermatitis.

Trapping the dust of hydroquinone ethers with filter devices and their vapors with organic solvents and subsequent analysis by chromatography, spectroscopy, or other method suitable for the detection of the aromatic ring should be adequate for an accurate atmospheric analysis. Physical and chemical properties are presented in Table 72.1.

Table 72.16. Toxic Effects of Butylated Monochlorodiphenyl Oxide Mixtures and Related Compounds in Experimental Studies

Compound	Species	Test	Results	Reference
		Acute Exposure		
Butylated monochlorodiphenyl oxide mixture	Rat	Oral LD_{50}	>10 g/kg	305
	Rat	Inhalation at 25°	No observable	

		C, 50°C	effect	
	Rabbit	Eye irritation	No observable effect	
	Rabbit	Skin irritation	No observable effect	
	Rabbit	Ear acneigenicity	No observable effect	
	Guinea pig	Skin sensitization	No observable effect	
	Fathead minnow	96-h static LC_{50}	15.4 mg/L	
		Flow-through threshold	1.81 mg/L	
	Daphnia magna	48-h static LC_{50}	0.24 mg/L	
	Rat	Pharmacokinetic profile, gavage	Radio-labeled compound is 90% absorbed from the gut. The elimination is biphasic and 75% excreted in feces within 3 days. Monobutylated component half-life is 65 hr. Dibutylated component half-life is 71 h.	306
	Monkey	Pharmacokinetic profile, gavage	Radiolabeled compound was 90% recovered. Major route of excretion was urine. Animal was constipated.	306
Monochlorodiphenyl oxide	Fathead minnow	96 h static LC_{50}	1.75 mg/L	307
		Flow-through threshold	0.090 mg/L	
	Daphnia magna	48 h static LC_{50}	0.39 mg/L	
		Subacute Exposure		
Butylated monochlorodiphenyl oxide mixture	Rabbit	Skin irritation	Very slight effect	307
	Rat	Diet feeding	At levels of 5 to 90 mg/(kg)(day) for 90 or 156 days, no treatment effect noted for demeanor, hematology, urinalysis, clinical	307

			chemistry, porphyrin excretion, or ophthalmology. Body weight reduction noted. Reversible liver and kidney changes noted at 45 and 90 mg/(kg)(day). Test material stored in fat.	
	Rat	Teratology	At levels of 500-1000 mg/(kg)(day), no teratogenic response was noted.	308
	Rabbit	Teratology	At levels of 1 to 10 mg/(kg)(day), no teratogenic response was noted.	308

Table 72.17. Chlorinated Phenyl Ethers Survey of Single-Dose Oral Feeding Studies on Guinea Pigs

	After 4 Days		After 30 days	
Material	**Lethal Dose (g/kg)**	**Survival Dose (g/kg)**	**Lethal Dose (g/kg)**	**Survival Dose (g/kg)**
1X	0.7	0.2	0.60	0.1
2X	1.3	0.4	1.00	0.05
3X	2.2	0.4	1.20	0.2
4X	3.0	0.4	0.05	0.0005
5X	3.4	1.8	0.10	0.005
6X	3.6	0.4	0.05	0.005

Table 72.18. Chlorinated Phenyl Ethers Results of Repeated Oral Feeding

of Rabbits

Material	Dose, g/kg	No. of Doses	No. of Days	Effect
1X	0.1	19	29	None
2X	0.1	19	29	Mild liver injury
3X	0.1	5	12	Death
	0.05	20	29	Slight liver injury
	0.01	20	29	No effect
4X	0.05	4	10	Death
	0.005	20	29	Severe liver injury
5X	0.05	8	21	Death
Pentachlorophenyl ether (highly purified)	0.1	20	29	Moderate liver injury; no growth
	0.01	20	29	Slight liver injury
6X	0.001	20	29	No effect
	0.005	8	10	Death
	0.001	20	28	Severe liver injury
	0.0001	20	28	No effect

Ethers
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H. Cyclic Ethers
General Information
38.0 Cellulose Ethers
General Physical and Chemical Properties
The cellulose ethers—methylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium salt, ethylcellulose, and hydroxyethylcellulose—are all formed by reacting alkali-cellulose of predetermined average molecular weight with various materials to form the respective ether.

Each anhydroglucose unit of the cellulose polymer has three free hydroxyl groups that can be etherified. The degree to which this is effected and the nature of the substituent group influence markedly the physical properties, particularly solubility, of the product. The molecular weight of the alkali-cellulose markedly affects the viscosity of the final product. All the ethers are odorless, tasteless, and very stable chemically (304).
Exposure Assessment
All the cellulose ethers may be trapped from the air by filtration through a membrane filter. The water-soluble ethers can also be trapped in cold water. Ethylcellulose can be trapped in organic solvents.

The determination of methylcellulose and ethylcellulose can be accomplished in various media for methoxyl and ethoxyl groups. ASTM methods D1347-56 for methylcellulose and D914-50 for ethylcellulose should be consulted. The colorimetric methods of Samsel and DeLap (313) and of Kanzaki and Berger (314) for methylcellulose and of Samsel and Aldrich (315) for ethylcellulose also are very useful.

The method of Morgan (316) is generally the basis for determining the hydroxyalkyl ethers of cellulose. It is based on the hydrolysis of the ether with hydriodic acid, which yields the alkyl iodide and the corresponding olefin. Measurement of the olefin formed can be accomplished by absorbing in Wijs solution with subsequent determination of the iodine number (174).

Hydroxypropyl methylcellulose may be determined by employing the method of Samsel and McHard (317) to determine the methoxyl content, and the method of Lemieux and Purves (318) as modified (319) for determining hydroxypropyl content.

Carboxymethylcellulose can be determined by the anthrone colorimetric method described by Black (320). It can also be estimated by hydrolyzing and determining the resulting glycolic acid by the method of Calkins (321). ASTM method D1439-58T may also be adaptable.

Toxic Effects

The cellulose ethers are all very low in toxicity when administered by normal routes. They are not irritating to the skin or other delicate membranes of the body. When swallowed, they are not absorbed to any appreciable degree and appear unchanged in the feces. No inhalation studies have been conducted, but exposure of humans to the dust in manufacturing operations over many years has not led to any known adverse effects. Parenteral administration of the water-soluble ethers has led to serious adverse effects in animals and it would seem unwise to administer them by such routes to human subjects (304).

Ethers

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I. Crown Ethers

44.0a 6-Crown-2-Ether

44.0b 12-Crown-4-Ether

44.0c 15-Crown-5-Ether

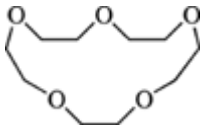
44.0d 18-Crown-6-Ether

44.0e Dicyclohexyl-18-Crown Ether

44.1 Chemical and Physical Properties

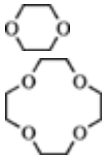
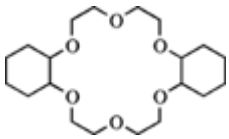
44.2 Production and Use

Very little information exists in the literature on the physical and chemical properties of the crown ethers. The name “crown” was first used in 1967 (322) and derives from the stereochemical structure, which for 15-crown-5 may be drawn as follows:



Available chemical and physical properties are presented in Table 72.19. During distillation 18-crown-6-ethers may convert to *p*-dioxane and present an explosion hazard due to clogging of traps (323–325).

Table 72.19. Chemical and Physical Properties of the Crown Ethers

Compound		CAS Number	Molecular Formula
6-Crown-2-Ether 12-Crown-24-Ether		[*294-93-9*]	$C_8H_{16}O_4$
15-Crown-25-Ether		[*33100-27-5*]	$C_{10}H_{20}O_5$
18-Crown-26-Ether		[*17455-13-9*]	$C_{12}H_{24}O_6$
Dicyclohexyl-18-Crown-6		[*16069-36-6*]	$C_{20}H_{36}O_6$

These compounds may be liquid or solid at room temperature. No satisfactory procedure has been developed for analyzing these materials in the atmosphere (326).

44.4 Toxic Effects

44.4.1 Experimental Studies 44.4.1.1 Acute Toxicity The oral LD_{50} for the following crown ethers has been determined to be as follows:

Ether	Mice (327) Oral LD_{50}, g/kg	Time to Death	Rats (328) Oral LD_{50}, mL/kg
6-Crown-2	6.0		
12-Crown-4	3.15	<15 min	2.83
15-Crown-5	1.02	1 hr	1.41
18-Crown-6	0.705	>1 day	1.39

Oral administration of 18-crown-6 to healthy dogs produced transitory signs of tremulous movement and paralysis of the hind limbs 2–12 h after administration (329). Leong (330) reported that a single

oral dose of 12-crown-4 at a level of approximately 100 mg/kg in rats produced central nervous system (CNS) effects and testicular atrophy. The dosages of higher aliphatic crowns, which were capable of producing CNS effects, were 1–10 times higher. This author also reported that skin absorption of 12-crown-4 in rabbits could produce CNS effects, but larger macrocyclic crowns only produced slight skin redness.

Pedersen (322) reported the approximate lethal dose of 300 mg/kg for dicyclohexyl-18-crown-6 by ingestion in rats. Death occurred within 11 min. No deaths occurred at 200 mg/kg. Skin absorption in experimental animals was fatal at a dose level of 130 mg/kg for dicyclohexyl-18-crown-6. This material was irritating to the skin and eyes. It was reported that permanent eye damage may result if the eye is not washed with water after exposure.

44.4.1.2 Chronic Toxicity Leong et al. (326) exposed rats to 0.5 and 1.0 ppm of 12-crown-4 vapors 7 h/day, 5 days/week, for 3 weeks. Both levels produced marked testicular atrophy that was associated with degeneration of the germinal epithelium. This effect persisted up to 4 months postexposure. Atrophy of the prostate and seminal vesicles was also noted. Exposure to 1 ppm of 12-crown-4 vapors produced prominent degradation of conditioned behavioral performances, depression of food and water intake, retardation of growth, and body tremors. These effects were reversible.

44.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms It is believed that the crown ethers complex with electrolytes, thus changing the permeability of Na^+ and K^+ across cell membranes (326, 331–334). Investigations thus far indicate the nerve conduction changes are fully reversible.

44.4.1.7 Neurological Gad et al. exposed three species to 18-crown-6 with a repeated dose regimen that involved ever-increasing dose levels in each animal over the exposure time period (328). Rabbits were exposed intravenously 5 days/week at dose levels increasing from 6 mg/kg to 12.5 mg/kg for 3 weeks. Rats were dosed intraperitoneally to ever-increasing dose levels of 20 mg/kg through 80 mg/kg for more than 1 month. Mice were intraperitoneally dosed from 20 mg/kg to 160 mg/kg. Signs of nervous system effects included tremors, hyperactivity, loss of limb strength, muscle twitching, and decreased awareness of light stimuli. Exposure levels were increased in each species because of accommodation to each dose level in a few hours to 3 days. No clinical or histopathological changes were observed. These authors claim to have observed increasing behavior changes, which are completely reversible, with increasing molecular size of crown ethers.

44.5 Standards, Regulations, or Guidelines of Exposure

No hygienic standards for occupational exposure have been established for the crown ethers.

Ethers

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Aldehydes and Acetals
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A. Saturated Aliphatic Aldehydes

Aldehydes and Acetals
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B. Unsaturated Aliphatic Aldehydes

Alpha and beta unsaturated carbonyl compounds (enals) are ubiquitous in the human environment. They are used in the manufacture of chemicals for the production of plastics, pharmaceutical drugs, and cosmetics, and in the rubber industry. They are also formed endogenously, for example, during lipid peroxidation or after oxidative stress. These compounds are highly reactive and are suspected genotoxic mutagens or carcinogens (204, 205). Unsaturated carbonyl compounds are mutagenic toward *S. typhimurium* in the absence of an activating system (206–208) but not in some strains (209, 210).

Table 73.3 shows the effect of unsaturation on the inhalation toxicity of aldehydes.

Table 73.3. Effect of Unsaturation on the Inhalation Toxicity of Aldehydes

Compound	Formula	LC_{50} (ppm) in Rats	Time of exposure (min)
Acetaldehyde	CH_3CHO	20,000	30
Ketene	$CH_2{=}CHO$	130	30
Proionaldehyde	CH_3CH_2CHO	26,000	30
Acrolein	$CH_2{=}CHCHO$	130	30
Isobutyraldehyde	$(CH_3)_2CHCHO$	> 8,000	4 h
Methacrolein	$CH_2{=}C(CH_3)CHO$	250	4 h
n-Butyraldehyde	$CH_3(CH_2)_2CHO$	60,000	30
Crotonaldehyde	$CH_3CH{=}CHCHO$	1,400	30

Table 73.4. Physical and Chemical Properties of Unsaturated Aliphatic Aldehydes

Compound	CAS Number	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (°C)	Specific Gravity	Sol. in Water at 68°F	Vap press (mm
Acrolein	[*107-02-8*]	CH_2═CHCHO	56.06	52.6	–87.7	0.84	4	21(
Citronellal	[*106-23-0*]	CH_3═CHCHO	152.23	229.0		0.8898	2	5
Crotonaldehyde	[*4170-30-3*]	CH_3CH═CHCHO	70.10	104.0		0.87		19
2-Ethyl-3-propylacrolein	[*26266-68-2*]	C_4H_9CH═$C(CH_3)$CHO	126.22					
Ketene	[*463-51-4*]	CH_2═CO	42.02	–49.8	–151.0	Gas		> 76
Methacrylaldehyde	[*78-85-3*]	CH_2═$C(CH_3)$CHO	70.09	68.4		0.84	5	
Methyl-b-ethylacrolein	[*623-36-9*]	$C_6H_{10}O$	98.14	136.5		0.8581	1	
Mucochline	[*87-56-9*]	CHOCCl═CClCOOH	168.97		125.0			
Propionaldehyde	[*624-67-9*]	CH═C═CHO	54.05	60.0		0.9152	5	
trans-2-Hexenal	[*6728-26-3*]	C_3H_7CH═CHCHO	98.14	146.5		0.8491		

Table 73.5. Toxic Effects of Unsaturated Aliphatic Aldehydes

Chemical Name	Species	Exposure Route	Approximate Dose	Treatment Regimen	Ob
Ketene	Mouse	Inh	23 ppm/30 m	LC_{Lo}	Conv effec thres
	Monkey	Inh	200 ppm/10 m	LC_{Lo}	Ptosi pulm
	Cat	Inh	750 ppm/10 m	LC_{Lo}	Acut edem struc of sa

	Rabbit	Inh	53 ppm/2 H	LC_{Lo}	Acut edem
	Guinea pig	Inh		LC_{Lo}	
Acrolein	Man	Inh	153 ppm/10 m	LC_{Lo}	
	Rat	Inh	18 mg/m^3/4 h	LC_{50}	
	Rat	I.p.	4 mg/kg	LD_{50}	
	Rat	Inh		Pre-treatment with 15 ppm HCHO, 6 h/d, 9 d; challenge on the 10th day	$RD_{5($
	Rat	Inh	0.25, 0.67, 1.40 ppm	6 h/d, 1–3 d	Redu glutat trans glutat after expos activi ghuta perox
	Rat liver		14 mmol/L	*In vitro*	Inhib reduc
	Mouse	Oral	13900 mg/kg	LD_{50}	Somn loss c weigl
	Mouse	I.p.	9008 mg/kg	LD_{50}	
	Mouse	S.c.	30 mg/kg	LD_{50}	Gene fatty degen
	Cat	Inh	1570 mg/m^3/2 h	LC_{Lo}	
	Rabbit	Inh	4900 ppb/6 h/13 W-I	TC_{Lo}	Chan weigl
	Hamster	Inh	4 ppm/7 h/52 W-I	TC_{Lo}	Chan lung, weigl
	Human	Eye	500 ppb/12 m	Acute toxicity	
	Rabbit	Skin	5 mg open	Acute toxicity	Sever
	Rabbit	Eye	1 mg	Acute toxicity	Sever
			10 mM	*In vitro*	Inhib tyros phosp
	Human: alveolar macrophages		10 mM		Inhib macr cytok and a
	S. typhimurium		50 mg/plate (+S9)	Mutation in	

			microorganisms	
E. coli		286 nmol/L	DNA adduct	
Fibroblasta			DNA adduct	
D. melanogaster	Oral	5, 10, 20 mmol/L	SMART	Nonp induc spots
D.melanogaster	Parenteral	0.5, 1, 2.5, 5, 10 mmol/L	Sex-linked recessive lethal	No e
D. melanogaster-parenteral	I.p.	0.5, 1, 2.5, 5 mmol/L	Sex linded recesaive lethal	Incre frequ decre 5 mM morta
D. melanogaster			Sex linked recessive	Cell repai mec.
Human		30 mmol/L	DNA damage	
Human pulmonary alrety endothelial cells	*In vitro*	1.0, 3.0, 4.5 mM	Monothelial cells were incubated in an acrolein-containing solution	Dose incre dehy releas decre gluta sulfh no ef oxidi
Human fibroblast		100 mmol/L	DNA adduct	
		5 mmol/L	Sister chromatid exchange	
Human:fibroblast		200 nmol/L	Gene mutation in mammalian cells	
Hamster:lung		500 nmol/L	Gene mutation in mammalian cells	
Calf thymus DNA		58 gm/L/3 h	DNA adduct	
E. coli	*In vitro*	150 mM	pUC13 plasmid labeling/incobation in media	One 270 k
Mammal:lymphocyte		80 mmol/L	DNA inhibition	
Chinese hamster ovary				Siste excha
S. typhimurium			TA100	No e
S. typhimurium			TA 100	Stron effec
S. typhimurium	Ames test, TA104	0.9 mmol	Incubation in serum/food	Muta
S. typhimurium	Ames Test	0, 3.13, 6.25, 12.5, 25, 50, 100, 200	Plate incorporation method with metabolic asctivation	Dose reapo effec capal

		Skin/eye irritant			
Methacryladehyde	Rat	Oral	140 mg/kg	LD_{50}	
	Rat	Inh	125 ppm/4 h	LC_{Lo}	
	Rabbit	Skin	430 mL/kg	LD_{50}	
	S. typhimurium		500 mmol/L(+s9)	Ames test, TA104	Muta
	S. typhimurium		500 mmol/L(–S9)	mutation in microorganisms	
2-Ethyl-3-propylacrlein	Rat	Inh	8400 ppm/45 m	LC_{Lo}	Ataxi gener orver dyspr
	Rat	I.p.	800 mg/kg	LD_{50}	Alter musc
	Mouse	Oral	> 3200 mg/kg	LD_{50}	somn weak
	Mouse	I.p.	400 mg/kg	LD_{50}	Musc ataxi
	Dog	Inh	> 1000 ppm/4 h	LC_{Lo}	Chan or fu saliv naus
	Rabbit	Skin	2520 mL/kg	LD_{50}	Somn conv effec thres
	Rabbit	Eye	5 mL/24 h		Mod
	Guinea pig	Skin	> 10 mL/kg	LD_{50}	
Crotonaldehyde	Rat	Inh		Pretreatment with 15 ppm HCHO, 6 h/d, 9 d; challenge on the 10th day	RD_{5}
	E. coli	*In vitro*	8.5 mM	pUC13 plasmid labeling/incubation in media	One plasn
	Human lymphoblast cells		10, 100, 500 mM	Shuttle vector treated and then transgened	Dose incre frequ
	Human lymphocyte cells/Namalva cells	Incubation	5–250 mM	Incubated in medium, stimulation of lymphocytes with phytohemagglutinine	Signi relate SCE micr struc chro aberr clast
		Skin/eye irritant			

Methyl-b-ethylacrolein	Rat	Oral	4290 mg/kg	LD_{50}	
	Rat	Inh	2000 ppm/4 h	LC_{50}	
	Rabbit	Skin	4500 mL/kg	LD_{50}	
		Skin/eye irritant			
trans-2-Hexenal	Rat	Oral	780 mg/kg	LD_{50}	Lacri regio arteri dilati struct of sal
	Rat	I.p.	180 mg/kg	LD_{50}	Lacri regio arteri dilati struct of sal
	Mouse	I.p.	100 mg/kg	LD_{50}	Lacri regio arteri dilati struct of sal
	Rabbit	Skin	600 mg/kg	LD_{50}	
	Rabbit	Skin	500 mg/24 h	Acute toxicity	Mode
	Human buccal cells	Oral	10 ppm	4 Mouth rinses/d 3 day; analysis of buacal smear	Incre micr muta
	Human lymphocyte cells/Namalva cells	Oral	5–250 mM	Incubated in medium, stimulation of lymphocytes with phytohemagglutinine	Signi relate SCE micr aneu induc aneu
	S. typhimurium		2 mM, serum, lipid peroxidation, food	Ames test, TA104	Muta

C. Halogenated and Other Substituted Aldehydes
Halogenation tends to increase the local irritating action and general toxicity of the aldehyde.
31.0 Chloroacetaldehyde
31.0.1 CAS Number: [*107-20-0*]

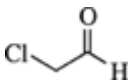
31.0.2 Synonyms: 2-Chloro-1-ethanal; 2-chloroacetaldehyde; monochloroacetaldehyde; 2-chloroethanal; chloroethanal; alpha-chloroacetaldehyde; chloroacetaldehyde, 45% aqueous solution (CAA)

31.0.3 Trade Names: NA

31.0.4 Molecular Weight: 78.50

31.0.5 Molecular Formula: C_2H_3ClO

31.0.6 Molecular Structure:



31.1 Chemical and Physical Properties
See Table 73.6.

Table 73.6. Physical and Chemical Properties of Halogenated Aldehydes

Compound	CAS Number	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (°C)	Specific Gravity	Sol. in Water (at 68°F)	Vapor Pressure (mmHg)	Lel Uel (%)
Chloral hydrate	[*302-17-0*]	$CCl_3CH{=}O \cdot H_2O$	165.40	98.0	62.0	1.9081	4		
Chloroacetaldehyde	[*107-20-0*]	$ClCH_2CHO$	78.50	85.5	–16.3			100	
Fluoroacetaldehyde	[*1544-46-3*]	$FCH_3CH{=}O$	62.05						
Trichloroacetaldehyde	[*75-87-6*]	$CCl_3CH{=}O$	147.39	97.8	–57.5	1.512	4	35	
Trifluoroacetaldehyde	[*421-53-4*]	$C_2{-}H_3{-}F_3O_2$	116.05						

31.2 Production and Use
Chloroacetaldehyde is used in the manufacture of 2-aminothiazole and other compounds. It is also used to facilitate bark removal from tree trunks and as a fungicide.
31.3 Exposure Assessment
31.3.2 Background Levels Chloroacetaldehyde has been identified as a chlorination by-product in drinking water supplies and is also a metabolite of vinyl chloride (287).

31.3.3 Workplace Methods NIOSH Method 2015 is recomended for determining workplace exposures to chloroacetaldehyde (141).
31.4 Toxic Effects
31.4.1 Experimental Studies 31.4.1.1 Acute Toxicity The LD_{50}, for chloroacetaldehyde in four species via three routes of entry were rat: 23.0 mg/kg oral and 2.0 mg/kg intraperitoneal; mouse: 21.0 mg/kg oral and 2.0 mg/kg intraperitoneal; rabbit: 1.39 mg/kg intraperitoneal and 67.0 mg/kg skin; and guinea pig: 0.636 mg/kg intraperitoneal (288). Chloroacetaldehyde is acutely toxic to mice via inhalation (289).

31.4.1.2 Chronic and Subchronic Toxicity At doses less than the acute LD_{50}, rats that succumbed after 30 days of injections of chloroacetaldehyde exhibited hematological disturbances, but the most obvious effects were bronchitits and pneumonitis (289).

31.4.1.6 Genetic and Related Cellular Effects Studies Chloroacetaldehyde was mutagenic in the *S. typhimurium* reversion test, the forward mutation system of the *Aspergillus nidulans* and the forward and backward mutation system of *Streptomyces coelicor* (288). Chlroacetaldehyde is a potent toxicant and has DNA reactivity (287). It is an effective inhibitor of DNA synthesis, forms interstrand linkage with DNA *in vitro*, modifies DNA conformation (292), and reacts with nucleotide bases (292a).

For additional information on the toxic effects of chloroacetaldehyde, see Table 73.7.

Table 73.7. Toxic Effects of Halogenated Aldehydes

Chemical Name	Species	Exposure Route	Approximate Dose	Treatment Regimen	Observ Effec
Chloroacetaldehyde	Rat	Oral	89 mg/kg	LD_{50}	
	Rat	Inh	650 mg/m^3/1 h	LC_{50}	BP elevati not characteriz autonomic section; respiratory obstructior
	Rat	Parenteral	58 mg/kg/12 W-I	TD_{Lo}	Lung fibro changes in erythrocyt count, deat
	Rat	I.p.	113 mg/kg/30 D-I	TD_{Lo}	Changes ir brain and kidney wei
	Rat	I.v.	5 gm/kg	DNA inhibition	
	Mouse	Oral	17 mg/kg/day/104 w	TD_{Lo}	Increase in weight, hepatocellu necrosis, a liver tumor
	Rabbit	Skin	267 mg/kg	LD_{50}	
	Rabbit	I.p.	5522 ug/kg	LD_{50}	

	Guinea pig	Inh	400 pm/30 M	LC_{Lo}	Hallucinati distorted perception dyspnea
	S. typhimurium		400 umol/L (+S9)	Mutation in microorganisms	
	E. coli		1 mmol/L (–S9)	Mutation in microoganisms	
	E. coli		10 mg/plate	DNA repair	
	B. subtilis		5 mmol/L (–S9)	Mutation in microorganisms	
	B. subtilis		100 mmol/L	DNA repair	
	S. cerevisiae		3100 mmol/L (+S9)	Mutation in microorganisms	
	A. nidulans		40 ml/plate (–S9)	Mutation in microorganisms	
	S. coelicolor		25 ml/plate (–S9)	Mutation in microorganisms	
	S. pombe		6250 mmol/L (+S9), 20 mmol/L (–S9)	Mutation in microorganisms	
	Salmon; sperm		20 mmol/L	DNA damage	
	Human; lymphocyte		100 umol/L	DNA damage	
	Rat liver cells		47 mmol/L		
	Salmon:testis		3 gm	DNA adduct	
	Rat liver cells	*In vitro*	47 mM	Incubation at 37°C for 30 min	Duplicated percentage IF-DNA
Trichloroacetaldehyde	Rat	Inh	440 mg/m^3/4 h	LC_{50}	Ptosis; somnolenc dyspnea
	Rat	Inh	80 mg/m^3/4 h/2 W-I	TC_{Lo}	Acute pulmonary edema; cha in adrenal weight, we loss or decreased weight gai
	Dog	Inh	5900 mg/m^3/4 h	LC_{50}	Lacrimatio convulsion effect on s threshold,
	S. typhimurium		1 mg/plate (+S9), 10 mg/plage (–S9)		Mutation i microorgar
	S. cerevisiae		1 gm/L (+S9)		Mutation i microorgar

	S. coloericolor		40 mg/plate		Mutation i microorgar
		Hepatotoxic			
Chloral hydrate	Mouse	Oral	15.7 mg/kg day	LOAEL	
	Mouse	Oral	3 g/t (3 W pre-3 W post)	TD_{Lo}	Effects in newborn
	Mouse	Oral	10 mg/kg	TD_{Lo}	Hepatic adenoma
	Mouse	Oral	166 mg/kg day	TD_{Lo}	Hepatocell necrosis, hyperplasi
	Mouse	Intratesticular	300 mg/kg		Decreased spermatog
	Mouse	Oral			Hepatic DI damage
	Mouse lymphoma cells	Suspension	0 to 1600 mg/ml	*In vitro* incubation without metabolic activation	Induced cytotoxicit very weak mutagenic response, weakly clastogenic
	Man/woman	Oral	1000/960 mg/kg	TD_{Lo}	Pulse rate increased without fal BP
	Child	Oral	219 mg/kg	TD_{Lo}	Arrythmia
	Child	I.v.	39 mg/kg	TD_{Lo}	Somnolenc
	Human-lymphocyte	*In vitro*	211–1000 mg/L		Aneuploid sister-chro exchanges
	S. typhimurium		1 mg/plate (+/S9)	mutation in microorganisms	
	S. coloericolor		10 mg/plate	mutation in microorgaaisms	
	Rat liver cells	*In vitro*	25, 100, or 250 mM	Incubation at 37°C for 30 min	No detecta effect
Trifluoroacetaldehyde	Mouse	Oral/I.p.	600 mg/kg	LD_{50}	
	Mouse	I.v.	660 mg/kg	LD_{50}	Change in motor activ

31.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH ceiling/STEL for chloroacetaldehyde is 1 ppm. The OSHA PEL and the NIOSH REL are also 1 ppm.
32.0 Trichloroacetaldehyde
32.0.1 CAS Number: [*75-87-6*]

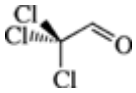
32.0.2 Synonyms: Chloral; grasex; 2,2,2-trichloroacetaldehyde; trichloroethanal; chloral, anhydrous, inhibited

32.0.3 Trade Names: NA

32.0.4 Molecular Weight: 147.39

32.0.5 Molecular Formula: C_2HCl_3O

32.0.6 Molecular Structure:



32.1 Chemical and Physical Properties
See Table 73.6.
32.4 Toxic Effects
For information on the toxic effects of trichloroacetaldehyde, see Table 73.7.
33.0 Chloral Hydrate
33.0.1 CAS Number: [*302-17-0*]

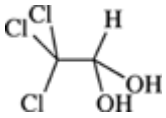
33.0.2 Synonyms: Trichloroacetaldehyde monohydrate; 1,1,1-trichloro-2,2-ethanediol; nycton; rectules; somnos; nortec; kessodrate; hydral; trichloroacetaldehyde hydrate; bi 3411; sk-chloral hydrate; trawotox; Escre; 2,2,2-trichloro-1,1-ethanediol

33.0.3 Trade Names: Noctec; Aquachloral; Chloraldurat; Dormal; 1,1-Ethanediol, 2,2,2-trichloro- (9CI); Felsules; Hydral; Lorinal; Nycoton; Phaldrone; Somni SED; Somnos; Sontec

33.0.4 Molecular Weight: 165.40

33.0.5 Molecular Formula: $C_2H_3Cl_3O_2$

33.0.6 Molecular Structure:



33.1 Chemical and Physical Properties
See Table 73.6.
33.2 Production and Use
Chloral hydrate is made by adding water to trichloroacetaldehyde. The major use of chloral hydrate is in medicinals.

Chloral hydrate is used before some surgeries or procedures to help relieve anxiety and to induce sleep. It is widely used to sedate children undergoing dental and medical procedures and imaging studies (294). Chloral hydrate is available as a suppository, syrup, or capsule.
33.4 Toxic Effects
33.4.1.2 Chronic and Subchronic Toxicity Sanders et al. (295) dissolved chloral in water to form chloral hydrate. Groups of 140 male and 140 female CD-1 mice were maintained on the aqueous solution at concentrations of 0.07 or 0.7 mg/mL as chloral, for 90 days starting at 4 weeks of age; 260 mice/sex received deionized water and served as controls. Low and high TWA dosages based on

measured water intake were reportedly 15.7 and 159.8 mg/kg/day for the males and 18.2 and 173.4 mg/kg/day for females, respectively. Growth, hematology, and serum chemistry parameters, liver enzyme activities and microsomal parameters, organ (liver, lungs, spleen, thymus, kidneys, testes and brain) weights, and gross pathology were evaluated. Significant effects included dose-related increased final body weights in males, increased final body weights in high-dose females, dose-related increased relative liver weights in males, increased serum LDH and SGOT in high-dose males, and increased microsomal cytochrome b5 content and aminopyrine *N*-demethylase and aniline hydroxylase activities in high- and low- dose males. Therefore, the liver appears to be a target organ for chloral toxicity, and the dose of 15.7 mg/kg/day in males is the LOAEL. Because this was the lowest dose tested, this study does not define a NOAEL or NOEL. Dividing the LOAEL of 15.7 mg/kg/day by an uncertainty factor of 10,000 yields an RfD of 0.002 mg/kg/day, or 0.1 mg/day for a 70-kg person.

In female mice, the immune system, particularly the ability to produce IgM antibody to a T-dependent antigen, is the most sensitive indicator (296). In male mice, the liver is the most sensitive organ. Both effects occurred at the lowest concentration tested, 0.07 mg/mL or 15.7 mg/kg (295). The adverse effects on the immune system observed at the 15.7-mg dosage level support the LOAEL used to derive the RfD.

Offspring from mice that were exposed throughout pregnancy to 204 mg/kg/day but not 21.3 mg/kg/day chloral in the drinking water had a behavioral impairment (impaired learning retention of a passive avoidance task) (293). Gross malformations or effects on maternal reproductive parameters were not noted.

33.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Some concern regarding the potential carcinogenicity of chloral hydrate is based on the assumption that it is a reactive metabolite of trichloroethylene and is responsible for the carcinogenicity of this compound (295). Nevertheless, it has been proven that the carcinogenicity of trichloroethylene is due to a reactive epoxide metabolite, rather than chloral hydrate (297).

33.4.1.4 Reproductive and Developmental Intratesticular injection of 300 mg/kg chloral hydrate produced decreased spermatogenesis in mice (298).

33.4.1.5 Carcinogenesis Chloral hydrate has not been adequately tested for teratogenicity, reproductive effects, or chronic toxicity. Similarly, no histological evaluations have been conducted.

33.4.1.6 Genetic and Related Cellular Effects Studies Administration of 40 ml/plate of chloral hydrate to *S. coloericolor* induces mutagenic activity and death in the cell. No effect is noted with a dose of 10 mg/plate of *A. nidulans* (288).

33.4.2 Human Experience Chloral hydrate acts on the central nervous system to induce sleep. At normal doses, this sleep induction does not affect breathing, blood pressure, or reflexes. When used in combination with analgesics, it can be used to manage pain.

33.4.2.2.1 Acute Toxicity Acute overdoses may cause cardiorespiratory depression (298). On rare occasions excessive or repetitive doses have been associated with cardiac arrythmias (299).

Side effects in adults include drowsiness, low body temperature, slurred speech, weakness, difficulty breathing, shortness of breath, nausea, vomiting, confusion, convulsions, and hallucination.

33.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Chloral hydrate is metabolized to trichloroethanol and trichloroacetic acid, both of which are pharmacologically active and may contribute to the acute toxicity of chloral hydrate. The half-life of trichloroethanol ranges from 9 to 40 hours, depending on the age of the subject (300). The younger the patient, the longer the half-life. This induces the accumulation of active metabolites during repetitive doses (300). In fact, toxicity

characterized by respiratory depression and hypotonia associated with a trichloroethanol plasma concentration seven times that associated with sedation in adults was reported in an infant who received multiple doses of chloral hydrate while on mechanical ventilation (294). There is evidence that chloral hydrate and/or trichloroethanol may increase the risk of both direct and indirect hyperbilirubinemia in newborns (301).

34.0 Fluoroacetaldehyde

34.0.1 CAS Number: [*1544-46-3*]

34.0.2 Synonyms: NA

34.0.3 Trade Names: NA

34.0.4 Molecular Weight: 62.05

34.0.5 Molecular Formula: C_2H_4FO

34.1 Chemical and Physical Properties

See Table 73.6.

35.0 Trifluoroacetaldehyde Monohydrate

35.0.1 CAS Number: [*421-53-4*]

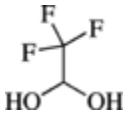
35.0.2 Synonyms: Trifluoroacetaldehyde monohydrate; trifluoroacetaldehyde hydrate; trifluoroacetaldehyde monohydrate, tech.

35.0.3 Trade Names: NA

35.0.4 Molecular Weight: 116.05

35.0.5 Molecular Formula: $C_2H_3F_3O_2$

35.0.6 Molecular Structure:



35.1 Chemical and Physical Properties

See Table 73.6.

35.2 Production and Use

Trifluoroacetaldehyde monohydrate is used as an agricultural chemical, a drug and therapeutic agent, a fungicide, bactericide, and wood preservative.

35.5 Standards, Regulations or Guidelines

Russia has a STEL of 5 mg/m^3 for trifluoroacetaldehyde monohydrate.

Aldehydes and Acetals

Maria T. Morandi, Ph.D., CIH, Silvia Maberti, MS

D. Aliphatic Dialdehydes

A number of dialdehydes have become available commercially and although not all of their properties are completely known, some toxicological data have become available. These materials

have many of the same properties as the monoaldehydes but because of their bifunctionality, may provide different types of useful cross-linking reactions. They tend to polymerize readily and are sometimes available only in an aqueous solution in the presence of polymerization inhibitors.

Table 73.8. Physical and Chemical Properties of Aliphatic Dialdehydes

Compound	CAS Number	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (°C)	Specific Gravity	Sol. in Water (at 68°F)	Vapo pressu (mmH
Glutaraldehyde	[*111-30-8*]	$O{=}CH(CH_2)_3CH{=}O$	100.12	188.0		1.1	5	17
Glutaraldehyde disodium bisulfite	[*7420-89-5*]	$C_5H_{12}O_8S_2$	264.47					
3-Methylglutar-aldehyde	not known	$CH_3CH(CH_2CH{=}O)_2$						
Glyoxal	[*107-22-2*]	$O{=}CHCH{=}O$	58.04	50.4	15.0	1.3826	4	
Hexa-2,4-dienal	[*142-83-6*]	$CH_3(C_2H_2)_2CH{=}O$	96.13	174.0		0.898		
Succinaldehyde	[*638-37-9*]	$O{=}CH(CH_2)CH{=}O$	86.10	169.0		1.064		1
Succinaldehyde disodium bisulfite	[*5450-96-4*]	$C_4{-}H_8{-}O_8{-}S_2{\cdot}2Na$	294.22					
Adipaldehyde	not known	$C_6H_{10}O_2$	114.14					

Table 73.9. Toxic Effects of Aliphatic Dialdehydes

Chemical Name	Species	Exposure Route	Approximate Dose	Treatment Regimen	Observed Effect
Hexa-2,4dienal	Rat	Oral	300 mg/kg	LD_{50}	
	Rat	Inh	2000 ppm/4 h	LC_{Lo}	
	Rabbit	Skin	270 mL/kg	LD_{50}	
	Guinea pig	Skin	2500 mg/kg	LC_{Lo}	
	S. typhimurium		1 mM, lipid peroxidation	Ames test, TA 104	Mutagenic
Glutaralde-	Rat	Inh	480 mg/m^3/4 h	LD_{50}	

hyde					
	Rat	I.v.	9800 mg/kg	LD_{50}	
	Rabbit	Skin	560 mL/kg	LD_{50}	
	Duck	Oral	820 mg/kg	LD_{50}	Somnolence, food intake
	Rat	Oral	12376 mg/kg/2Y-C	TD_{Lo}	Changes in urine composition and kidney weight, weig loss or decreased weight gain
	Rat	Oral	11410 mg/kg/7D-I	TD_{Lo}	Weight loss decreased weight gain
	Rat	Inh	5 ppm/6 h/2 W-I	TC_{Lo}	Effects on olfactory system, changes in lung, death
	Rat	Inh	1000 ppb/6 h/13 W-I	TC_{Lo}	Weight loss decreased weight gain
	Rat	Oral	0, 25, 50, 100 mg/Kg	Once a day by intraperitoneal intubation on days 6–15 of pregnancy	Dose-related response of maternal lethality, no effect below 50 mg/kg, decrease of liver weight and skeleton malfonnatio no teratogen effects
	Mouse	Oral	50 gm/kg (6–15 D preg)	TD_{Lo}	Specific developmen abnormalitie (central nervous syst craniofacial, musculoskel system)
	Mouse	Inh	1000 ppb/6 h/13 W-I	TC_{Lo}	Effects on olfactory system, changes in lung, weight loss or decreased

				weight gain, death
Mouse:lymphocyte		8 mg/L	Gene mutation in mammalian cells	
Hamster:ovary		160 mg/L	Cytogenetic analysis	
Hamster:ovary		110 mg/L	Sister chromatid exchange	
E. coli	*In vitro*	8 mM	pUC13 plasmid labeling/Incubation in media	One cross-li per 270 kbp DNA
Human	Skin	6 mg/3DI	Acute toxicity	Severe irritation
Human:lymphocyte		10 mmol/L	DNA damage	
Rabbit	Skin	13 mg open	Acute toxicity	Mild irritatic
Rabbit	Eye	1 mg	Acute toxicity	Severe irritation
S. typhimurium		500 nmol/L (+S9)	Mutation in microorganisms	
S. typhimurium		500 nmol/L (+S9)	Mutation in microorganisms	
S. typhimurium	Ames Test	0–1000 mg/plate	Plate incorporation method without metabolic activation	Dose-related response mutagenic effect, cross-linking capability
E. Coli	Ames Test	0–1000 mg/plate	Plate incorporation method without metabolic activation	Dose-related response mutagenic effect, cross-linking capability
B. subtilis	Ames Test	1 mg/L	Incubation with and without metabolic stimulation	RD_{50} = 2.4. Dose-related mutagenic effect on bot strains
S. typhimurium	Preincubation	mg/l?? ± S9	Mutagenicity	Mutagenic
S. typhimurium	Vaporization	mg/l?? ± S9	Mutagenicity	Mutagenic
S. typhimurium		> 0.5 mM	Ames test, TA104	Mutagenic

Aldehydes and Acetals
Maria T. Morandi, Ph.D., CIH, Silvia Maberti, MS

E. Aromatic and Heterocyclic Aldehydes

The chemical and physical properties of a number of the aromatic and heterocyclic aldehydes are summarized in Table 73.10. The toxic effects are summarized in Table 73.11. Additional information about these compounds is provided with the specific chemical.

Table 73.10. Physical and Chemical Properties of Aromatic and Heterocyclic Ald

Compound	CAS Number	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (° C)	Specific Gravity	Sol. in Wa 68°F
Cinnamaldehyde	[*104-55-2*]	C_6H_5—CH═CH- -CH═O	132.16	251	–7.5		slight
Furfural	[*98-01-1*]	$C_5H_{14}O_2$	96.09	161.7	–36.5	1.1594	3
m-Nitrobenzaldehyde	[*99-61-6*]	$C_7H_5NO_3$	151.12	164.0	58.5	1.2792	2
p-(Dimethylamino) benzaldehyde	[*100-10-7*]	$C_9H_{11}NO$	149.19	176.0	74.5	1.0254	2
p-(*n*-Propoxy) benzaldehyde	[*5736-85-6*]	$C_{10}H_{12}O_2$	164.20				
p-Acetamidobenzaldehyde	[*122-85-0*]	$C_9H_9NO_2$	163.18		154		
p-Aminobenzaldehyde	[*17625-83-1*]	C_7H_7NO	121.15				
p-Hydroxybenzaldehyde	[*123-08-0*]	HOC_6H_4CHO	122.12		117.0	1.1294	2
Piperonal	[*120-57-0*]	C_8—H_6—O_3	150.14		37.0		2
p-Nitrobenzaldehyde	[*555-16-8*]	$C_7H_5NO_3$	151.12		107.0	1.496	2
p-Tolualdehyde	[*104-87-0*]	C_8H_8O	120.15	204.5		1.0194	2
Salicyladehyde	[*90-02-8*]	$C_7H_6O_2$	122.12	197.0	–7.0	1.1674	2
Benzaldehyde	[*100-52-7*]	C_7H_6O	106.12	179	–26	1.045	< 0.01 g/10 19.5°C

Table 73.11. Toxic Effects of Aromatic and Heterocyclic Aldehyd

Chemical Name	Species	Exposure Route	Approximate Dose	Treatment Regimen

p-Nitrobenzaldehyde	Rat	Oral	4700 mg/kg	LD_{50}	Sc no
	Rat	Skin	16 mg/kg	LD_{50}	Sc no
	S. typhimurium		100 mg/plate (S9+)		M
	B. subtilis		500 mg/disv		DI
		Skin/Eye Irritant			
p-Tolualdehyde	Rat	Oral	1600 mg/kg	LD_{50}	Sc
	Rat	Inh	> 2200 mg/m^3	LC	
	Rat	I.p.	800 mg/kg	LD_{50}	Sc
	Mouse	Oral	3200 mg/kg	LD_{50}	Sc
	Mouse	I.p.	400 mg/kg	LD_{50}	Sc
	Rabbit	Skin	500 mg	Acute toxicity	M
	Rabbit	Eye	100 mg	Acute toxicity	M
	S. typhimurium		1 mM in expired air	Ames tast, TA 104	Nc
Furfural	Rat	Inh	175 ppm/6 h	LC_{50}	W de
	Rat	I.p.	20 mg/kg	LD_{50}	
	Rat	S.c.	148 mg/kg	LD_{50}	Cc on
	Mouse	Oral	400 mg/kg	LD_{50}	Tu an
	Dog	Oral	950 mg/kg	LD_{50}	Cc on ata vo
	Guinea pig	Oral	541 mg/kg	LD_{50}	He he zo
	Rat	Inh	500 mg/m^3/4 h/4W-I	TC_{Lo}	Cl tul
	Rabbit	Skin	500 mg/24 h	Acute toxicity	M
	Mouse	Oral	90125 mg/kg/2Y-C	TD_{Lo}	Tu (ca RT
	D. melanogaster—oral		5000 ppm	Specific locus	
	D. melanogaster—oral		5000 ppm	Sex chromosome loss and nondisjunction	
	D. melanogaster—parenteral		100 ppm	Sex chromosome loss and	

				nondisjunction	
	Human:Hela cell		3 mmol/L	DNA inhibition	
	Human:lymphocyte		70 mmol/L	Sister chromatid exchange	
	Mouse:lymphocyte		200 mg/L	Gene mutation in mammalian cells	
	Hamster:lung		1 gm/L	Cytogenetic analysis	
	Hamster:ovary		11,700 mg/L	Sister chromatid exchange	
	S. typhimurium		1 mM in food, plasma, urine	Ames test, TA 104	Nc
		Skin/Eye Irritant			
Benzaldehyde	Rat	Oral	52 gm/kg/13W-I	TD_{Lo}	Fa de in
	Rat	Inh	500 ppm/6h/14d	TC_{Lo}	Hy re ac na
	Rat	S.c	5 mg/kg	LD_{50}	
	Mouse	Oral	28 mg/kg	LD_{50}	Re
	Mouse	I.p.	9 mg/kg	LD_{50}	Sc
	Rabbit	Skin	500 mg/24 h	Acute toxicity	M
	Human lymphocyte		1 mmol/L	Sister chromatid exchange	
	Mouse lymphocytes		400 mg/L	Specific locus	
	Mouse lymphocytes		400 mg/L	Gene mutation in cells	
	Hamster ovary cells		50 mg/L	Sister chromatid exchange	
	Mouse	Oral	154 g/kg/2Y-C	TD_{Lo}	Tc tu
	S. typhimurium	Preincubation	mg/1??+/-S9	Mutagenicity	Nc
	S. typhimurium	Vaporization	mg/1??+/-S9	Mutagenicity	Nc
Salicylaldehyde	Rat	Oral	520 mg/kg	LD_{50}	
	Rat	Subc	900 mg/kg	LD_{50}	
	Mouse	Oral	504 mg/kg	LD_{50}	
	Rabbit	Skin	3 mg/kg	LD_{50}	

	Guinea pig	Skin	20 ml/kg	LD_{50}	
	Rat	S.c.	400 mg/kg (11D preg)	TD_{Lo}	Po mo cra de ab
p-Aminobenzaldehyde	Mouse	I.p.	912 mg/kg	LD_{50}	M ca
m-Nitrobenzaldehyde	Mouse	I.p.	> 500 mg/kg	LD_{50}	
	Mouse	I.v.	180 mg/kg	LD_{50}	
	S. typhimurium		600 mg/plate(+S9), 300 mg/plate(–S9)	Mutation in microorganisms	
	B. subtilis		5 mg/disc	DNA repair	
2,4-Dihydroxybenzaldehyde	Rat	Oral	400 mg/kg	LD_{50}	So co on res
	Mouse	Oral	1380 mg/kg	LD_{50}	
2,5-Dimethoxybenzaldehyde	Rat	Oral	> 3200 mg/kg	LD_{50}	M reg art dil
	Rat	I.p.	800 mg/kg	LD_{50}	Dy
	Mouse	Oral	1600 mg/kg	LD_{50}	So ex we
Piperonal	Rat	Oral	2700 mg/kg	LD_{50}	So ex
	Rat	Skin	> 5 mg/kg	LD_{50}	
	Rat	I.p.	1500 mg/kg	LD_{Lo}	So we
	Mouse	I.p.	480 mg/kg	LD_{50}	Re
Cinnamaldehyde	Rat	Oral	2.2 g/kg	LD_{50}	De an ap wi
	Guinea pig	Oral	1.6 g/kg	LD_{50}	Co 4 d
	Mouse	I.p.	0.2 g/kg	LD_{50}	
	Mouse	I.p.	2.3 g/kg	LD_{50}	
	Rabbit	Skin	0.59 mL/kg	LD_{50}	
	S. typhimurium		I mM in expired air	Ames test, TA 104	No

A number of these aldehydes occur naturally as components of essential oils or plant products. They are widely used in perfumes and as flavoring agents.

There has been a limited number of studies of their toxicity, but a considerable amount of work devoted to studying their metabolic fate was summarized initially by Williams in 1959 (313). Recent information is provided when available for a specific chemical.

The metabolism of these aromatic aldehydes follows the pattern established for aromatic acids. In general, the aldehyde grouping in compounds such as benzaldehyde is converted to the acid, probably by liver aldehyde dehydrogenases. This may occur at a relatively slow rate, but it is usually complete. If the aromatic ring contains phenolic groups, as in the case of *p*-hydroxybenzaldehyde, the compound may be excreted partially as the glucuronide and partially as the free acid or as the conjugated acid. Reduction of the aromatic aldehyde group to an alcohol has not been observed. Benzaldehyde itself is not excreted in any such appreciable amounts as an ester glucuronide, but some substituted aldehydes such as 3,4-dimethoxybenzaldehyde are oxidized to the corresponding acid and excreted as ester glucuronides. Nitrobenzaldehydes are oxidized to nitrobenzoic acids which are either excreted as such or in conjugation with hippuric acid or as acetamidobenzoic acids. *p*-Dimethylaminobenzaldehyde may undergo partial demethylation.

The literature references to the aromatic aldehydes did not give many details of the type of toxic reactions found in the past (314). Dr. Fassett did mention, however, the following observations noted in the course of screening tests:

p-Acetamidobenzaldehyde:	the only symptoms noted were moderate weakness in rats that received up to 3200 mg/kg orally.
p-Dimethylaminobenzaldehyde:	weakness, ataxia, unconsciousness, and tremors were noted in mice that received up to 1600 mg/kg orally or up to 400 mg/kg intraperitoneally. Repeated intraperitoneal injection in mice at levels of 100 to 200 mg/kg caused weakness and ataxia, but there was no significant reduction of hemoglobin during such treatment. No difference was found between the pure and technical grade samples.
p-Nitrobenzaldehyde:	in doses of 50 or 400 mg/kg orally in the rat, the symptoms were prostration and cyanosis.
2,4-Dihydroxybenzaldehyde:	rats that received 50 to 3200 mg/kg orally showed weakness, tremors, and violent convulsions.
2-Hydroxyl-5-chlorobenzaldehyde:	the symptoms in mice (either orally or intraperitoneally) were weakness, ataxia, gasping respirations, and unconsciousness. Skin irritation was more marked with this compound than with the corresponding 5-bromo compound.
2-Hydroxy-5-bromobenzaldehyde:	oral or intraperitoneal admnistration in mice or rats caused weakness, ataxia, and unconsciousness.

Aldehydes and Acetals
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F. Acetals

Since 1963, when D. W. Fassett provided information about the physical properties and toxicity of acetals, the published literature about their toxicity changed very little. Much of the information

provided in the 2nd edition of *Patty's Industrial Hygiene and Toxicology* is reprinted here for the use and convenience of the reader (314).

Any additional information, such as the CAS number, the molecular structure, synonyms and trade names, etc., is provided as currently available in the information from the previous edition.

Acetals or ketals are produced by reactions of aldehydes with alcohols. Their industrial use is increasing, and they may be used as solvents, chemical intermediates, plasticizers, or they may be used to generate aldehydes in the presence of acid. These materials have some of the properties of ethers and are stable under neutral or slightly alkaline conditions but hydrolyze readily in the presence of acids to generate aldehydes (see Table 73.12). This latter reaction makes them capable of hardening natural adhesives, such as glue or casein (333).

Table 73.12. Physical and Chemical Properties of Acetals

Compound	CAS Number	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting point (°C)	Specific Gravity	Sol. in Water (at 68°F)	Vapor Pressure (mmHg)	Lel-Uel (%)
Acetal	[*105-57-7*]	$CH_3CH(OC_2H_5)_2$	118.18	102.2	–100.0	1.3834	3		
Chloroacetal	[*621-62-5*]	$CH_2ClCH(OC_2H_5)_2$	152.60	157.0		1.026		20	
Dibutylacetal	[*871-22-7*]	$CH_3CH(OC_4H_9)_2$	174.28	203.3	–69.1	0.8319			
Dichloroethylformal	[*111-91-1*]	$C_5H_{10}Cl_2O_2$							
Dimethylacetal	[*534-15-6*]	$CH_3CH(OCH_3)_2$	90.12	64.5	–113.2	0.8501	3		
Ethylal	[*462-95-3*]	$CH_2(OC_2H_5)_2$	104.20	89.0	–67.0	0.824	2	60	
Ketoacetal	[*5436-21-5*]	$C_8H_{18}N_2O_2$	132.16						
Methylal	[*109-87-5*]	$CH_2(OCH_3)_2$	76.10	42.0	–104.8	0.8593			

The hazards of using acetals in industry are not known with certainty, but a number of them have received a certain amount of experimental study, some of which is summarized in Table 73.13. The physiological properties of the simple unsubstituted acetals are characterized by an etherlike anesthetic action and by a relatively low degree of primary irritation compared to the parent aldehyde. A number of them have been studied for their anesthetic properties, although at present they are not used for this purpose. Bacq and Dallemagne (334–335) and Knoefel (336–338) have investigated methylal, acetal, and a number of other similar materials. The toxicity of methylal has

recently been investigated by Weaver et al. (339). These authors reviewed some of the older literature and pointed out that a number of attempts have been made to use methylal as an anesthetic and that Bacq and Dallemagne (334–335) had investigated this intensively in both dogs and humans. Apparently, anesthesia could be produced in humans, but the onset was slower than with ether and the effect more transitory.

Table 73.13. Toxic Effects of Acetals

Chemical Name	Species	Exposure Route	Approximate Dose	Treatment Regimen	Observed Effect	Reference
Methylal	Rat	Inh	15,000 ppm	LC_{50}		482
	Rat	I.p.	5 gm/kg	LD_{Lo}		483
	Rabit	Skin	> 16 mL/kg	LD	Iritis	484
	Mouse	Inh	35,100 mg/m^3/7 h/22D-I	TCLo	Ataxia	485
Ethylal	Rabbit	Oral	2604 mg/kg	LD_{50}		486
Dimethylacetal	Rabbit	Dermal	20 g/kg	LD_{50}		487
	Rat	Inh	3000 ppm/4 h	LC_{50}	Anesthetic	488
Acetal	Rabbit	Skin	500 mg/24 h	Acute toxicity	Mild	489
	Rabbit	Oral	3545 mg/kg	LD_{50}		486
	Rat	I.p.	900 mg/kg	LD_{50}		490

The experiments of Weaver et al. (339) were concerned principally with the effects on guinea pigs and mice of inhaling various concentrations. At extremely high levels, 153,000 ppm, anesthesia occurred in 20 minutes, and death occurred in about 2 hours. At these levels, definite evidence of irritation was noted in the guinea pig, including squinting, lacrimation, sneezing, and nasal discharge. Other pronounced signs of eye and respiratory-tract irritation were also noted at lower levels, and the LC_{50} in mice for a 7-hour exposure was about 18,000 ppm. Most of the deaths occurred during exposure.

Experiments were also carried out with repeated inhalations in the case of mice. A group of fifty mice received fifteen 7-hour exposures at concentrations of approximately 11,000 ppm. Only minor irritation was noted at this level, although lack of coordination appeared after about 3 or 4 hours of exposure. Recovery was usually complete in 1 hour after removal from the chamber. Six deaths occurred in the fifty animals during the 22-day exposure period. Repetition of these experiments at 14,000 ppm showed more evidence of irritation a greater degree of anesthesia. About 30% of the group of mice succumbed during a 17-day exposure.

Attempts were made to determine the metabolism of methylal in these animals by testing for formaldehyde and formic acid in vitreous humor and urine. No evidences of these metabolic products were found. However, in view of the rather marked irritation that occurred during inhalation and the necrosis following subcutaneous injections in guinea pigs, it seems possible that hydrolysis to formaldehyde takes place. This is readily metabolized so that it would be difficult to

detect under these conditions.

Histopathological studies were made on the guinea pigs and mice exposed by inhalation. Guinea pigs exposed to very high levels and sacrificed 16 to 74 hours after the beginning of exposure showed moderate to severe fatty degeneration of the liver and kidney and extensive bronchopneumonia. Other guinea pigs sacrificed 23 hours after three successive 7-hour exposures showed similar changes in the lungs, liver, and kidneys. However, guinea pigs exposed to five daily 7-hour inhalations at levels of about 45,000 ppm showed no significant changes. Mice that had about 15 seven-hour exposures at levels up to 14,000 ppm showed occasional evidence of pulmonary edema and slight fatty changes in the kidney.

No changes were found in the optic nerves or retinas of mice that could be attributed to methylal. Occasionally some corneal blebs were seen, but these could not be attributed with certainty to the methylal exposure.

These authors conclude that the threshold for producing toxic effects in guinea pigs and mice is of the order of 11,000 ppm. They extrapolate from this to the conclusion that 1000 ppm might be safe for an 8-hour working day. The present threshold limit is 1000 ppm (27). No studies of workers exposed to such concentrations over long periods of time have been reported, and the validity of this level is uncertain now.

Safe handling precautions should include the use of adequate ventilation to be certain that the average concentrations are well below 1000 ppm and avoidance of excessive or prolonged skin contact. Methylal should be handled with due regard for its flammable properties.

Ethylal produced only minor symptoms of weakness in the rat; even at high dose levels, no typical anesthesia was noted (37). It is of interest that the halogenated compound, dichloroethyl formal, possesses a high degree of toxicity in the rat orally or in the guinea pig by skin contact. It was also highly potent by inhalation in the rat, giving 100% fatalities at levels as low as 120 ppm. It was only a slight skin or eye irritant in the rabbit (340). It is obvious that this halogenated material should be handled with considerable care.

Dimethylacetal in animal experiments is somewhat similar to methylal. The pathological effects have not been reported, however (21, 341).

Acetal also has anesthetic properties (342). Knoefel (336) believes that it is probably rapidly hydrolyzed in the stomach. Hydrolysis would give rise to either a hemiacetal or to acetaldehyde and ethyl alcohol.

The introduction of a halogen, as in chloroacetal, also greatly increased toxic properties upon oral administration in rats. (Note the similarity to the toxicity increase in the case of dichloroethylformal.) This suggests that the hydrolysis of this compound gives rise to chloracetaldehyde and ethanol (37). The influence of unsaturation on an acetal is indicated by the high degree of intraperitoneal toxicity in the mouse for crotonaldehyde acetal (340).

Ketoacetal is interesting in that the presence of the keto group in the beta position to the acetal grouping did not enhance the toxicity (37). Not enough compounds have been studied to predict the effect of unsaturation on aldehyde groups adjacent to acetal groups, but from the fragmentary data available, the same principles would apply as mentioned for aldehydes.

In the view of the lack of specific information, it is well to regard substituted acetals as capable of hydrolysis to the component alcohols and aldehydes and to take precautions to avoid excessive skin contact or inhalation.

Aldehydes and Acetals

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Acetone
David A. Morgott, Ph.D., DABT, CIH

1.0 Acetone
1.0.1 CAS Number:
[*67-64-1*]
1.0.2 Synonyms:
2-Propanone; b-ketopropane; dimethyl ketone; dimethyl formaldehyde; methyl ketone; propanone; pyroacetic acid; pyroacetic ether; allylic alcohol; dimethylketal; ketone propane; and acetone oil
1.0.3 Trade Names:
NA
1.0.4 Molecular Weight:
58.08
1.0.5 Molecular Formula:
$(CH_3)_2CO$
1.0.6 Molecular Structure:

1.1 Chemical and Physical Properties
The commercial grade of acetone is generally 99.5% pure and contains less than 0.4% water and 0.1% organic matter (1). Other important chemical and physical properties of the material are listed in Table 74.1 (2–8).

Table 74.1. Important Chemical and Physical Properties of Acetone

Property	Value	Reference
Empirical formula	C_3H_6O	
Freezing point	–94.7°C	2
Boiling point	56.2°C at 760 mmHg	2
Density	0.790 g/cm^3 at 20°C	1
	0.784 g/cm^3 at 25°C	
	0.780 g/cm^3 at 30°C	
Vapor pressure	70 mmHg at 0°C	3
	185 mmHg at 20°C	
	410 mmHg at 40°C	
Partition coefficient	–0.24 (log $K_{octanol/water}$)	4
	–0.50 (log $K_{oil/water}$)	5
	–2.82 (log $K_{air/water}$)	6
	–2.34 (log $K_{air/saline}$)	5
	–2.44 (log $K_{air/blood}$)	7
Henry's law constant	2.05 atm	6
Water solubility	Infinite	1
Vapor density	2.0 (air = 1.0)	8
Flash point	Cleveland open cup: –9°C	1
	Tag closed cup: –17°C	
Autoignition temperature	465°C	8

Flammability	Lower limit: 2.5% (v/v) at 25°C Upper limit: 13.0% (v/v) at 25°C	8
Hazard identification code	Health: 1 (slight) Flammability: 3 (high) Reactivity: 0 (stable)	8

Acetone

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Ketones of Four Or Five Carbons
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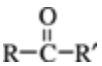
Introduction
A ketone is an organic compound containing a carbonyl group (C═O) attached to two carbon atoms and can be represented by the general formula



Several billion pounds of ketones are produced annually for industrial use in the United States. Those with the highest production volumes include acetone, methyl ethyl ketone, methyl isobutyl ketone, cyclohexanone, 4-hydroxy-4-methyl-2-pentanone, isophorone, mesityl oxide, and acetophenone. Common methods used to manufacture ketones include aliphatic hydrocarbon oxidation, alcohol dehydration with subsequent oxidation, dehydrogenation of phenol, alkyl aromatic hydrocarbon oxidation, and condensation reactions.

Ketones are used because of their ease of production, low manufacturing cost, excellent solvent properties, and desirable physical properties such as low viscosity, moderate vapor pressure, low to moderate boiling points, high evaporation rates, and a wide range of miscibility with other liquids. The low-molecular-weight aliphatic ketones are miscible with water and organic solvents, whereas the high-molecular-weight aliphatic and aromatic ketones are generally immiscible with water. Most ketones are chemically stable. The exceptions are mesityl oxide, which can form peroxides, and methyl isopropenyl ketone, which polymerizes. Most ketones are generally of low flammability.

Ketones are commonly used in industry as solvents, extractants, chemical intermediates, and to a lesser extent, flavor and fragrance ingredients. Ketones have also been reported in the ambient air, in wastewater treatment plants (1), and in oil field brine discharges (2).

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Occupational Exposures
In an occupational setting, the primary routes of exposure to ketones are inhalation and skin contact. Ingestion is rare. Since most ketones have a significant vapor pressure at room temperature, exposure by inhalation in the workplace is likely to occur. The principal hazard associated with exposure to ketone vapors is irritation of the eyes, nose, and throat. Many ketones have excellent warning properties and can be easily detected by their odor. Accidental overexposure should be relatively rare provided warning properties are not ignored and olfactory fatigue does not occur. The classic symptoms produced by an overexposure to ketones include, progressively, irritation of the eyes, nose, and throat, headache, nausea, vertigo, uncoordination, central nervous system depression, narcosis, and cardiorespiratory failure. Recovery is usually rapid and without residual toxic effects. In the case of accidental spills, personnel should wear protective clothing including respiratory protection. Contaminated clothing should be removed promptly, and the exposed areas of the body should be thoroughly flushed with water. Many ketones are absorbed through the skin; therefore,

caution should be exercised to avoid repeated or prolonged skin contact. The vapors produced by accidental spills may present a fire or explosion hazard.

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Toxic Effects

Although the relative toxicity of most ketones is low and the effects of acute exposures are well recognized, the effects of chronic exposure have received less study. In some cases, metabolic studies have helped to elucidate the toxic effects of several ketones. Generally, when ketones are absorbed into the bloodstream, they may be eliminated unchanged in the expired air, or metabolized by a variety of metabolic pathways to secondary alcohols, hydroxyketones, diketones, and carbon dioxide. Recent studies indicate that carbonyl reduction, a and  –l oxidation, decarboxylation, and transamination play important roles in the metabolism of aliphatic ketones. Aromatic ketones and ketones such as cyclohexanone and isophorone may undergo oxidative metabolism by dehydrogenation, ring hydroxylation, or substituent group oxidation. In addition, aromatic and aliphatic ketones may be conjugated with glucuronic acid, sulfuric acid, or glutathione prior to excretion in the urine. Glucuronic and sulfuric acid conjugation usually occur after a ketone is reduced to a secondary alcohol or oxidized to a carboxylic acid. Of the various conjugation mechanisms that occur, glucuronic acid conjugation appears to be the predominant pathway.

Ketone exposure may alter the toxicity of other chemicals, including other ketones that are metabolized by cytochrome P450 enzymes. Under certain circumstances non-neurotoxic ketones may potentiate the neurotoxicity of other ketones or organophosphates or the hepatotoxicity and renal toxicity of haloalkanes. Data on these interactions are referred to in sections on specific ketyones in Chapters 74, 75, and 76.

Table 75.1. Physical–Chemical Properties

Compound	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (°C)	Specific Gravity[ab]	Refractive Index (20° C)	Vapor Pressure (mmHg)	Vapour Density (Air = 1)	M V Co (p 2(
Acetone	C_3H_6O	58.08	56.2	–95.4	0.791	1.3588	180	2.0	23
Methyl ethyl ketone	C_4H_8O	72.11	79.6	–86.6	0.807 (20/4)	1.3788	77.5 (20)	2.4	10
3-Butyn-2-one	C_4H_4O	68.08	85.0	—	0.879	1.4024	40.0		
Methyl *n*-propyl ketone	$C_5H_{10}O$	86.17	102.2	–76.9	0.809 (20/4)	1.3895	16.0	3.0	21
Methyl		86.14	93.0	–92.0	0.803	1.3879			

isopropyl ketone	$C_5H_{10}O$				(20/0)				52
3-Pentyn-2-one	C_5H_6O	82.10	133.0	–28.7	0.910	1.141			
Methyl isopropenyl ketone	C_5H_8O	84.12	97.7	–53.7	0.855	1.4220	42.0		54
2,4-Pentanedione	$C_5H_8O_2$	100.12	138.3	–23.2	0.976	1.4494	7.0	3.5	4,

[d] S = readily soluble, Sl = slightly soluble, I = insoluble.
[e] At 25°C, 760 mmHg.
[a] Specific gravity is at 20/20°C unless otherwise noted.
[b] Vapor pressure is at 25°C unless otherwise noted.
[c] Closed cup unless otherwise noted, [O.C.] open cup. Figures in parentheses are °C.

Table 75.2. Comparison of the MEK Concentrations Found in Different Environmental Samples

	Airborne Concentration		
Sample Type	**(mg/m^3)**	**(ppb)**	**Reference**
Composting effluent	7800		27
Poultry manure dryers		8–260	28
Inside home	0–19		29
Indoor air		4.1–14.3	30
Summer indoor air		1.4–6.9	31
Summer outdoor air		0.8–2.7	31
Outside ambient air	0–3		29
Urban air		1.9–8.5	32
City air		0.2–58	33
Inside office area		2.4	33
Ventilation return air	5.7–40.9		34
Inside machine shop		1.2	33
Outside furniture factory		0.7–1.2	33
Outside paint incinerator		0.9	33
Automobile exhaust		90	35
Oil fire	10–170		36
Chemical waste site	1.5–33.0		37
Factory exhaust gas	20–680		38
Outside laboratory oven	1800		39
Municipal land fill gas		3092–5200	40

Table 75.3. Toxicologic Properties of Ketones

Compound	Approximate Oral Rat LD_{50} (mL/kg)	Lowest Reported Lethal Air Conc. Rat (ppm/h)	Skin Irritation[a]	Ocular Injury[a]
Acetone	8–11	16,000/4	Sl	M
Methyl ethyl ketone	3–7	2,000/4	Sl	Sl
3-Butyn-2-one	0.01	10/4	SV	SV
Methyl *n*-propyl ketone	3.7	30,000/1	Sl	M
Methyl isopropyl ketone	4–7	5,700/4	Sl	Sl
3-Pentyn-2-one	0.1	Sat'd./0.1	SV	SV
Methyl isopropenyl ketone	0.2	125/4	M	M
2,4-Pentanedione	1	1,000/4	Sl	M

[a] Sl, slight; M, moderate; SV, severe; skin irritation and ocular injury ratings are for direct application of liquids.

Table 75.4. Hygienic Standards for Ketones

	ACGIH TLV[a]		OSHA PEL[d]		NIOSH REL[e]		
Compound	TWA[b]	STEL[c]	TWA	STEL	TWA	STEL	DFG MAK[f] TWA
Methyl ethyl ketone	200	300	200	—	200	300	200
3-Butyn-2-one	—	—	—	—	—	—	—
Methyl *n*-propyl ketone	200	250	200	—	150	—	200
Methyl isopropyl ketone	200	—	—	—	200	—	—
3-Pentyn-2-one	—	—	—	—	—	—	—
Methyl isopropenyl ketone	—	—	—	—	—	—	—
2,4-Pentanedione	—	—	—	—	—	—	—

[a] American Conference of Governmental Industrial Hygienists threshold limit values.
[d] Occupational Safety and Health Administration permissible exposure limits.
[e] U.S. National Institute for Occupational Safety and Health recommended exposure limit.
[f] Deutsche Forschungsgemeinschaft (Federal Republic of Germany) maximum concentration values in the workplace.
[b] Time-wighted average (ppm).
[c] Short-term exposure limit (ppm).

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Introduction

Ketones of carbon number 6–13 are important commercial and industrial materials. Their primary use is as solvents that find use in numerous products and industrial applications. Due to their volatility, environmental regulations have been directed at restricting emissions, particularly to the atmosphere. A number of the ketones discussed in this chapter can undergo photochemical transformations that contribute to their abiotic degradation but may also contribute to the formation of smog. Regulations limiting or prohibiting release of materials that may contribute to smog formation are leading to reductions in the use of some of these materials.

Ketones of Six To Thirteen Carbons
Douglas C. Topping, Ph.D., DABT, David A. Morgott, Ph.D., DABT, CIH, John L. O'Donoghue, VMD, Ph.D., DABT

Occupational Exposures

As for the short-chain ketones discussed in Chapter 75, the ketones covered in this chapter are mainly of concern due to inhalation and dermal exposure routes. Acute exposure to high vapor concentrations of these materials may result in narcosis; however, such exposures are rare except in cases of accidents.

Low levels of exposure to many of these ketones can be expected in the environment and through endogenous exposure because ketones are common substrates for many of the enzymes associated with intermediary metabolism in organisms from bacteria to man.

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Toxic Effects
Acute exposures to ketone vapors may result in irritation to the eyes and throat. Repeated dermal exposures may result in defatting of the skin, resulting in dryness, cracking, peeling, and inflammation of the epidermis.

The more serious effect of exposure to some of the ketones covered in this chapter is peripheral neuropathy, which has been reported to occur in occupational environments. Other effects including hematologic effects and altered activity levels of various enzyme systems have been reported in experimental animal systems but not in human clinical cases.

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Structure–Activity Relationships
Alkanes, primary and secondary alcohols, carboxylic acids, glycols, diketones, epoxides, hydroxy acids, and ketones are metabolically related in many biologic systems. Thus a knowledge of the structure–activity relationships of these various compounds adds to our understanding of their individual and/or combined toxicities. Much of our present knowledge about the structure–activity relationships of ketones has been developed in response to an occupationally related outbreak of neurotoxicity. Since this incident, the emphasis on ketone toxicity has been directed primarily toward neurotoxicity. It must be realized, however, that these same ketones produce effects other than neurotoxicity.

Table 76.1 lists ketones and related compounds that have been examined for neurotoxicity (1–18). Those indicated as positive are substances that showed a specific anatomic and morphologic types of nerve degeneration characterized by large multifocal axonal swellings, often referred to as “giant axonal” neuropathy. These swellings are filled with masses of disorganized neurofilaments and other organelles. Myelin damage also occurs but is generally considered to be a secondary effect. Clinical symptomatology in man includes bilaterally symmetrical paresthesia, best described as a “pins and needles” feeling, and muscle weakness, primarily in the legs and arms.

Table 76.1. Neurotoxicity of Ketones and Related Substances

Chemical	Structure	Neurotoxicity[a]	Ref.
	Six-Carbon Structures		
n-Hexane	$CH_3(CH_2)_4CH_3$	+	1
Practical-grade hexanes	Mixed hexanes	+	1
1-Hexanol	$HOCH_2(CH_2)_4CH_3$	–	1, 2
2-Hexanol	$CH_3CHOH(CH_2)_3CH_3$	+	1, 2
6-Amino-1-hexanol	$HOCH_2(CH_2)_5NH_2$	–	3

Methyl *n*-butyl ketone	$CH_3CO(CH_2)_3CH_3$	+	1, 3–7
Methyl isobutyl ketone	$CH_3COCH_2CH(CH_3)_2$	–	3, 6, 7
2,5-Hexanediol	$CH_3CHOH(CH_2)_2CHOHCH_3$	+	1, 8
1,6-Hexanediol	$HOCH_2(CH_2)_4CH_2OH$	–	8
5-Hydroxy-2-hexanone	$CH_3CO(CH_2)_2CHOHCH_3$	+	1
2,3-Hexanedione	$CH_3COCO(CH_2)_2CH_3$	–	3, 8, 9
2,4-Hexanedione	$CH_3COCH_2COCH_2CH_3$	–	3, 8, 9
2,5-Hexanedione	$CH_3CO(CH_2)_2COCH_3$	+	1, 3, 8–10
	Seven-Carbon Structures		
n-Heptane	$CH_3(CH_2)_5CH_3$	–	3
Methyl *n*-amyl ketone	$CH_3CO(CH_2)_4CH_3$	–	11
Methyl isoamyl ketone	$CH_3CO(CH_2)_2CH(CH_3)_2$	–	3
Ethyl *n*-butyl ketone[b]	$CH_3CH_2CO(CH_2)_3CH_3$	+	3
Di-*n*-propyl ketone	$CH_3(CH_2)_2CO(CH_2)_2CH_3$	–	3
2,5-Heptanedione	$CH_3CO(CH_2)_2COCH_2CH_3$	+	3, 9
2,6-Heptanedione	$CH_3CO(CH_2)_3COCH_3$	–	3, 9
3,5-Heptanedione	$CH_3CH_2COCH_2COCH_2CH_3$	–	8
3-Methyl-2,5-hexanedione	$CH_3COCHCH_3CH_2COCH_3$	+	12
	Eight-Carbon Structures		
3,6-Octanedione	$CH_3CH_2CO(CH_2)_2COCH_2CH_3$	+	3, 9
5-Methyl-3-heptanone	$CH_3CH_2COCH_2CHCH_3CH_2CH_3$	+	13
3-Acetyl-2,5-hexanedione	$CH_3COC(CH_3CO)CH_2COCH_3$	–	14
3,4-Dimethyl-2,5-hexanedione	$CH_3COCHCH_3CHCH_3COCH_3$	+	14–17
3,3-Dimethyl-2,5-hexanedione	$CH_3COC(CH_3)_2CH_2COCH_3$	–	15
	Nine-Carbon Structures		
5-Nonanone	$CH_3(CH_2)_3CO(CH_2)_3CH_3$	+	3
5-Methyl-2-	$CH_3CO(CH_2)_2CHCH_3(CH_2)_2CH_3$	[c]	3

octanone			
Diisobutyl ketone	$(CH_3)_2CHCH_2COCH_2CH(CH_3)_2$	–	3
	Ten-Carbon Structure		
3,4-Diethyl-2,5-hexanedione	$CH_3COCH(CH_3CH_2)CH(CH_3CH_2)$-COCH	–	16
	Eleven-Carbon Structures		
Diisoamyl ketone	$(CH_3)_2CH(CH_2)_2CO(CH_2)_2CH$-$(CH_3)_2$	–	3
	Twelve-Carbon Structure		
3,4-Diisopropyl-2,5-hexanedione	$CH_3COCH(CH_3CH_3CH_2)CH$-$(CH_3CH_3CH_2)COCH_3$	–	18

[a] – Indicates that the material was tested experimentally and found not to be neurotoxic; + indicates the material may produce giant axonal neuropathy.
[b] Ethyl *n*-butyl ketone is metabolized to 2,5-heptanedione, which is neurotoxic.
[c] Commercial samples of 5-methyl-2-octanone may contain 5-nonanone, which is neurotoxic. 5-Methyl-2-octanone enhances 5-nonanone neurotoxicity.

The metabolic interrelationships of some of these neurotoxins are shown in Figure 76.1. Initially, studies of *n*-hexane and methyl *n*-butyl ketone neurotoxicity revealed that the g-diketone 2,5-hexanedione was a neurotoxin. Subsequently, a series of diketones were examined for their ability to produce "giant axonal" neuropathy in rats. Table 76.2 lists these compounds and further emphasizes the necessity of the g-diketone spacing for the production of neuropathy. These findings have led to the theory that neurotoxicity is related to a common metabolic pathway leading to the formation of a g-diketone, which is the toxic metabolite that produces the neuropathy. Except for 2,5-heptanedione and 3,6-octanedione, all metabolic interconversions are oxidation of the  -1 carbon(s), first to an alcohol or diol, then to a g-diketone. In the case of *n*-heptane, where  -1 oxidation may occur, the ketone formed would be a d-diketone such as 2,6-heptanedione, which is not neurotoxic. When the  carbon is oxidized in preference to the  -1 carbon, as when *n*-hexane is converted to 1-hexanol, no g-diketone is formed.

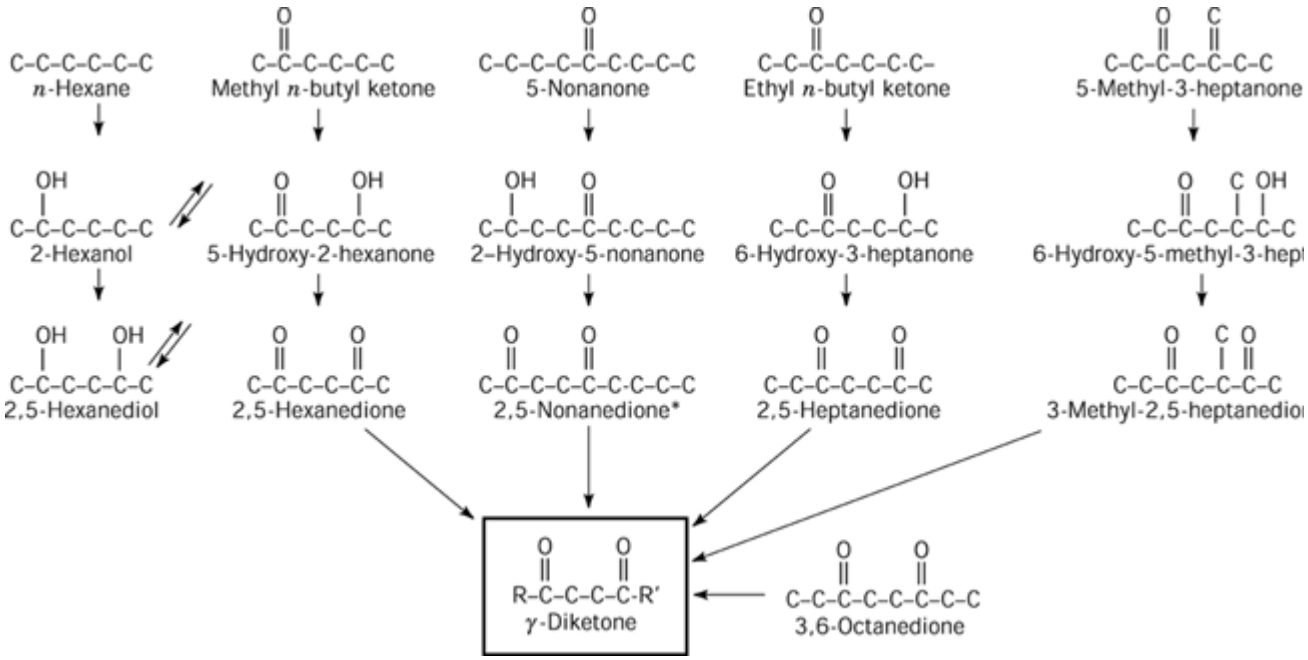

Figure 76.1. Relationships of alkanes, alcohols, and ketones that produce "giant axonal" neuropathy. Hydrogen atoms are included only when present as hydroxyl ions. * Further oxidative and decarboxylative pathways lead to the formation of methyl *n*-butyl ketone and 2,5-hexanedione (see Fig. 76.2). **The 5-methyl-3-heptanone metabolic scheme is an hypothesized pathway that is consistent with the observed neurotoxicity of this material.

Table 76.2. Structure–Activity Relationships of Diketones

Ketone Structure	Spacing	Ketone Neuropathy	Giant Axonal
2,4-Pentanedione	$CH_3COCH_2COCH_3$	b	–[a]
2,3-Hexanedione	$CH_3COCO(CH_2)_2CH_3$	a	–
2,4-Hexanedione	$CH_3COCH_2COCH_2CH_3$	b	–
2,5-Hexanedione	$CH_3CO(CH_2)_2COCH_3$	g	+
3-Methyl-2,5-hexanedione	$CH_3COCHCH_3CH_2COCH_3$	g	+
3,4-Dimethyl-2,5-hexanedione	$CH_3COCHCH_3CHCH_3COCH_3$	g	+
3,3-Dimethyl-2,5-hexanedione	$CH_3COC(CH_3)_2CH_2COCH_3$	g	–
2,3-Heptanedione	$CH_3CH_2COCH_2COCH_2CH_3$	b	–
2,5-Heptanedione	$CH_3CO(CH_2)_2COCH_2CH_3$	g	+
2,6-Heptanedione	$CH_3CO(CH_2)_3COCH_3$	d	–
3,6-Octanedione	$CH_3CH_2CO(CH_2)_2COCH_2CH_3$	g	+

3-Acetyl-2,5-hexanedione	$CH_3COC(CH_3CO)CH_2COCH_3$	g	–
3,4-Diethyl-2,5-hexanedione	$CH_3COCH(CH_3CH_2)CH(CH_3CH_2)COCH_3$	g	–
3,4-diisopropyl-2,5-hexanedione	$CH_3COCH(CH_3CH_3CH_2)CH(CH_3CH_3CH_2)COCH_3$	g	–

[a] 2,4-Pentanedione produces central nervous system damage, which is clinically, anatomically, and morphologically distinguishable from "giant" axonal neuropathy.

These data also suggest that, as chain length increases, the neurotoxicity of the diketone decreases, possibly owing to steric hindrance. However, chain length may not be as important for some materials such as 5-nonanone. The neurotoxicity of 5-nonanone appears to involve two metabolic pathways, one to 2,5-nonanedione, a mechanism similar to that of the other compounds shown in Figure 76.1, and the other to methyl *n*-butyl ketone via a series of oxidative and decarboxylative pathways (Fig. 76.2).

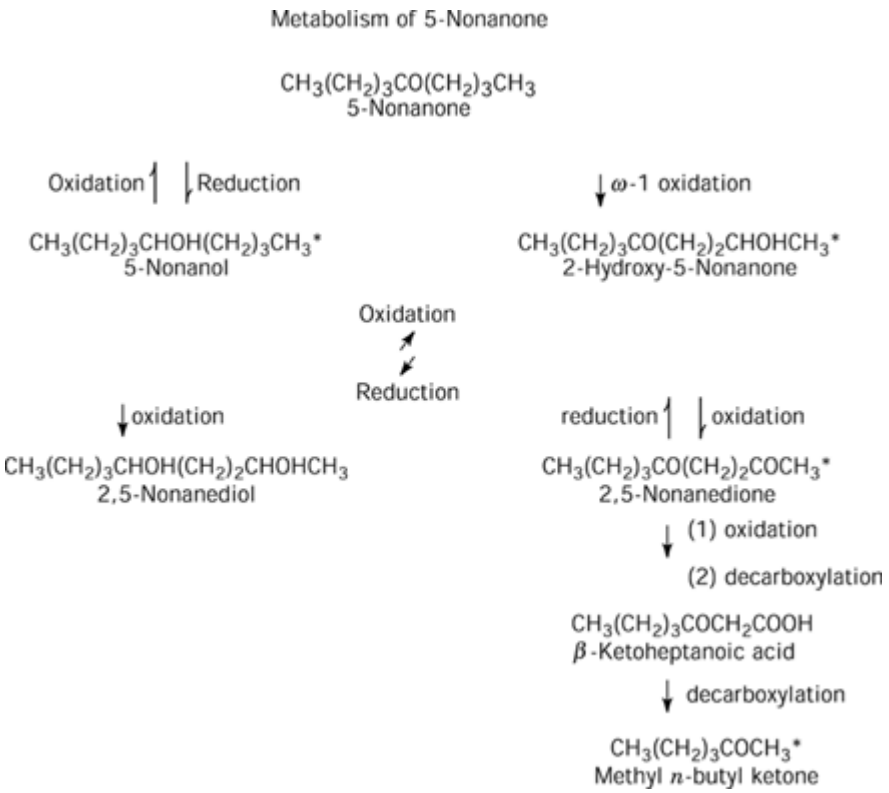

Figure 76.2. Metabolism of 5-Nonanone. *Designates actual metabolites found in blood or urine.

A third modifying factor affecting the neurotoxic potential of these substances is the number and size of substituent groups located between the g-spaced carbonyls. Single methyl groups on the carbons located between the carbonyl groups increase the potential neurotoxicity of the g-diketone (i.e., 3-methyl-2,5-hexanedione or 3,4-dimethyl-2,5-hexanedione, Table 76.1). Two methyl groups positioned on one of the methyl groups between the carbonyls (i.e., 3,3-dimethyl-2,5-hexanedione) eliminate neurotoxicity. Metabolism to a substituted g-diketone may play a role in the neurotoxicity of 5-methyl-3-heptanone (Fig. 76.1).

Ketones of Six To Thirteen Carbons

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Summary

A summary of the acute toxicologic properties of the ketones is presented in Table 76.3. During the past 30 years, a significant amount of data has been accumulated on the biologic and toxicologic effects of ketones in experimental animals and man. With the exception of certain studies that have shown that ketones with a particular structure produce a toxic polyneuropathy, these findings support the existing concepts of the relatively innocuous biologic effects of most ketones. The most widely and extensively used ketones appear to be the least toxic.

Table 76.3. Toxicologic Properties of Ketones

Compound	Approximate Oral Rat LD_{50} (mL/kg)	Lowest Reported Lethal Air Conc. Rat (ppm/h)	Skin Irritation[a]	Ocular Injury[a]
Methyl *n*-butyl ketone	3	8000/4	Sl	Sl
Methyl isobutyl ketone	5–6	4000/4	Sl	Sl
Mesityl oxide	1	500/8	Sl	M
4-Hydroxy-4-methyl-2-pentanone	4	>Sat'd./8	Sl	M
Methyl *n*-amyl ketone	2	4000/4	M	Sl
Methyl isoamyl ketone	4	3813/6	Sl	Sl
Ethyl *n*-butyl ketone	3	4000/4	M	Sl
Di-*n*-propyl ketone	4	2670/6	Sl	Sl
Diisopropyl ketone	4	>2765/6	Sl	Sl
2-Octanone	3	>1673/6	M	Sl
3-Octanone	>5	—	M	—
5-Methyl-3-heptanone	4	3484/4	Sl	M
5-Nonanone	>2	—	—	—
Diisobutyl ketone	6	Sat'd./8	Sl	Sl
Trimethyl nonanone	9	>Sat'd./4	Sl	Sl
2,5-Hexanedione	3	>Sat'd./1	Sl	M
Cyclohexanone	2	2000/4	M	M

Methyl cyclohexanones	2	2800/4	M	M
Acetophenone	3	>Sat'd./8	M	SV
Propiophenone	>4	>Sat'd./8	Sl	Sl
Isophorone	2–>3	1840/4	Sl	SV
Benzophenone	2–3	—	Sl	Sl

[a] Sl, slight; M, moderate; SV, severe. Skin irritation and ocular injury ratings are for direct application of liquids.

Table 76.4. Physical–Chemical Pr

Compound	CAS Number	Molecular Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (°C)	Specific Gravity[a]	Refractive Index (20°C)	Vapor Pressure (mmHg)[b]
Methyl *n*-butyl ketone	[*591-78-6*]	$C_6H_{12}O$	100.16	127.5	–59.6	0.821	1.4007	3.8
Methyl isobutyl ketone	[*108-10-1*]	$C_6H_{12}O$	100.16	115.8	–84.7	0.802	1.3959	18.8
Mesityl oxide	[*141-79-7*]	$C_6H_{10}O$	98.14	129.6	–53	0.857	1.4440	9.5
4-Hydroxy-4-methyl-2-pentanone	[*123-42-2*]	$C_6H_{12}O_2$	116.16	168.0	–43	0.941	1.4242	1.2
2,5-Hexanedione	[*110-13-4*]	$C_6H_{10}O_2$	114.14	194.0	–5.5	0.973	1.4230	1.6
Cyclohexanone	[*108-94-1*]	$C_6H_{10}O$	98.14	155.7	–32.1	0.948 (20/4)	1.4507	4.8
Methyl *n*-amyl ketone	[*110-43-0*]	$C_7H_{14}O$	114.19	151.1	–35	0.817	1.4073	2.1
Methyl isoamyl ketone	[*110-12-3*]	$C_7H_{14}O$	114.19	144.0	–73.9	0.813	1.4062	4.5 (20)
Ethyl *n*-butyl ketone	[*106-35-4*]	$C_7H_{14}O$	114.19	147.4	–39.0	0.818	1.3994	5.6
Di-*n*-propyl ketone	[*123-19-3*]	$C_7H_{14}O$	114.19	143.7	–32.6	0.817 (20/4)	1.4069	5.5 (20)
Diisopropyl ketone	[*565-80-0*]	$C_7H_{14}O$	114.19	124.0	–69	0.803 (20/4)		10 (37)
2-Methylcyclohexanone	[*583-60-8*]	$C_7H_{12}O$	112.17	165	–13.9	0.925	1.4440 (25)	
3-	[*591-24-*	$C_7H_{12}O$	112.17	169	–73.5	0.914	1.4449	

Methylcyclohexanone	*2*]					(20/4)		
4-Methylcyclohexanone	[*589-92-4*]	$C_7H_{12}O$	112.17	170	–40.6	0.914 (20/4)	1.4451	10 (54)
Acetophenone	[*98-86-2*]	C_8H_8O	120.13	202.0	19.6	1.0281 (20/4)	1.5363	0.37 (25)
2-Octanone	[*111-13-7*]	$C_8H_{16}O$	128.21	172.9	–16.0	0.819 (20/4)	1.4151	1.2
3-Octanone	[*106-68-3*]	$C_8H_{16}O$	128.21	167.0		0.822	1.4150	2.0
5-Methyl-3-heptanone	[*541-85-5*]	$C_8H_{16}O$	128.21	160.5	–56.7	0.820 (0/4)	1.4160	2.0
Propiophenone	[*93-55-0*]	$C_9H_{10}O$	134.19	218.0	18.6	1.010	1.5269	1.5 (25)
Isophorone	[*78-59-1*]	$C_9H_{14}O$	138.21	215.2	–8.0	0.923	1.478	0.26 (20)
5-Nonanone	[*502-56-7*]	$C_9H_{18}O$	142.24	188.4	–50	0.822	1.4195	
Diisobutyl ketone	[*108-83-8*]	$C_9H_{18}O$	142.24	168.1	–46.0	0.807	1.4210	1.7
Trimethyl nonanone	[*123-18-2*]	$C_{12}H_{24}O$	184.32	207–228		0.817	1.4273	
Benzophenone	[*119-61-9*]	$C_{13}H_{10}O$	182.22	305.4	48.5	1.1108 (18/4)	1.5975 (45.2)	1 (108)

[a] Specific gravity is at 20/20°C unless otherwise noted.
[b] Vapor pressure is at 25°C unless otherwise noted.
[c] Closed cup unless otherwise noted, [OC] open cup. Figures in parentheses are °C.
[d] S, readily soluble; Sl, slightly soluble; I, insoluble.
[e] At 25°C, 760 mm Hg.

Table 76.5. Hygienic Standards for Ketones

		ACGIH TLV[a]		OSHA PEL[d]		NIOSH REL[e]		
Compound	**CAS No.**	**TWA[b]**	**STEL[c]**	**TWA**	**STEL**	**TWA**	**STEL**	**DFG MAK[f] TWA**
Methyl *n*-butyl ketone	[*591-78-6*]	5(S)[g]	10	100	—	1	—	5
Methyl isobutyl ketone	[*108-10-1*]	50	75	100	—	50	75	20
Mesityl oxide	[*147-79-7*]	15	25	25	—	10	—	25
4-Hydroxy-4-	[*123-*	50	—	50	—	50	—	50

methyl-2-pentanone	*42-2*]							
2,5-Hexanedione	[*110-13-4*]	—	—	—	—	—	—	—
Cyclohexanone	[*108-94-1*]	25(S)[g] A4[j]	—	50	—	25(S)	—	—
Methyl *n*-amyl ketone	[*110-43-0*]	50	—	100	—	100	—	—
Methyl isoamyl ketone	[*110-12-3*]	50	—	100	—	50	—	—
Ethyl *n*-butyl ketone	[*106-35-4*]	50	75	50	—	50	—	—
Di-*n*-propyl ketone	[*123-19-3*]	50	—	—	—	50	—	—
Diisopropyl ketone	[*565-80-0*]	—	—	—	—	—	—	—
Methyl cyclohexanone	[*583-60-8*]	50(S)[g]	75	100 (S)[g]	—	50(S) [g]	75	50
Acetophenone	[*98-86-2*]	10	—	—	—	—	—	—
2-Octanone	[*111-13-7*]	—	—	—	—	—	—	—
3-Octanone	[*106-68-3*]	—	—	—	—	—	—	—
5-Methyl-3-heptanone	[*541-85-5*]	25	—	25	—	25	—	—
Propiophenone	[*93-55-0*]	—	—	—	—	—	—	—
Isophorone	[*78-59-1*]	—	5(CL)[h] A3[i]	25	—	4	—	2
5-Nonanone	[*502-56-7*]	—	—	—	—	—	—	—
Diisobutyl ketone	[*108-83-8*]	25	—	50	—	25	—	50
Trimethyl nonanone	[*123-18-2*]	—	—	—	—	—	—	—
Benzophenone	[*119-61-9*]	—	—	—	—	—	—	—

[a] American Conference of Governmental Industrial Hygienists Threshold Limit Values.

[d] Occupational Safety and Health Administration Permissible Exposure Limits.

[e] U.S. National Institute for Occupational Safety and Health Recommended Exposure Limit.

[f] Deutsche Forschungsgemeinschaft (Federal Republic of Germany) maximum concentration values in the workplace.

[b] Time-weighted average (ppm).

[c] Short-term exposure limit (ppm).

[g] Indicates a skin notation applicable to TLV.

[j] A4 Not classifiable as a human carcinogen.

[h] Indicates ceiling limit applies.

[i] A3 Confirmed animal carcinogen with unknown relevance to humans.

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Monohydric Alcohols—C_1 to C_6

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Chemical and Physical Properties

The physical and chemical properties for the C_1 to C_6 monohydric alcohols are listed in Table 77.1. At ambient temperature, the vapor pressure decreases with increasing carbon number as shown in Table 77.1. The water solubility also decreases with an increasing carbon number. The National Fire Protection Association (NFPA) has prepared a rating system to assess the physical and chemical hazards of chemicals with respect to flammability, health, and reactivity (1, 2). The C_1 to C_6 monohydric alcohols are flammable, but not reactive.

Table 77.1. Chemical and Physical Properties of C_1 to C

Compound	CAS #	Mol. formula	Mol. wt.	Boiling point (°C)	Melting point (° C)	Sp. gr.	Refractive index (20° C)	Vapor pressure (mmHg) (°C)	Maxin vap concn (°C
Methanol	[*67-56-1*]	CH_4O	32.0	65	–97.8	0.792	1.3285	160 (30)	21.05
Ethanol	[*64-17-5*]	C_2H_6O	46.1	79	–114.1	0.789	1.3614	50 (25)	6.58 (
1-Propanol	[*71-23-8*]	C_3H_8O	60.1	97	–126.2	0.804	1.3850	21 (25)	2.7 (
Isopropanol	[*67-63-0*]	C_3H_8O	60.1	83	–88.5	0.785	1.3777	44 (25)	5.8 (
1-Butanol	[*71-36-3*]	$C_4H_{10}O$	74.1	118	–90.0	0.810	1.3991	6.5 (25)	0.86 (
Isobutanol	[*78-83-1*]	$C_4H_{10}O$	74.1	108	–108.0	0.803	1.3959	12.2 (25)	1.61 (
2-Butanol	[*78-92-2*]	$C_4H_{10}O$	74.1	100	–111.7	0.807	1.3972	23.9 (30)	31.4 (
tert-Butyl alcohol	[*75-65-0*]	$C_4H_{10}O$	74.1	82	25.6	0.787	1.3841	42.0 (25)	5.53 (
1-Pentanol	[*71-41-0*]	$C_5H_{12}O$	88.2	138	–79.0	0.815	1.4100	10 (44.9)	0.77 (
2-Pentanol	[*6032-29-7*]	$C_5H_{12}O$	88.2	119	—	0.809	1.4053	—	—
3-Pentanol	[*584-02-1*]	$C_5H_{12}O$	88.2	116	–75.0	0.822	1.4098	2 (20)	—
2-Methyl-1-butanol	[*137-32-6*]	$C_5H_{12}O$	88.2	128	<–70.0	0.816	1.4098	3.4 (25)	—
3-Methyl-1-butanol	[*123-51-3*]	$C_5H_{12}O$	88.2	131	–117.2	0.812	1.4078	2.8 (20)	1.02 (
tert-Amyl alcohol	[*75-85-4*]	$C_5H_{12}O$	88.2	102	–11.9	0.809	1.4052	10 (17.2)	—
3-Methyl-2-butanol	[*598-75-4*]	$C_5H_{12}O$	88.2	113	—	0.819	1.4095	—	—
2,2-Dimethyl-1-propanol	[*75-84-3*]	$C_5H_{12}O$	88.2	114	52.0	0.812	—	—	—
1-Hexanol	[*111-27-3*]	$C_6H_{14}O$	102.2	157	–51.6	0.814	1.4178	0.98 (20)	0.32 (
2-Hexanol	[*626-93-7*]	$C_6H_{14}O$	102.2	—	—	—	—	—	—
2-Methyl-1-	[*105-*		102.2	148	—	0.825	1.4190	1.5 (20)	—

pentanol	*30-6*]	$C_6H_{14}O$							
3-Methyl-1-pentanol	[*589-35-5*]	$C_6H_{14}O$	102.2	153	—	0.822	1.4182	—	—
4-Methyl-1-pentanol	[*626-89-1*]	$C_6H_{14}O$	102.2	152	—	0.821	1.4134	—	—
Methyl Isobutyl-carbinol	[*108-11-2*]	$C_6H_{14}O$	102.2	132	–90.0	0.807	1.4113	3.52 (20)	0.46 (
2-Ethyl-1-butanol	[*97-95-0*]	$C_6H_{14}O$	102.2	149	<–50.0	0.835	1.4224	1.8 (20)	0.22 (
2,2-Dimethyl-1-butanol	[*1185-33-7*]	$C_6H_{14}O$	102.2	—	—	—	—	—	—
3,3-Dimethyl-2-butanol	[*464-07-3*]	$C_6H_{14}O$	102.2	—	—	—	—	—	—

[a] Miscible at 25°C, 760 mmHg.

Production and Use

The C_1 to C_6 alcohols represent an important class of industrial chemicals with a wide number of uses. Based on production volume, the monohydric alcohols represent the most important group of the alcohol family (3). Methanol was in the top 50 chemicals produced in the United States in 1995 with a production volume of 11.3 billion pounds (4). In general, the alcohols of commercial significance are produced synthetically, although some alcohols are made from natural products or by fermentation. The most important industrial processes are the methanol process and the oxo process. The oxo process can be used to produce alcohols in the C_3 to C_{20} range by using alkenes as starting materials (3).

The uses of alcohols are numerous and can vary depending on their chemical and physical properties. In general, alcohols are used as solvents, cosolvents, and chemical intermediates. Among the higher alcohols, those containing six carbons or more, the C_6 to C_{11} alcohols are used in the manufacture of plasticizers. Some of the alcohols exist as pure chemicals, but higher monohydric alcohols (C_6 to C_{18}) can also exist as complex isomeric mixtures (3, 5, 6). The major routes of industrial or occupational exposure to alcohols is by dermal contact and/or inhalation. The extent of the exposure pathways depends on the use of the chemical and physical properties of the alcohol.

Metabolism and Disposition

A comparative uptake study has been conducted using human abdominal skin *in vitro* for the C_1 to C_{10} linear alcohols (7). The rate of dermal uptake for the neat material decreases with increasing carbon number.

Williams wrote an early general review on the metabolism and disposition of alcohols (8). Primary alcohols are readily oxidized to the corresponding aldehydes, which are further converted to the corresponding acids. Secondary alcohols are converted to ketones. Alcohols can be conjugated either directly or as a metabolite with glucuronic acid, sulfuric acid, or glycine, and excreted. Tertiary alcohols are more resistant to metabolism and are generally conjugated more readily than secondary or primary alcohols. Biomonitoring methods exist for several of the alcohols, including methanol, ethanol, isopropanol, and *n*-butanol (9). It is important to note that there are endogenous sources for some low molecular weight alcohols that must be considered in evaluating biomonitoring data for those alcohols.

Health Effects in Animals

The acute toxicity data for the monohydric alcohols indicate a low order of acute toxicity by oral, dermal, or inhalation routes of exposure. The C_1 to C_6 monohydric alcohols produce central nervous system depression. Based on the inhalation data, the secondary and tertiary alcohols are more biologically active than the primary alcohols. The C_1 to C_6 linear alcohols have been studied for their aspiration hazard (10). Except for methanol, the linear alcohols are aspiration hazards. Although not studied, the branched isomeric alcohols may be aspiration hazards. Sensory irritation increases with increasing carbon number (11).

Nelson et al. (12) investigated the developmental toxicity of aliphatic alcohols (C_1 to C_{10}) administered by inhalation to rats. Several of the alcohols (methanol, 1-propanol, isopropanol, 1-butanol) produced developmental toxicity but at concentrations that are at least an order of magnitude higher than existing occupational exposure standards and generally in the presence of maternal toxicity. Developmental toxicity did not, as predicted, increase as the carbon chain length was increased from six to eight carbons, after which toxicity would expected to decrease, although sufficiently high vapor concentrations of the longer chain alcohols could not be generated to produce maternal or fetal toxicity. Furthermore, behavioral teratogenic effects were not observed at concentrations lower than those that produced embryo toxicity (e.g., malformations) as revealed by traditional assessment. Although sporadic deviations in behavioral and neurochemical end points were observed with the alcohols, no pattern of effect was seen with any of the alcohols examined. The C_1 to C_6 monohydric alcohols are typically inactive in genotoxicity assays, but on occasion, some weak activity has been noted for methanol and ethanol.

Health Effects in Humans

This review discusses primarily dermal and inhalation routes of exposure, which are the major routes of occupational exposure to alcohols. Many of the high-production alcohols such as methanol, ethanol, propanols, and butanols cause adverse effects when ingested; ingestion, however, is not a major route of occupational exposure. There are some alcohols that have produced adverse effects in humans, including death, in an occupational environment. Nevertheless, alcohols have been used extensively in the workplace generally with few or minor problems. Occasionally, methanol, ethanol, and the propanols produce a skin sensitizing response in humans. In some, but not all, cases the sensitization response was considered to be due to contaminants and not to the alcohol itself.

A common property of some of the alcohols is to produce local irritation to the skin, eyes, and respiratory tract, and the effect or potency varies for the type of alcohol. Many alcohols produce minimal or no adverse effects in humans, possibly because of low exposure combined with the low toxicity potential of the alcohol.

Few alcohols produce neuropathic effects in humans. Abuse of products containing methanol and ethanol has produced some indications of neurotoxicity in humans, but nothing has been reported in an occupational environment. 2-Hexanol produces neurotoxicity by the oral and intraperitoneal routes in animals, but there is no evidence of such an effect having occurred in the workplace.

There is no clear evidence that occupational exposures to alcohols represent a carcinogenic risk to humans. Based on epidemiological data, there is an association between the manufacture of ethanol and isopropanol by the strong acid process (a process no longer used in the United States) and an excess of upper respiratory tract cancer in humans (13). The effect has been attributed to by-products such as dialkyl sulfates (14) and sulfuric acid (15), not the alcohols themselves.

Some of these alcohols such as ethanol and isopropanol can enhance the toxic effects of various chemicals, particularly hepatotoxins. It is thought that the effects may be due largely to an inductive effect of the alcohol on microsomal enzymes, particularly the cytochrome P450 system, which may allow a greater metabolic conversion of the hepatotoxin to its toxic metabolite.

Monohydric Alcohols—C_1 to C_6

C. Bevan, Ph.D., DABT

A. C_1 to C_3 Alcohols

The low molecular weight alcohols, including methanol, ethanol, 1-propanol, and isopropanol are used extensively in industry (16). These alcohols exist as volatile liquids at ambient temperatures, and exposure can occur in both industrial and nonindustrial environments.

The best studied monohydric alcohol is ethanol, although an extensive database exists for methanol and isopropanol. These alcohols have a low order of acute toxicity in animals, and the principal effects from inhalation exposure are local irritation and central nervous system depression. Inhalation studies in animals indicate a high no-observed-adverse-effect-level for developmental effects (12).

Table 77.2. Single-Dose Oral Toxicity Values for Methanol in Animals[a]

Species	LD_{50} values (g/kg)	Ref.
Rat	6.2	32
	9.1	32a
	12.9	33
	13.0	34
Rabbit	14.4	35
Monkey	2–3[b]	36
	7.0[b]	

[a] Taken from Rowe and McCollister (18).
[b] Minimal lethal dose.

Table 77.3. Results of Single Inhalation Exposures of Animals to Vapors of Methanol[a]

Animal	Concentration		Duration of exposure (h)	Signs of intoxication	Outcome	Ref.
	ppm	mg/L				
Mouse	72,600	95.0	54	Narcosis	Died	37
	72,600	95.0	28	Narcosis	Died	37
	54,000	70.7	54	Narcosis	Died	37
	48,000	62.8	24	Narcosis	Survived	37
	10,000	13.1	230	Ataxia	Survived	37

	152,800	200.0	94 min	Narcosis	Overall mortality 45%	38
	101,600	133.0	91 min	Narcosis		38
	91,700	120.0	95 min	Narcosis		38
	76,400	100.0	89 min	Narcosis		38
	61,100	80.0	134 min	Narcosis		38
	45,800	60.0	153 min	Narcosis		38
	30,600	40.0	190 min	Narcosis		38
Rat	60,000	78.5	2.5	Narcosis, convulsions		39
	31,600	41.4	18–20		Died	39
	22,500	29.5	8	Narcosis		39
	13,000	17.0	24	Prostration		39
	8,800	11.5	8	Lethargy		39
	4,800	6.3	8	None		39
	3,000	4.0	8	None		39
	50,000	65.4	1	Drowsiness	Survived	39a
Dog	37,000	48.4	8	Prostration, incoordination		39
	13,700	17.9	24	None		39
	2,000	2.6	24	None		39

[a] Taken from Rowe and McCollister (18).

Table 77.4. Single-dose Oral Toxicity Values for Ethanol in Animals[a]

Species	LD_{50} values (g/kg)	Ref.
Rat	13.7	34
	17.8[b]	32
	6.2[c]	32
	11.5[d]	32
Mouse	9.5	120a
	8.3	120b
Guinea pig	5.6	34
Rabbit	9.9	35
Rabbit	9.9[e]	121
	7.0[e]	121a
Dog	5.5–6.6[f]	120a

[a] Taken from Rowe and McCollister (18).
[b] Young adults.
[c] 14 days old.

[d] Older adults.
[e] Minimal lethal dose.
[f] Lethal dose.

Table 77.5. Results of Single Acute Inhalation Exposures of Animals to Vapors of Ethanol[a]

Animal	Concentration		Duration of exposure (h)	Signs of intoxication	Outcome	Ref.
	ppm	mg/L				
Mouse	31,900	70.0	0.33	Ataxia		122
	29,300	55.0	7.0	Narcosis	Died	122
	23,900	45.0	1.25	Narcosis		122
	13,300	25.0	1.33	Ataxia		122
Guinea pig	45,000	84.6	3.75	Incoordination		39
	44,000	82.7	7.5	Deep narcosis		39
	50,170	94.3	10.2	Deep narcosis	Died	39
	19,260	36.2	3.75	None		39
	20,000	37.6	6.5	Incoordination		39
	21,900	41.2	9.8	Deep narcosis	Died	39
	9,080	17.1	5.25	None		39
	12,850	24.2	8.75	Incoordination		39
	13,300	25.0	24.0	Light narcosis		39
	6,400	12.0	8.0	None	Survived	39
Rat	32,000	60.1	8.0	—	Some died	123
	16,000	30.1	8.0	—	Some died	123
	45,000	84.6	3.75	Deep narcosis		39
	44,000	82.7	6.5	Deep narcosis	Died	39
	19,260	36.2	2.0	Light narcosis		39
	21,960	41.2	9.8	Deep narcosis	Died	39
	18,200	34.2	1.0	Excitation		39
	18,200	34.2	1.75	Incoordination		39
	22,800	42.9	8.0	Deep narcosis		39
	22,100	41.5	15.0	Deep narcosis	Died	39
	10,750	20.2	0.5	None		39
	10,750	20.2	2.0	Incoordination		39
	12,400	23.3	8.5	Deep narcosis		39
	12,700	23.8	21.75	Deep narcosis	Died	39
	5,660	10.6	1.75	Incoordination		39
	6,400	12.3	12.0	Light narcosis	Survived	39

3,260	6.1	6.0	None		39
3,260	6.1	8.0	Drowsiness		39
4,580	8.6	21.13	Ataxia	Survived	39

[a] Taken from Rowe and McCollister (18).

Monohydric Alcohols—C_1 to C_6

C. Bevan, Ph.D., DABT

B. Butanols

Butanols consist of four structural isomers of the molecular formula $C_4H_{10}O$: two primary, one secondary, and one tertiary alcohol. There are two stereoisomers of 2-butanol due to an asymmetric carbon atom in the secondary alcohol. All the butanols exist as liquids at room temperature, except *tert*-butanol (melting point 25°C). A relatively good toxicity data base exists for these alcohols. Occupational exposure standards exist for all four butanols.

Monohydric Alcohols—C_1 to C_6

C. Bevan, Ph.D., DABT

C. Amyl Alcohols

This group consists of saturated aliphatic alcohols that contain five carbons. It includes three pentanols, four substituted butanols, and a disubstituted propanol, eight structural isomers that have the empirical formula $C_5H_{12}O$. There are four primary, three secondary, and one tertiary alcohol (347). In addition, 2-pentanol, 2-methyl-1-butanol, and 3-methyl-2-butanol are optically active.

The odd-numbered carbon structure and the extent of branching provide amyl alcohols with unique physical and solubility properties and often offer ideal characteristics for solvent, surfactant, extraction, gasoline additive, and fragrance applications. The original source of amyl alcohols was fusel oil, which is a by-product of the ethanol fermentation industry. Refined amyl alcohol from this source contained 85% 3-methyl-1-butanol and about 15% 2-methyl-1-butanol (347). Amyl alcohols were first produced synthetically from pentane by chlorination and hydrolysis (347). Today the most important industrial process for producing amyl alcohol is the oxo process based on butenes (347). Mixtures of isomeric amyl alcohols such as 1-pentanol and 2-methyl-1-butanol are often preferred because the different degree of branching imparts a more desirable combination of properties (347).

Inhalation of amyl alcohol vapors by humans have been reviewed by Rowe and McCollister (18). The vapors cause marked irritation of the eyes and respiratory tract, headache, vertigo, dyspnea and cough, nausea, vomiting, and diarrhea. Double vision, deafness, delirium, and occasionally fetal poisoning, preceded by severe nervous symptoms, have been attributed to the absorption of amyl alcohol. Coma, glycosuria, and sometimes methemoglobinemia have been reported as characteristic of amyl alcohol intoxication. A few cases of industrial poisoning were caused by amyl alcohol, although the presence of other solvents confounded the issue (18). Workers engaged in producing

smokeless powder reported cough, eye irritation, colic, diarrhea, vomiting, heart palpitation, nervous symptoms, headache, vertigo, vision disturbances, forgetfulness, insomnia, somnolence, weakness, and one fatality. Although other alcohols and ether were employed, the signs increased as the use of amyl alcohol (probably fusel oil) increased (348). Nonindustrial cases of poisoning from drinking fusel oil were characterized by coma, glycosuria, and methemoglobinuria (349). An occupational exposure standard exists only for 3-methyl-1-butanol.

Table 77.6. Pattern of Excretion of Secondary Amyl Alcohols by Rats after Intraperitoneal Injection (135)[a]

	Percent of administered dose				
	Expired air		Urine		
Isomer	Alcohol	Ketone	Alcohol	Ketone	Total Excreted
2-Pentanol	5.4	36.8	1.2	2.0	45.4
3-Pentanol	0.3	50.0	0.1	4.6	55.0
3-Methyl-2-butanol	8.1	48.0	2.9	2.4	61.4

[a] Taken from Rowe and McCollister (18).

Monohydric Alcohols—C_1 to C_6

C. Bevan, Ph.D., DABT

D. Hexanols

The C_6 alcohols consist of a number of primary, secondary, and tertiary structural isomers. Enantiomers can exist for 2-hexanol. The most important commercial members are 1-hexanol, 2-ethyl-1-butanol, and isohexyl alcohols (a mixture of branched C_6 alcohols). The most important member of the secondary alcohols, is methyl isobutyl carbinol. The major use of these alcohols is in the production of esters, such as plasticizers. No occupational exposure standards exist for the hexanols except for methyl isobutyl carbinol.

There is toxicological interest in 2-hexanol because it is a metabolite of *n*-hexane and methyl-*n*-butyl ketone, which are known neuropathic agents in humans and animals.

Monohydric Alcohols—C_1 to C_6

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Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

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Chemical and Physical Properties

The physical and chemical properties for these alcohols are listed in Table 78.1. The National Fire Protection Association (NFPA) has prepared a rating system to assess the physical and chemical hazards of chemicals with respect to flammability, health, and reactivity (1, 2). In general, these alcohols are not reactive chemicals, except for the unsaturated alcohols.

Compound	CAS Number	Mol. Formula	Mol. Wt.	Boiling Point (°C)	Melting Point (° C)	Sp. Gr.	Refractive Index (20° C)	Va Pres (mn (°
1-Heptanol	[*117-70-6*]	$C_7H_{16}O$	116.2	176	–35.0	0.824	1.4233	-
2-Heptanol[b]	[*543-47-7*]	$C_7H_{16}O$	116.2	159	—	0.817	1.4213	-
3-Heptanol[b]	[*3913-02-8*]	$C_7H_{16}O$	116.2	156	–70.0	0.821	1.4222	-
2,3-Dimethyl-1-pentanol	[*143-23-4*]	$C_7H_{16}O$	116.2	—	—	—	—	-
1-Octanol	[*111-87-5*]	$C_8H_{18}O$	130.2	195	–16.3	0.827	1.4300	-
2-Octanol	[*123-96-6*]	$C_8H_{18}O$	130.2	179	–38.6	0.821	1.4260	1.0 (
3-Octanol	[*589-29-1*]	$C_8H_{18}O$	130.2	—	—	—	—	-
2-Ethyl-1-hexanol	[*104-76-7*]	$C_8H_{18}O$	130.2	185	<–75.0	0.833	1.4315	0.05
2,2,4-Trimethyl-1-pentanol	[*123-44-4*]	$C_8H_{18}O$	130.2	168	–70.0	0.839	1.4300	-
2-Ethyl-4-methyl-1-pentanol	[*106-67-2*]	$C_8H_{18}O$	130.2	—	—	—	—	-
1-Nonanol	[*143-08-8*]	$C_9H_{20}O$	144.3	214	–5.0	0.827	1.4323	0.3
3,5,5-Trimethyl-1-hexanol[b]	[*3452-97-9*]	$C_9H_{20}O$	144.3	194	–70.0	0.824	1.4330	-
1-Decanol	[*112-30-1*]	$C_{10}H_{22}O$	158.3	234	6.4	0.832	1.4359	10 (
Isodecanol	[*2533-17-7*]	$C_{10}H_{22}O$	158.3	226	—	—	—	-
1-Undecanol[b]	[*112-42-5*]	$C_{11}H_{24}O$	172.3	245	14.3	0.830	1.4392	-
1-Dodecanol	[*112-53-8*]	$C_{12}H_{26}O$	186.3	259	23.8	0.831	1.4428	-
1-Tetradecanol[b]	[*112-72-1*]	$C_{14}H_{30}O$	214.4	—	38.0	0.817	1.4358	-
1-Hexadecanol	[*36653-82-4*]	$C_{16}H_{34}O$	242.5	—	49.0	0.816	1.4392	1 (1
1-Octadecanol	[*112-92-5*]	$C_{18}H_{38}O$	270.5	—	58.0	0.812	—	-
Eicosanol	[*629-96-9*]	$C_{20}H_{42}O$	298.6	—	66.0	—	—	-
Benzyl alcohol	[*100-51-6*]	C_7H_8O	108.1	205	15.2	—	1.5404	0.15
2-Phenylethanol	[*60-12-8*]	$C_8H_{10}O$	122.2	220	–25.8	—	1.5300	1.0
1-Phenylethanol	[*98-85-1*]	$C_8H_{10}O$	122.2	202	20.1	—	—	-
2-Phenyl-2-propanol	[*1123-85-9*]	$C_9H_{12}O$	134.2	—	—	—	—	-
p-tolyl alcohol	[*589-18-4*]	$C_8H_{10}O$	122.2	—	—	—	—	-
Cyclohexanol	[*108-93-0*]	$C_6H_{12}O$	100.2	161	24.0	—	1.4656	3.5

Methylcyclohexanol	[*25639-42-3*]	$C_7H_{14}O$	114.2	174	–50.0	0.913	1.4610	1.5
3,5,5-Trimethyl-cyclohexanol	[*116-02-9*]	$C_9H_{18}O$	142.0	—	—	—	—	-
Furfuryl alcohol	[*98-00-0*]	$C_5H_6O_2$	98.1	170	–14.6	—	1.4840	1.0 (
Tetrahydrofuran methanol	[*97-99-4*]	$C_5H_{10}O_2$	102.1	178	<–80.0	1.050	1.4520	2.3
Allyl alcohol	[*107-18-6*]	C_3H_6O	58.1	94	–50.0	0.848	1.4135	23.8
Propargyl alcohol	[*107-19-7*]	C_3H_4O	56.1	114	–50.0	0.972	1.4306	11.6
Hexynol	[*105-31-7*]	$C_6H_{10}O$	98.1	142	–80.0	0.882	—	13.0
Butynol[b]	[*2028-69-9*]	C_4H_8O	70.1	107	—	—	—	-
Methylbutynol[b]	115-9-5	C_5H_8O	84.1	—	—	—	—	-
Methylpentynol[b]	[*77-75-8*]	$C_6H_{10}O$	98.1	121	–197.2	—	—	-
Ethyloctynol[b]	[*5877-42-9*]	$C_{10}H_{18}O$	154.2	—	—	0.871	—	-
2-Chloroethanol	[*107-07-3*]	C_2H_5ClO	80.5	129	—	1.205	1.4419	4.9
1-Chloro-2-propanol	[*127-00-4*]	C_3H_7ClO	94.5	—	—	—	—	-
2-Chloro-1-propanol	[*78-89-7*]	C_3H_7ClO	94.5	—	—	—	—	-

[a] At 25°C, 760 mm Hg.
[b] Toxicity of these chemicals is formed in Table 78.4.
[c] Miscible.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

C. Bevan Ph.D., DABT

Production and Use

Alcohols represent an important class of industrial chemicals with a wide number of uses. Based on production volume, monohydric alcohols represent the most important group of the alcohol family (3). The most important alcohols in this chapter are the plasticizer alcohols (C_7 to C_{11}) and the detergent range alcohols (C_{12} to C_{18}). In 1997, the production volume of 2-ethylhexanol reached 7.68 billion pounds in the United States (4). In general, alcohols of commercial significance are produced synthetically, although some alcohols are made from natural products of fermentation. The most significant industrial process is the oxo process that can be used to produce alcohols in the C_3 to C_{20} range by using alkenes as starting materials (3).

The uses of alcohols are numerous and can vary depending on their chemical and physical properties. In general, alcohols are used as solvents, cosolvents, and chemical intermediates. Among the higher alcohols, defined as containing six carbons or more, the C_6 to C_{11} alcohols are used to manufacture plasticizers. Some of the alcohols are pure chemicals, but higher monohydric alcohols (C_6 to C_{18}) are also complex isomeric mixtures (3, 5, 6). The major routes of industrial or

occupational exposure to alcohols is by dermal contact and/or inhalation. The extent of the exposure pathways depends on the use of the chemical and the physical properties of the alcohol.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

C. Bevan Ph.D., DABT

Metabolism and Disposition
A comparative uptake study has been conducted using human abdominal skin *in vitro* for C_1 to C_{10} linear alcohols (7). The rate of dermal uptake for the neat material decreases with increasing carbon number.

Williams prepared an early general review on the metabolism and disposition of alcohols (8). Primary alcohols are readily oxidized to the corresponding aldehydes, which are further converted to the corresponding acids. Secondary alcohols are converted to ketones. Alcohols can be conjugated either directly or as a metabolite with glucuronic acid, sulfuric acid, or glycine, and excreted. Tertiary alcohols are more resistant to metabolism and are generally conjugated more readily than secondary or primary alcohols.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

C. Bevan Ph.D., DABT

Health Effects
A common property of some of the alcohols is to produce local irritation to the skin, eyes, and respiratory tract, and the effect or potency varies with the type of alcohol. Many alcohols produce minimal or no adverse effects in humans, possibly because of low exposure combined with the low toxicity potential of the alcohol.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

C. Bevan Ph.D., DABT

A. Heptanols
The most important commercial member of this group is isoheptyl alcohol, which is a mixture of branched C_7 alcohols. This alcohol is used for the manufacture of esters such as phthalate plasticizers. 1-Heptanol has little commercial value. Other C_7 alcohols are 2,3-dimethyl-1-pentanol and the secondary alcohols, 2-heptanol, 3-heptanol, 4-heptanol, and 2,4-dimethyl-3-pentanol. 2-Heptanol and 3-heptanol can exist as enantiomers.

The available toxicity data indicate that heptanols have a low order of acute toxicity and no occupational exposure standards exist for them.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

C. Bevan Ph.D., DABT

B. Octanols

The most important commercial C_8 alcohols are 2-ethylhexanol and a mixture of branched C_8 alcohols referred to as isooctyl alcohol. Other octanols of lesser commercial interest are 2-octanol, 1-octanol, 3,5-dimethyl-1-hexanol, 2,2,4-trimethyl-1-pentanol, and 2-ethyl-4-methyl-1-pentanol. These alcohols are liquids at ambient temperature and are used primarily in producing esters, such as plasticizers. No occupational exposure standards exist for octanols except for isooctyl alcohol.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

C. Bevan Ph.D., DABT

C. Nonanols

The most important commercial members of this subgroup of alcohols are the C_9 oxo alcohols, which are a mixture of predominantly C_9 branched alcohols, diisobutyl carbinol, and 2,6-dimethyl-4-heptanol. Two C_9 alcohols of lesser commercial importance are 1-nonanol and 3,5,5-trimethyl-1-hexanol. All of these alcohols are liquids at ambient temperatures.

Acute studies in animals indicate a low order of toxicity. These alcohols are irritating to the skin, eyes, and respiratory tract. They are also aspirations hazard. No serious adverse effects from industrial exposure were reported in humans. Prolonged or excessive exposure to the alcohols can produce local irritation and narcosis. No occupational exposure standards have been established for any of the nonanols.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

C. Bevan Ph.D., DABT

D. Decanols

The decanols consist of more than 20 structural isomers, including a number of enantiomers. The most important commercial members are the C_{10} oxo alcohols, which exist as a mixture of C_{10} branched alcohols. Many of these alcohols are liquids. Unlike the lower alcohols, the decanols are less volatile and flammable (Table 78.1). Toxicity studies indicate that these alcohols have a low order of acute toxicity but they are irritating to both the skin and eyes. No serious industrial intoxication has been reported for the decanols. No occupational exposure standards exist for the decanols.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

C. Bevan Ph.D., DABT

E. Dodecanols

These alcohols consist of more than 20 structural isomers, including a number of enantiomers. The two most prominent members of this group of alcohols are 1-dodecanol and isodecyl alcohol, a mixture of predominantly C_{12} branched alcohols. Toxicity studies indicate that dodecanols have a low order of acute toxicity. 1-Dodecanol is the most studied C_{12} alcohol and is a tumor promoter in mice. There have been no reports of adverse effects in humans. No occupational exposure standards have been established for any of the decanols.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

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F. Tridecanols

19.0 Isotridecyl Alcohol

19.0.1 CAS Number:

19.0.2 Synonym: C_{13} oxo alcohols

19.0.3 Trade Names: NA

19.0.4 Molecular Weight: 200.3

19.0.5 Molecular Formula: $C_{13}H_{28}O$

19.1 Chemical and Physical Properties

Isotridecyl alcohols are liquids or solids.

19.2 Production and Use

Isotridecyl alcohol is produced by the oxo process in which dodecenes are reacted with carbon monoxide and hydrogen in the presence of a catalyst, followed by hydrogenation (3). A major isomer of a commercial-grade product is tetramethyl-1-nonanol. Because of their low volatility these alcohols are used to produce plasticizers, they are also used as surfactant raw materials, as lubricant intermediates, and as solvents (3).

19.4 Toxic Effects

19.4.1 Experimental Studies 19.4.1.1 Acute Toxicity The acute oral LD_{50} is 4.75 g/kg in rats (42), and the dermal LD_{50} in rabbits is greater than 2.6 g/kg (42). No deaths were observed in rats, mice, or guinea pigs exposed to saturated vapors (12 ppm) for 6 h (42). Animals exhibited slight irritation to the eyes, nose, and throat.

These alcohols are reportedly moderately irritating to rabbit skin when applied for 24-h under an occlusive wrap, but slightly irritating when applied under 4-h semiocclusive conditions (17). Isotridecyl alcohol was moderately irritating to eyes of rabbits (42).

19.4.2 Human Experience 19.4.2.1 General Information No adverse effects in humans were reported from exposure to these alcohols.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

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G. Higher Alcohols

Most of the toxicity data on the higher alcohols exist on the C_{16} and the C_{18} alcohols. Limited data exist for 1-tetradecanol and eicosnol (see Table 78.4). No occupational exposure standards have been established for the higher alcohols.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

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H. Aromatic Alcohols

There are at least five aromatic alcohols of commercial interest; three primary alcohols (benzyl alcohol, 2-phenylethanol, and *p*-tolyl alcohol) and two secondary alcohols (1-phenylethanol and 2-phenyl-2-propanol). All of these alcohols are liquids at ambient temperatures. No valid NIOSH methods exist to measure these alcohols in air.

The toxicities of benzyl alcohol and 2-phenylethanol are the most studied of the aromatic alcohols. As a group, these alcohols have a low to moderate order of acute toxicity and have been both active and inactive in genotoxicity assays. No occupational exposure standards have been set for these alcohols.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

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M. Alicyclic Alcohols

There are at least four alicyclic alcohols of commercial interest, two from the cyclohexyl family (cyclohexanol, methylcyclohexanols) and two from the furan family (furfuryl alcohol and tetrahydrofuran methanol). These alcohols are liquids. Cyclohexanol and furfuryl alcohol are the best studied alcohols of this group. Occupational exposure standards exist for these alcohols, except for tetrahydrofuran methanol.

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N. Unsaturated Alcohols

Unsaturated alcohols can be divided into olefinic (double-bond) and acetylenic (triple-bond) alcohols. Allyl alcohol is the most important olefinic alcohol as well as the most studied in this subset; propargyl alcohol and hexynol alcohol are the most commercially important acetylenic

alcohols. There are also a number of other olefinic alcohols (C_5) and acetylenic alcohols (C_4 to C_{10}) with toxicity data (see Table 78.4). In general, these alcohols are liquids and are quite reactive. Occupational exposure standards exist for allyl alcohol and propargyl alcohol.

Table 78.2. Results of Single or Short-term Exposures of Animals to Vapors of Allyl Alcohol[a]

Concentration (ppm)	Animal	Duration of Exposure (h)	Outcome	Ref.
1000	Monkey	4	Death	199
1000	Rabbit	4	100% lethal	199
200	Rabbit	18 × 7	100% lethal	199
1000	Rat	4	100% lethal	199
1060	Rat	1	LC_{50}	200
1000	Rat	1	LC_{67}	198
500	Rat	1	Survived	201
250	Rat	4	Some deaths	201
165	Rat	4	LC_{50}	200
76	Rat	8	LC_{50}	200
200	Rat	2 × 7	100% lethal	199

[a] Taken from Ref. 34.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

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O. Halogenated Alcohols

The most important commercial members of the halogenated alcohol series are 2-chloroethanol, or ethylene chlorohydrin, and chloropropanols, which are two isomers. These three alcohols exist as volatile liquids. Some of the other halogenated alcohols not covered in this chapter have been reviewed by Rowe and McCollister (34).

Table 78.3. Results of Single Exposures of Animals to the Vapors of 2-Chloroethanol[a]

	Dose			
Animal	(mg/L)	(ppm)	Duration of Exposure (h)	Outcome	Ref.

Guinea pig	18.0	5468	0.25	Death	235
	5.0	1544	0.9	Survived	227
	3.6	1094	1.0	Death	235
	3.0	911	1.8	Death	227
	3.0	911	0.5	Survived	227
Mouse	7.0	2430	2.0	Death	227
	4.5	1367	0.5	Death	227
	4.0	1215	0.25	LC_{67}	227
	3.0	911	1.0	Death	227
	1.2	365	2	LC_{17}	232
	1.0	304	2	Survived	227
	0.38	115	?	LC_{50}	230
Rat	4.0	1215	0.5	Death	227
	3.4	1033	0.25 × 3, 6, or 11	Death	227
	3.0	911	0.25	Survived	227
	0.29	88	?	LC_{50}	230
	0.11	33	4	LC_{50}	233

[a] Taken from Rowe and McCollister (34).

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

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P. Miscellaneous Alcohols

Limited toxicity data exist on a number of alcohols of lesser industrial importance, which are listed in Table 78.4. These alcohols include six monohydric alcohols, one alicyclic alcohol, and four acetylenic alcohols. It should be noted that a number of these alcohols exist as stereoisomers with different CAS registry numbers. The CAS registry numbers listed in Table 78.4 represent the mixed product. It is not known whether biological differences exist among the different isomers.

Table 78.4. Toxicity Data on Miscellaneous Alcohols

Alcohol	Acute Oral Rat LD_{50}	Acute Dermal Rabbit LD_{50}	Acute Inhalation Rat LC_{50}	Skin Irritation	Eye Irritation	Skin Sensitization	Ref.
2-Heptanol (CAS *#543-47-7*)	2.58 g/kg	1.78 mL/kg	No deaths, 8 hr satd. vapor	Slight	Severe	—	273

3-Heptanol (CAS *#3913-02-8*)	1.87 g/kg	4.36 mL/kg	No deaths, 4 hr satd. vapor	Slight	Moderate	—	105
1-Undecanol (CAS *#112-42-5*)	3 g/kg	>5 g/kg	—	Moderate	—	—	274
1-Tetradecanol (CAS *#112-72-1*)	>5 g/kg	>5 g/kg	—	No	Slight	—	275
Eicosanol (mixed isomers) (CAS *#629-96-9*)	>64 mL/kg	>20 mL/kg	No deaths, 8 hr satd. vapor	Slight	Slight	—	43
3,5,5-Trimethyl cyclohexanol (CAS *#116-02-9*)	3.45 g/kg	2.8 mL/kg	—	Moderate	Very severe	—	102
3-Butyn-2-ol (CAS *#2028-69-9*)	34 mg/kg	32–36 mg/kg	1 hr LC_{50}; std. vapor 6 min exposure, 100% lethal	—	Very severe	—	216
Methyl butynol (CAS *#115-9-5*)	1.9 g/kg	>5 g/kg	1 hr LC_{50}; >20 mg/L[a]	None	Severe (10% in H_2O not irritating)	Possibly	216
Methyl pentynol (CAS *#77-75-8*)	0.8 g/kg	>1 g/kg	1 hr LC_{50}; >20 mg/L[b]	Slight	Severe	Possibly	216
Ethyl octynol (CAS # [*5877-42-9*])	2.1 g/kg	0.2–1.0 g/kg	—	—	—	Possibly	34
3,7-Dimethyl-1-octonol (CAS *#106-21-8*)	>5 g/kg	2.4 g/kg	—	Yes. unspec.	—	—	106

[a] A single 4-hr exposure of rats to 3000 ppm methyl butynol caused death, but a 7-hr exposure to 2000 ppm did not. Both exposures caused liver and kidney injury. A single 7-hr exposure to 1000 ppm did not cause grossly apparent injury. Rats that received 81 7-hr exposures to 76 ppm for 115 day exhibited no adverse effects.

[b] A single 4-hr or 7-hr exposure of rats to 4600 ppm methyl pentynol caused anesthesia, considerable injury to the lungs, liver, and kidney, and death. A 2-hr exposure did not cause death but did cause kidney injury and weight loss. A few deaths occurred after 4- and 7-hr exposures to 2000 ppm, whereas all survived a 7-hr exposure to 1000 ppm, although kidney

injury was noted. Groups of rats tolerated 67 7-hr exposures to 100 ppm for 98 days without adverse effects.

Monohydric Alcohols—C_7 to C_{18}, Aromatic, and Other Alcohols

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Esters of Mono- and Alkenyl Carboxylic Acids and Mono- and Polyalcohols
Michael S. Bisesi, Ph.D., CIH

A. Introduction

Overview

This volume contains three chapters reviewing 12 classes of the organic compounds called *esters*. Chapter 79, this chapter, reviews (*1*) esters of monocarboxylic acids and mono- and polyalcohols and (*2*) esters of alkenyl carboxylic acids and monoalcohols; Chapter 80 reviews (*3*) esters of aromatic monocarboxylic acids and monoalcohols, (*4*) esters of monocarboxylic acids and di-, tri-, and polyalcohol; (*5*) dicarboxylic acid esters; (*6*) alkenyl dicarboxylic esters; (*7*) esters of aromatic diacids; (*8*) tricarboxylic acid esters; and, Chapter 81 covers (*9*) esters of carbonic and orthocarbonic acid; (*10*) esters of organic phosphorous compounds; (*11*) esters of monocarboxylic halogenated acids, alkanols, or haloalcohols; and (*12*) organic silicon esters.

The sequence of the compounds has been organized according to the chemical structure of the major functional metabolites. This involves the ester hydrolyzates, primarily the acid and secondarily the alcohol. The reason for this sequence was the general observation that the degree of toxic effect, in addition to that of the original material, more often was the result of the toxicity of the acid rather than the response of the alcohol.

Esters are important from an industrial hygiene perspective since exposure can occur during the process of manufacturing esters, the process of manufacturing materials containing or composed of esters, handling and use of products containing or composed of esters, and treatment of wastes containing esters. In turn, exposure to esters is important from a toxicological perspective because of the correlated observations of adverse physiological responses exhibited by laboratory animals and humans.

Overviews of the physical, chemical and toxicologic (*i.e.*, physiologic responses) properties of many subclasses of esters and/or of specific compounds are provided. In addition, summaries of relative manufacturing and use information are also included for many compounds.

General Properties of Some Esters

Chemically, esters are organic compounds commonly formed via the combination of an acid, typically an organic (—COOH) mono- or polyacid, plus a hydroxyl (—OH) group of a mono-or polyalcohol or phenol; water (H—OH) is generated as a by-product of the reaction. For example, the reaction (esterfication) of acetic acid (CH_3COOH) with methyl alcohol (CH_3OH) to form methyl acetate proceeds [$CH_3(C{=}O)OCH_3$] as follows:

$$CH_3COOH + CH_3OH \leftrightarrow CH_3(C=O)OCH_3 + H_2O$$

The forward reaction (right; k_1) is known as *esterification*; the reverse (left; k_2) as *hydrolysis*. The occurrence of esterification or hydrolysis reactions depends on the differential reaction rates k_1 *versus* k_2 and the physical properties of the respective final products. The ratio of the concentrations of products [*C*] of k_1 divided by k_2 will give a reaction constant K_s indicative of the stability of the final product:

$$K_s = \frac{[C_{ester}] \times [C_{H_2O}]}{[C_{alcohol}] \times [C_{acid}]}$$

The esters are widely used in industry and commerce. They can be prepared by the reactions of acids with alcohols, by reacting metal salts of acids with alkyl halides, acid halides with alcohols, or acid anhydrides with alcohols by the interchange of radicals between esters. Most esters exist in liquid form at ambient temperatures, but some possess lower boiling points than their original starting

materials. They are relatively water-insoluble, except for the lower molecular weight members. Their flash points are in the flammable range. The monocarboxylic acid esters have high volatility and pleasant odors, whereas the di- and polyacid esters are relatively nonvolatile and exhibit essentially no odor. The monocarboxylic esters occur frequently in natural products, as, for example, in fruits, to which they lend their pleasant odor and taste. Because of the different properties of esters from the original acids and alcohols, esterification can be used for their isolation or to chemically protect specific carboxy or hydroxy functions.

General Toxicity of Some Esters

Absorbed esters and/or metabolites derived from biotransformed esters can initiate toxic effects in some mammalian systems, including humans, and cause adverse physiological responses. Indeed, the underlying causes of physiological responses are due to initial interactions biochemically within a system. Within these chapters, a summary of reviewed literature will reveal that, in general, toxic effects associated with exposure to various esters include primary irritation to ocular, upper and lower respiratory, and dermal systems; depression of the central nervous system (CNS) (*e.g.*, anesthesia, narcosis); dermal hypersensitization; impact to the gastrointestinal (GI), hepatic, and renal systems; abnormal cardiac rhythm; and carcinogenesis. Indeed, these and some additional effects, are based predominantly on rodent studies. A review of the literature reported here, however, indicates that the most commonly reported effects in animals and humans are irritation and, to some extent, CNS depression. Data are reported in this chapter for several classes of esters, including formates (1), acetates (2), acrylates and methacrylates (3), propionates (4), and lactates (5).

Ocular, dermal, respiratory, and even GI irritation is reportedly associated with both the parent ester compounds and the corresponding acid metabolites produced via hydrolytic cleavage reactions (1). Some compounds, such as the aliphatic esters used as lacquer solvents, may cause CNS depression when inhaled in sufficiently high concentrations (6). As expected from Overton theories substantiated by Munch (7) in experiments using rabbits and tadpoles, the more highly water-soluble, lower molecular weight derivatives, such as the methyl and ethyl formates and acetates, are less potent than butyl and amyl acetates. Thus, when Munch used tadpoles to evaluate the potency of aliphatic alcohols and their alkyl esters, he observed a direct relationship between CNS depression and increase in homologous series (7). He concluded that the intact ester was the primary causative agent.

Their anesthetic potency is weaker than that of lower chlorinated hydrocarbons and usually less than that of ethyl ether, but greater than that of ethanol, acetone or pentane. When inhaled, aliphatic esters readily pass through the alveoli, owing to their relatively high solubility in plasma fluid. Those materials with higher water solubility have higher blood–air distribution coefficients and thus presumably reach saturation more slowly. This group of esters appears to be readily hydrolyzed and the resulting alcohols and acids rapidly metabolized.

Most of the aliphatic esters possess some degree of irritation on exposed surfaces. The formates are especially irritating to the eyes and respiratory tract. Ethyl acetates may be irritating at concentrations of 400–800 ppm, whereas ethanol is devoid of effects up to 1000 ppm. The irritant range of butyl acetate, however, coincides with that of its corresponding alcohol. The irritant effect of the higher homolog is a function of the esterified rather than the hydrolyzed material. The local skin effects resemble those of other solvents; namely, defatting and cracking may occur.

Practically all the common aliphatic and aromatic esters, except for some phosphates used as plasticizers, are inert. At the most, minor degrees of irritation may follow inhalation of heated vapors or prolonged skin exposure. Some of the literature also suggests that reported skin sensitization appears more likely in the presence of impurities or side products. Many of the materials are so inert that any LD_{50} value is impractical to determine. Specific pathology is usually absent, even when the materials is fed in massive quantities to the point of nutritional deprivation. Oily or watery excretion products, sometimes observed at high feeding levels, indicate lack of absorption. The apparent nontoxicity may also be a sign of rapid hydrolysis, metabolism, and excretion. The resins are

completely inert, unabsorbed in the gastrointestinal tract, and nonirritant at the surface of the skin and pulmonary system.

Industrial Hygiene Evaluation

One part of industrial hygiene evaluation of esters involves collecting and analyzing air samples to determine their airborne concentrations. To date, published industrial hygiene air sampling and analytical methods are available for relatively few esters compared to the number of ester compounds. In addition, although methods for biological monitoring of laboratory animals and exposed humans can be conducted to determine levels of absorbed esters and metabolites that originate from biotransformed esters, there are few established limits for comparing biological monitoring data.

Contemporary air sampling methods most commonly involve the use of solid absorbents, such as charcoal, carbosieve, and XAD (8, 9). Following desorption of the solid adsorbents using a specified solvent, samples are typically analyzed using gas chromatography with flame ionization detection (GC-FID). The concentration of a given sample is determined by dividing the mass of the ester detected and measured using GC-FID by the volume of air sampled. Concentrations of air samples may be subsequently used to calculate time-weighted averages (TWAs) for comparison to applicable occupational exposure limits (OELs).

Presently, there also are relatively few OELs compared to the number of ester compounds. There are threshold limit values (TLVs) and permissible exposure limits (PELs) established by the American Conference of Governmental Industrial Hygienists (ACGIH) and the Occupational Safety and Health Administration (OSHA), respectively, for some of the ester compounds discussed in this chapter (9–11). In addition, other applicable agencies, such as the National Institute for Occupational Safety and Health (NIOSH), provide published recommendations concerning limits for occupational exposure to some esters (9).

Industrial hygiene sampling and analytical methods for some ester compounds are presented in Table 79.1 along with their respective OELs. Since sampling and analytical methods and occupational exposure limits are subject to periodic revision; however, the reader is encouraged to refer to current publications of ACGIH, OSHA, and NIOSH.

Table 79.1. Summary of Occupational Exposure Limits (OELs) and Monitoring Methods for Some Esters (8–11)

Compound	OSHA (ppm)			ACGIH (ppm)			NIOSH (ppm)			OEL Notations	Monitoring
	PEL	STEL	C	TLV	STEL	C	REL	STEL	C		
Methyl formate	100	—	—	100	150	—	100	150	—	—	Carbosieve B tube GC-FID
Ethyl formate	100	—	—	100	—	—	100	—	—	—	Charcoal tube GC-FID
Methyl acetate	200	—	—	200	250	—	200	250	—	—	Charcoal tube GC-FID
Ethyl acetate	400	—	—	400	—	—	400	—	—	—	Charcoal

											tube GC-FID
n-Propyl acetate	200	—	—	200	250	—	200	250	—	—	Charcoal tube GC-FID
Isopropyl acetate	250	—	—	250	310	—	—	—	—	—	Charcoal tube GC-FID
n-Butyl acetate	150	—	—	150	200	—	150	200	—	—	Charcoal tube GC-FID
sec-Butyl acetate	200	—	—	200	—	—	200	—	—	—	Charcoal tube GC-FID
tert-Butyl acetate	200	—	—	200	—	—	200	—	—	—	Charcoal tube GC-FID
Isobutyl acetate	150	—	—	150	—	—	150	—	—	—	Charcoal tube GC-FID
n-Amyl acetate	100	—	—	50[a]	100[a]	—	100	—	—	—	Charcoal tube GC-FID
sec-amyl acetate	125	—	—	125	—	—	125	—	—	—	Charcoal tube GC-FID
Isoamyl acetate	100	—	—	100[a]	—	—	100	—	—	—	Charcoal tube GC-FID
sec-Hexyl acetate	50	—	—	50	—	—	50	—	—	—	Charcoal tube GC-FID
Vinyl acetate	—	—	—	10	15	—	—	—	4	NIOSH carcinogen ACGIH A3	Carbosieve B tube GC-FID
Methyl acrylate	10	—	—	2	—	—	10	—	—	Skin ACGIH A4	Charcoal tube GC-FID
Ethyl acrylate	25	—	—	5	15	—	—	—	—	Skin ACGIH A4	Charcoal tube GC-FID
n-Butyl acrylate	—	—	—	2	—	—	10	—	—	Sensitizer ACGIH A4	Charcoal tube GC-FID
Methyl methacrylate	100	—	—	100	—	—	100	—	—	ACGIH A4	XAD-2 tube GC-FID
Butyl lactate	—	—	—	5	—	—	5	—	—	—	—

[a] Notice of intended change, changed as of 2000.

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B. Esters of Monocarboxylic Acids and Mono- and Polyalcohols
Grouped into this category are the naturally occurring fatty acid esters of C1–C24 acids and C1–C30 alcohols.

Esters of Mono- and Alkenyl Carboxylic Acids and Mono- and Polyalcohols
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Formates
The esters called *formates* are alkyl or aryl derivatives of formic acid HCOOH. These esters have various uses ranging from flavoring agents to industrial solvents. As is the case for most esters of toxicological significance, ocular, respiratory, and dermal irritation, and, at higher concentrations, CNS depression, are the major effects associated with exposure. The inhalation hazard decreases with increased molecular weight due to an observed progressive decrease in vapor pressure. There also is an observed decrease in water solubility with increasing molecular weight. von Oettingen reports that the decreased water solubility is associated with increased resistance to acid hydrolysis of the higher homologues. Accordingly, the lowest homologe, methyl formate, may pose a higher hazard potential because of its high vapor pressure and water solubility, but the higher homologs exhibit higher potency as central nervous system depressants (1). A summary of physical and chemical properties is found in Table 79.2 (12) and summaries of toxicologic data are shown in Tables 79.3 (13–16) and 79.4 (17).

Table 79.2. Summary of Physical and Chemical Properties of Some For

Compound	CAS Number	Molecular Formula	Molecular Weight	Boiling Point (°C)	Melting Ponint (°C)	Specific Gravity (at 25° C)	Solubility[a] in Water (at 68°F)	Refractive Index (at 20°C)	Vap Dens (Air =
Methyl formate	[*107-31-3*]	$C_2H_4O_2$	60.05	31.5	–100	0.987	v	1.3433	2.0
Ethyl formate	[*109-94-4*]	$C_3H_6O_2$	74.08	54.3	–80	0.923	s	1.3598	2.5
n-Propyl formate	[*110-74-7*]	$C_4H_8O_2$	88.12	81.3	–92.9	0.91	d	1.3779	3.0
Isopropyl formate	[*625-55-8*]	$C_4H_8O_2$	88.12	68.2	—	0.873	d	1.3678	3.(
n-Butyl	[*592-84-*		102.13	106.8	–91.9	0.911	d	1.3912	3.5

formate	*7*]	$C_5H_{10}O_2$							
Isobutyl formate	[*542-55-2*]	$C_5H_{10}O_2$	102.13	98.4	–95.8	0.89	d	1.3857	—
n-Amyl formate	[*638-49-3*]	$C_6H_{12}O_2$	116.16	132.1	–73.5	0.893	d	1.3922	4.(
Isoamyl formate	[*110-45-2*]	$C_6H_{12}O_2$	116.15	124.2	–93.5	0.89	d	1.3976	4.(
Vinyl formate	[*692-45-5*]	$C_3H_4O_2$	72.08	—	—	—	—	—	2.4
Cyclohexyl formate	[*4351-54-6*]	$C_7H_{12}O_2$	128.17	162.5	—	—	i	1.4430	4.4
Benzyl formate	[*104-57-4*]	$C_8H_8O_2$	136.16	203[b]	—	1.081	i	1.5154	4.7

[a] Solubility in water: v = very soluble; s = soluble; d = slightly soluble; i = insoluble.
[b] At 747 mm Hg.

Table 79.3. Summary of Inhalation Toxicity Data for Some Formates

Compound	Species	Exposure Mode	Approximate Dose or Concentration	Treatment Regimen	Observed Effect	Ref.
Methyl-formate	Human	Inhalation	1,500 ppm	1 min	No symptoms	13
	Guinea pig	Inhalation	50,000 ppm	30 min	Lethal	13
	Guinea pig	Inhalation	25,000 ppm	60 min	Lethal	13
	Guinea pig	Inhalation	10,000 ppm	3–4 h	Lethal	13
	Guinea pig	Inhalation	3,500 ppm	8 h	No deaths	13
Ethyl formate	Human	Inhalation	330 ppm	5 min	Eye and nose irritation	13
	Rat	Inhalation	Satd. vap.	5 min	No deaths	14
	Rat	Inhalation	8,000 ppm	4 h	5/6 deaths	1
	Rat	Inhalation	4,000 ppm	4 h	No deaths	15
	Mouse	Inhalation	10,000 ppm	20 min	Eye irritation, dyspnea	16
	Mouse	Inhalation	5,000 ppm	20 min	Eye irritation, dyspnea	16
	Cat	Inhalation	10,000 ppm	80 min	Eye	16

					irritation, dyspnea	
	Cat	Inhalation	5,000 ppm	20 min	Eye irritation, dyspnea	16
	Dog	Inhalation	10,000 ppm	4 h	Pulmonary edema, death	16
n-Butyl-formate	Human	Inhalation	10,000 ppm	<1 min	Intolerable irritation	16
	Dog	Inhalation	10,000 ppm	60 min	Irritation, narcosis, and recovery	16
	Cat	Inhalation	10,000 ppm	60 min	Irritation, narcosis and death	16

Table 79.4. Summary of Oral and Dermal Toxicity Data for Some Formates

Compound	Parameter	Species	Dose (g/kg)	Effect or Time to Death	Ref.
Methyl formate	Oral LD_{LO}	Human	0.500	20–30 min	17
	Oral LD_{50}	Rabbit	1.622	—	7
Ethyl formate	Oral LD_{50}	Rat	4.3	Lowest reported lethal dose	14
	Oral LD_{50}	Rat	1.850	15 min–2h	4
	Oral LD_{50}	Rabbit	2.075	—	7
	Oral LD_{50}	Guinea pig	1.110	—	4
	Dermal LD_{50}	Rabbit	>20 mL	No absorption	14
Propyl formate	Oral LD_{50}	Rat	3.980	4–18 h	4
	Oral LD_{50}	Mouse	3.4	Few min–6 h	4
n-Butyl formate	Oral LD_{50}	Rabbit	2.656	—	7
Isoamyl formate	Oral LD_{50}	Rat	9.84	Depression immediately following administration	4
		Rabbit	3.0	4 h–4 days	7

Vinyl formate	Oral LD_{50}	Rat	2.820	—	14
	Dermal LD_{50}	Rabbit	3.170	—	14
Allyl formate	Oral LD_{50}	Rat	0.124	—	4

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Acetates
The saturated aliphatic acetates, especially the ethyl and butyl acetates, serve as important solvents in the lacquer industry. The aromatic and cyclic acetates are used as flavoring agents for food and scenting of perfumes, soap, and similar articles.

Physiological effects of some are relatively low, since some acetates are, resemble, or convert into natural body metabolites. In both humans and experimental animals, however, administration of excessive quantities produce effects that consist of eye, throat, and nose irritation, followed by gradual onset of narcosis and slow recovery after termination of the exposure (2, 6)). Orally administered high concentrations of acetates to rabbits appeared to cause loss of coordination in decreasing order: ethyl = isopropyl > butyl > methyl = isoamyl acetate (30). This may be due to the rapid hydrolysis into acetic acid and the corresponding alcohols, causing a simultaneous decrease of the blood P_{CO2} and P_{O2} (30). There is a tendency to acidosis, especially with high concentrations of methyl acetate (30).

No anesthetic symptoms developed in men exposed to 400–600 ppm of ethyl or butyl acetate for 2–3 hrs. Eye irritation has been reported with 200–300 ppm exposure concentrations, but not the characteristic temporary corneal edema, which is caused by the corresponding alcohol (31). An eye injury healed promptly with the C4 but more slowly with the C3 acetate (32). No skin sensitization or dryness has been reported to date. The alkyl acetates possess increased narcotic potential (7), and the C3 and C8 members may have neurotoxic tendencies (33). The cyclic and aromatic acetates produce narcosis and death more readily than do the aliphatic esters. This may be due to the resulting hydrolytic products, which, however, are normally rapidly hydroxylated and excreted (2). For example, phenylacetyglutamine has been found to be excreted daily in 250–500-mg quantities in human urine (34).

A study indicated that thresholds for nasal pungency, odor, and eye irritation decreased logarithmically with the length of carbon chains for acetates, as observed for homologous series of alcohols, and also as seen with narcotic and other toxic responses (35). Data from another study that rated ocular irritation based on corneal thickness suggest that the rating potential for irritation is alcohols >acetates or ketones >aromatics (36).

Physical and chemical properties are summarized in Table 79.5, and toxicologic data are summarized in Tables 79.6 (37–43) and 79.7 (44, 45).

Table 79.5. Summary of Physical and Chemical Properties of Some Ace

Compound	CAS Number	Molecular Formula	Molecular Weight	Boiling Point (°C)	Melting Point (° C)	Specific Gravity at (25° C)	Solubility[a] in Water at (68 ° F)	Refractive Index at (20°C)	Vap dens (Air =
Methyl acetate	[*79-20-9*]	$C_3H_6O_2$	74.08	56.9	–98	0.9342	v	1.3593	2.5
Ethyl acetate	[*141-78-6*]	$C_4H_8O_2$	88.10	77	–83.6	0.902	s	1.3723	3.0
n-Propyl acetate	[*109-60-4*]	$C_5H_{10}O_2$	102.13	101.6	–95	0.887	d	1.3842	3.5
Isopropyl acetate	[*108-21-4*]	$C_5H_{10}O_2$	102.13	89	–73.4	0.870	s	1.3773	3.5
n-Butyl acetate	[*123-86-4*]	$C_6H_{12}O_2$	116.16	126	–77	0.882	d	1.3941	4.(
Isobutyl acetate	[*110-19-0*]	$C_6H_{12}O_2$	116.16	116	–99	0.871	d	1.3902	4.(
tert-Butyl acetate	[*540-88-5*]	$C_6H_{12}O_2$	116.16	96	—	—	i	1.3853	4.(
n-Amyl acetate	[*628-63-7*]	$C_7H_{14}O_2$	130.18	148.8	–70	0.879	d	1.4023	4.5
Isoamyl acetate	[*624-41-9*]	$C_7H_{14}O_2$	130.19	142	–78.5	0.870	d	1.4003	4.4
2-Amyl acetate	[*626-38-0*]	$C_7H_{14}O_2$	130	134	–78.5	0.861	i	1.3960	4.5
n-Hexyl acetate	[*142-92-7*]	$C_8H_{16}O_2$	144.22	338	—	—	i	1.4092	—
n-Ocyl acetate	[*112-14-1*]	$C_{10}H_{20}O_2$	172.27	205	–38.5	—	i	1.4190	—
Vinyl acetate	[*108-05-4*]	$C_4H_6O_2$	86.09	72.3	–93.2	0.9317	i	1.3959	3.(

[a] S = Solubility in water; v = very soluble; s = soluble; d = slightly soluble; i = insoluble.

Table 79.6. Summary of Inhalation Toxicity Data for Some Acetates

Compound	Species	Approximate Dose or Concentration	Treatment Regimen	Observed Effects	Ref.
Methyl acetate	Human	330 ppm	Short	Fruity odor	22

Human	4,950 ppm	Short	Ocular and respiratory irritation	22
Human	9,900 ppm	Short	Ocular and respiratory irritation	
Mouse	55,440 ppm	10–20 min	Immediate irritation, dyspnea, narcosis, lethal from pulmonary edema	37
Mouse	41,580 ppm	23–35 min	Irritation, dyspnea, convulsion, 1/2 deaths, 3 min postexposure	37
Mouse	26,400 ppm	31–42 min	Moderate eye irritation, narcosis, 1/2 deaths, 3 h postexposure	37
Mouse	11,220 ppm	4–5 h	Eye irritation, fatigue, dyspnea, narcosis, lethal 10 h postexposure due to pneumonia	37
Mouse	7,900 ppm	6 h	1/2 narcosis, irritation, dyspnea, recovery, 1/2 no effects	37
Mouse	5,000 ppm	20 min	No effect	37
Cat	53,790 ppm	14–18 min	Irritation, salivation, dyspnea, 1/2 convulsions, narcosis, lethal 1–9 min, later with diffuse pulmonary edema	37
Cat	34,980 ppm	29–30 min	Irritation, salivation, dyspnea, 1/2 convulsions, narcosis, histology: lateral emphysema or edema	37
Cat	18,480 ppm	4–4.5 h	Eye irritation, dyspnea, 1/2 vomiting and convulsions, narcosis, slow recovery	37
Cat	9,900 ppm	10 h	Eye irritation, salivation,	37

				somnolence, recovery	
	Cat	5,000 ppm	20 min	Eye irritation, salivation	37
	Cat	6,600 ppm	6 h / day	Weight loss, weakness, slow recovery	37
	Cat	19,000 ppm	6 h	Narcosis	22
Ethyl acetate	Human	278 ppm	Short	Fruity odor	37
	Human	400 ppm	Short	Irritation of nose and throat	38
	Human	4,170 ppm	Short	Ocular and respiratory irritation	37
	Mouse	20,000 ppm	45 min	Toleration of side position	2
	Mouse	12,225 ppm	3 h	10/20 died	39
	Mouse	10,000 ppm	45 min	1/2 lethal, corneal turbidity; 1/4 lethal, immediately. 1/4 in 24 h	2
	Mouse	5,000 ppm	3–4 h	Corneal turbidity	2
	Mouse	2,000 ppm	17 h	Irritation to eyes and nose, dyspnea	2
	Guinea pig	2,000 ppm	65 exposures	No notable effects	6
	Cat	8,000 ppm	20 min	Ocular and respiratory irritation	2
	Cat	9,000 ppm	450 min	Irritation and moderate dyspnea	2
	Cat	43,000 ppm	14–16 min	Deep narcosis, death	2
	Cat	20,000 ppm	45 min	Deep narcosis, recovery	2
	Cat	12,000 ppm	5 h	Lowest narcotic concentration	22
Vinyl acetate	Rat	4,000 ppm	4	Lowest lethal dose	40
n-Propyl acetate	Human	240 ppm	Short	Ocular, nose, pharyngeal irritation	22
	Human	4,595	Short	Ocular and respiratory irritation	22
	Cat	24,000 ppm	0.5 h	Within 5–16 min assumes side	2

				position; 13–18 min narcosis; 1/4 death 4 days postexposure	
	Cat	7,400 ppm	5.5 h	Staggering within 30–45 min; deep narcosis 4.5–5.5 h; 1/4 death after 5.5 h	2
	Cat	5,300 ppm	6 h/day	Moderate irritation, salivation	2
Isopropyl acetate	Human	200 ppm	—	Eye irritation	41
	Rat	Concentrated vapor	>30 min	Lethal	14
	Rat	32,000 ppm	4 h	Lethal 5/6 animals	2
n-Butyl acetate	Human	3,300 ppm	Brief	Marked irritation to eyes and nose	42
	Human	200–300 ppm	Brief	Mild irritation to eyes and nose	2
	Mouse	7,400 ppm	3 h	Narcosis, recovery	2
	Guinea pig	14,000 ppm	4 h	Eye irritation, narcosis, lethal	42
	Guinea pig	7,000 ppm	13 h	Eye irriation, deep narcosis, recovery	42
	Guinea pig	3,300 ppm	13 h	Eye irritation, no other symptoms	42
	Cat	17,500 ppm	30 min	Narcosis, lethal to some	2
	Cat	12,000 ppm	30 min	Narcosis, recovery	2
	Cat	4,200 ppm	6 h/6 days	Weakness, loss of weight, minor blood changes	2
	Cat	900 ppm	65 experi-ments,6 h/day	Weakness	6
Isobutyl acetate	Rat	21,000 ppm	150 min	Narcosis, lethal, 6/6	22
	Rat	3,000 ppm	6 h	No symptoms	22
Isomyl acetate	Human	950 ppm	30 min	Irritation of nose and throat, headache, weakness	2
	Dog	5,000 ppm	1 h	Nasal irritation, drowsiness	2
	Cat	7,200 ppm	24 h	Light narcosis, delayed death due to pneumonia	2
	Cat	4,000 ppm	20 min	Irritation to eyes and nose	2

n-Amyl acetate	Human	200 ppm	30 min	Lowest irrirated dose	38
	Cat	2,182 ppm	215 min	Salivation, no other effects	2
	Cat	10,600 ppm	115 min	Marked salivation, lacrimation, irregular respiration, loss of reflexes after 85 min	2
sec-Amyl acetate	Human	1,000 ppm	1 h	Serious toxic effects	2
	Guinea pig	10,000 ppm	5 h	Eye and nose irritation, narcosis, lethal	2
	Guinea pig	5,000 ppm	13 h	Eye and nose irritation, narcosis recovered	2
	Guinea pig	2,000 ppm	13 h	Eye and nose irritation, no narcosis, recovered	2
n-Hexyl acetate	Rat	4,000 ppm	4 h	Lowest lethal dose	2
Cyclohexyl acetate	Human	516 ppm	Brief	Irritation to eyes and throat	2
	Rabbit	700 ppm	4.8 h	Irritation to nose and eyes, recovery	43
	Rabbit	1,700 ppm	4.8 h	Lethal	43
	Cat	1,700 ppm	10 h	Deep narcosis and death	43
	Cat	860 ppm	9 h	Irritation plus light narcosis	2
	Cat	1,600 ppm	8 h/5 days		2
	Cat	637 ppm	8 h/30 days	No symptoms	2
	Dog	637 ppm	8 h/30 days	No symptoms	2

Table 79.7. Summary of Oral, Dermal, Subcutaneous, and Intraperitoneal Toxicity Data for Some Acetates

Compound	Route of Entry	Parameter Determined	Species Tested	Dose or Concentration	Ref.
Methyl	Oral	LD_{50}	Rabbit	3.7 g/kg	7
		LD_{LO}	Guinea pig	3.0 g/kg	44

	SC	LD_{LO}	Cat	3.0 g/kg	7
		TLm96	Aquatic	1000–100 ppm	17
Ethyl	Oral	LD_{LO}	Rat	11 g/kg	14
		LD_{50}	Rabbit	4.94 g/kg	7
	SC	LD_{50}	Guinea pig	3.0 g/kg	44
		LD_{50}	Cat	3.0 g/kg	44
		TLm96	Aquatic	1000–100 ppm	17
n-Propyl	Oral	LD_{50}	Rabbit	6.64 g/kg	7
	SC	LD_{50}	Guinea pig	3.0 g/kg	44
		LD_{LO}	Cat	3.0 g/kg	44
		TLm96	Aquatic	1000–100 ppm	17
Isopropyl	Oral	LD_{50}	Rabbit	6.95 g/kg	7
		TLm96	Aquatic	>1000 ppm	17
Cyclohexyl	Oral	LD_{50}	Rat	6.73 g/kg	
	Dermal	LD_{50}	Rabbit	10.1 g/kg	
Phenyl	Oral	LD_{50}	Rat	1.63 g/kg	45

Table 79.8. Summary of Physical and Chemical Properties of Some Fatty

Compound	CAS Number	Molecular Formula	Molecular Weight	Boiling Point (°C)	Melting Point (°C)	Specific Gravity at (25°C)	Solubility[a] in Water at (68°F)	Refractive Index at (20°C)
Methyl propionate	[*554-12-1*]	$C_4H_8O_2$	88.10	79.85	–87.5	0.910	d	1.3775
Ethyl propionate	[*105-37-3*]	$C_5H_{10}O_2$	102.13	210	–99.4	0.891	d	1.3839
Ethyl 3-ethoxypropionate	[*763-69-9*]		146.19	170.1	–75	0.95	—	—
Methyl butyrate	[*623-42-7*]	$C_5H_{10}O_2$	102.13	102.3	–95	0.8721	d	1.3878
Methyl isobutyrate	[*547-63-7*]	$C_5H_{10}O_2$	102.13	92.3	–84.7	0.8930	d	1.3840
Ethyl butyrate	[*105-54-4*]	$C_6H_{12}O_2$	116.16	252	–135.4	0.879	d	1.4000
Ethyl isovalerate	[*108-64-5*]	$C_7H_{14}O_2$	130.19	271	–146.2	0.868	—	1.3962

Ethyl caproate	[*123-66-0*]	$C_8H_{16}O_2$	144.22	168	–67	0.873	i	1.4073
Ethyl enanthate	[*106-30-9*]	$C_9H_{18}O_2$	158.24	372	–86.8	0.868	d	1.4100
Ethyl caprylate	[*106-32-1*]	$C_{10}H_{20}O_2$	172.27	208.5	–47	—	i	1.4178
Ethyl pelargonate	[*123-29-5*]	$C_{11}H_{22}O_2$	186.30	119	–36.7	0.865	i	1.4220
Ethyl caprate	[*110-38-3*]	$C_{12}H_{24}O_2$	200.33	245	–20	0.862	i	1.4256
Ethyl crotonate	[*623-70-1*]	$C_6H_{10}O_2$	114.14	143	+45	0.92	i	1.4243
Vinyl crotonate	[*14861-06-4*]	$C_6H_8O_2$	112.13	134	—	0.94	—	—

[a] Solubility in water: v = very soluble; s = soluble; d = slightly soluble; i = insoluble.

Table 79.9. Summary of Toxicity Data for Some Propionates, Butyrates, and Higher Esters

Compound	Species	Route of Entry	Parameter	Result (g/kg)	Time to Death	Ref.
			Propionate			
Methyl	Rabbit	Oral	LD_{50}	2.02		7
Ethyl	Rabbit	Oral	LD_{50}	5.71		7
n-Propyl	Rabbit	Oral	LD_{50}	3.94		7
Isobutyl	Rabbit	Oral	LD_{50}	5.6		7
Isoamyl	Rabbit	Oral	LD_{50}	6.9		7
Ethylethoxy	Rat	Oral	LD_{50}	5.0		97
		Dermal	LD_{50}	>10.0		97
			Butyrate			
Methyl	Rabbit	Oral	LD_{50}	3.38		7
Ethyl	Rat	Oral	LD_{50}	13.0		4
	Rabbit	Oral	LD_{50}	5.23	4–18 h	7
n-Propyl	Rat	Oral	LD_{50}	15.0	1–3 days	4
Amyl	Rat	Oral	LD_{50}	12.2	Few min–2 h	4
	Guinea pig	Oral	LD_{50}	11.95	2 h–6 days	4
Allyl	Rat	Oral	LD_{50}	.25	4 years–5 days	4

Linalyl iso-	Rat	Oral	LD_{LO}	>36.3		4
	Mouse	Oral	LD_{LO}	15.1	4 h–4 days	4
Benzyl	Rat	Oral	LD_{LO}	2.33	4 h–4 days	4
Pentyl pentanoate	Rat	Oral	LD_{50}	>35.4		4
	Guinea pig	Oral	LD_{50}	>17.3	2–6 days	4
Allyl heptanoate	Rat	Oral	LD_{50}	0.50	4–18 h	4
	Guinea pig	Oral	LD_{50}	0.44	4 h–3 days	4
Ethyl caprylate	Rat	Oral	LD_{50}	25.9	4 h–4 days	4
Ethyl nonanoate	Rat	Oral	LD_{50}	>43.0		4
	Guinea pig	Oral	LD_{50}	>24.2		4
Butyl stearate	Rat	Oral	LD_{50}	>32		4
	Rat	IP	LD_{50}	>32		4

Esters of Mono- and Alkenyl Carboxylic Acids and Mono- and Polyalcohols
Michael S. Bisesi, Ph.D., CIH

C. Esters of Alkenylcarboxylic Acids and Monoalcohols

Esters of Mono- and Alkenyl Carboxylic Acids and Mono- and Polyalcohols
Michael S. Bisesi, Ph.D., CIH

Acrylates, Methacrylates, and Crotonates
Acrylates are esters of propenoic acids and mono- or polyalcohols. Chemically, the acrylic monomers are substituted 2-propene carboxylic acid esters of the type CH_2: CHCOOR. They polymerize readily, with heat or even on standing;the latter reaction is catalyzed by light or oxygen, unless an inhibitor has been added. Uncontrolled polymerization is exothermic and may proceed with explosive force. Methacrylic esters are 2-methyl derivatives of acrylic esters. Chemically, they are of the general structure CH_2: $C(CH_3)COOR$. The higher molecular weight derivatives polymerize to gels or highly viscous liquids. Crotonates are 3-methyl isomers of methacrylates or

butanoic acid esters and bear the general structure CH_3CH: CHCOOR. Lower molecular weight acrylic monomers are liquids having relatively higher vapor pressures. The characteristic odors of the monomers can be unpleasant. See Table 79.10 for a summary of physical and chemical properties.

Table 79.10. Summary of Physical and Chemical Properties of Some Acrylates, Metha

Compound	CAS Number	Molecular Formula	Molecular Weight	Boiling Point (°C)	Melting Point (° C)	Specific Gravity at (25° C)	Solubility[a] in Water at (68° F)	Refractive Index at (20°C)	Va de (Ai
Methyl acrylate	[*96-33-3*]	$C_4H_6O_2$	86.09	80.5	–75	0.95	d	1.4040	2
Ethyl acrylate	[*140-88-5*]	$C_5H_8O_2$	100.11	99.4	–71.2	0.92	d	1.4068	3
n-Butyl Acrylate	[*141-32-2*]	$C_7H_{12}O_2$	128.17	146.8	–64	0.8986	i	1.4185	4
2-Ethylbutyl acrylate	[*3953-10-4*]	$C_9H_{16}O_2$	156.22	82	–70	0.896	—	—	5
2-Ethyl hexyl acrylate	[*103-11-7*]	$C_{11}H_{20}O_2$	184.28	213.5	–90	0.887	i	—	6
Methyl methacrylate	[*80-62-6*]	$C_5H_8O_2$	100.13	101	–48	0.945	d	1.4142	3
Ethyl methacrylate	[*97-63-2*]	$C_6H_{10}O_2$	114.14	117	–75	0.911	d	1.4147	3
n-Butyl methacrylate	[*97-88-1*]	$C_8H_{14}O_2$	142.20	160	–75	0.89	i	1.4240	4
Isobutyl methacrylate	[*97-86-9*]	$C_8H_{14}O_2$	142.20	155	—	0.886	—	—	-
2-Ethylisohexyl methacrylate	[*688-84-6*]	$C_{12}H_{22}O_2$	198.30	113	—	—	—	—	6
Methyl crotonate	[*623-43-8*]	$C_5H_8O_2$	100.12	121	–42	0.946	i	1.4242	3

[a] Solubility in water: v = very soluble; s = soluble; d = slightly soluble; i = insoluble.

Some acrylates occur naturally in several organisms as intermediates in lipid biosynthesis and degradation. The alkyl monomers exist primarily in liquid form, whereas the formed polymers range from clear, glass-like, brittle masses to highly flexible films, solids, or emulsions. They are widely used in commerce and industry as vinyl, acrylic, or higher molecular weight alkene resins. The acrylic monomers are highly important base components in the manufacture of thermoplastics, acrylic resins, and emulsion polymers. They are also used as solvents, plasticizers, latex coatings, adhesives, fibers, floor finishes, and lubricant additives and serve in medical and dental technology as surgical cement for medical devices and prostheses. The methacrylates sometimes serve as bases for acrylic resins with multifunctional effects. These materials find use in surgical organ repair, in compositing contact lenses, for adhesive dental pretreatment, and for a variety of other applications.

The acrylates can be manufactured by a number of procedures. These include dehydration of the corresponding hydroxyalkanoic acid, saponification of the alkene nitrile, catalytic hydration of acetylene and carbon monoxide, or the reaction of acetone with hydrocyanic acid. The methacrylates can be synthesized by catalytic oxidation of isobutylene and subsequent esterification with the appropriate alcohol, or by reacting acetone with hydrocyanic acid and subsequent esterification in sulfuric acid with the appropriate alcohol.

The low molecular weight monomers are lacrimators and irritants to the eyes, skin, and mucous membranes (3). The main potential for human exposure is by the dermal and respiratory routes;however, the irritating properties of these chemicals may serve as a deterrent to repeated exposures. Nonetheless, chronic inhalation of acrylic acid esters can lead to tissue changes or lesions due to local irritant or inflammatory reactions from acrylic acid or its esters that hydrolyze to form the acid. The acute toxicity of acrylates decreases with increasing molecular weight. For example, results from animal studies indicated that the acute lethal toxicity of methyl acrylate was twice that of ethyl acrylate based on inhalation exposure. Another study, based on 24-h LC_{50} concentrations using rats, indicated that the order of acute toxicity was methyl acrylate > ethyl acrylate > *n*-butyl acrylate > butyl methacrylate > methyl methacrylate. In the same study, rat inhalation exposures to 110 ppm 4 h/day, 5 days/week for 32 days did not cause significant changes in body weight, tissue weight, blood chemistry, gross metabolic performance, or small-intestine motor activities when compared to a control group (134). Structure-toxicity relationships of acrylates, including methacrylates, were analyzed in mice and found to be dependent on the log of the partition coefficient and log of rate order constant (135). In general, the toxicity is theorized to mechanistically involve alkylation of cellular nucelophies via Michael is addition (136).

The introduction of unsaturation into a fatty acid, as, for example, comparing the methyl or ethyl esters of propionic acid with the equivalent propenoic or acrylic acid derivatives, shows a tenfold increase in acute toxicity. Comparing acute toxicity of straight with branched-chain acrylates, ethyl acrylate by the oral route may be only half as toxic as methyl acrylate, but 8 times as toxic as methyl methacrylate, and 13 times as toxic as ethyl methacrylate (137). Acute inhalation of higher concentrations may cause narcosis, salivation, and pronounced nasal, occular, and pulmonary irritation or edema. Prolonged skin or eye contact may result in severe tissue damage. The pathology from single exposure is not particularly characteristic, contrary to repeated exposure effects, which include pulmonary congestion or hemorrhage and cloudy swelling and organ weight changes of the liver and kidney, reported following subchronic exposures to excessive concentrations. Acrylic acid and a series of methacrylates were shown to produce hemangiomas and increase resorptions following intraperitoneal injection of pregnant rats (138). Some compounds, such as the methyl-, ethyl-, *n*-propyl-, or butyl methacrylates, can produce inhibition of barium chloride–induced contraction of the isolated guinea pig ileum (139). Animal studies using rats revealed that some acrylates and methacrylates are embryotoxic. The doses of monomers used in the animal studies, however, were much higher than concentrations likely encountered by workers (3).

Allergic reactions have been reported for some acrylates. Although methyl, ethyl, and butyl methacrylates are potent skin sensitizers, experimental simulation proved rather difficult, owing to the rapid evaporation of the materials tested (140). Despite this, causes of human sensitization may occur. Methyl acrylate, methyl methacrylate, ethyl methacrylate, and butyl methacrylate caused allergic contact dermatitis due to working with artificial nail-bonding chemicals (141). Indeed, a study reviewing 10 y of patch testing data showed that 48 of 275 patients exhibited dermal allergic reactions to at least one acrylate. The most common acrylates that caused allergic reactions were 2-hydroxyenthyl acrylate (12.1%), 2-hydroxypropyl acrylate (12%), and 2-hydroxyethyl methacrylate (11.4%). No allergic response were recorded for 2-ethylhexyl acrylate (141).

Acrylates and methacrylates are detoxified predominantly via conjugation with glutathione via the Michaelis addition reaction or glutathoine-*S*-transferase. They are also likely to be hydrolyzed via

carboxylesterases (142). The lower molecular weight esters are rapidly metabolized and eliminated, therefore, will not likely cause cumulative toxicity (3).

The literature revealed much more data regarding methylacrylates than the crotonates. Although the irritant and lacrimatory effects of the crotonates are known, no low level exposure effects in humans have been reported so far. Physiologically, they are somewhat less reactive than the acrylates. They appear to be rapidly metabolized and excreted, possibly because crotonyl and methacrylyl groups are also formed during the normal metabolism of butyryl and isobutyryl derivatives (111). General toxicological data for acrylates, methacrylates, and crotonates are summarized in Tables 79.11 (143, 144) and 79.12 (145–150).

Table 79.11. Summary of Inhalation, Oral, Dermal, Subcutaneous, and Intraperitoneal To Acrylates

Acrylate	Oral LD_{50}		Dermal LD_{50} Rabbit (g/kg)	IP LD_{50} Mouse (g/kg)	Inhalation		Parameter	Species	Saturated Vapor, Rat LC_{00}	I
	Species	g/kg			Concen. (ppm)	Time (h)				
Methyl	Rat	0.300	1.3	0.256 (143)	1000	4	LC_{50}	Rat		M tc
	Rabbit[b]	0.280			95		TC_{LO}	Rabbit		N Ir
Ethyl	Rat	1.02	1.95	0.606 (143)	50,000	0.25	LC_{100}	Rat		S se
	Rabbit	1.0			4000	4	LC_{100}	Rat		S se
					2000	4	LC_{80}	Rat		
					1204	7	LC_{LO}	Rabbit		
		0.4			1204	7	LC_{LO}	Guinea pig		
					<1000	4	LC_{50}	Rat		
					540	19 days	LC_{66}	Rat		
					70	30	LC_7	Rat		
n-Butyl	Rat (105)	3.7	3.4 (105)	0.853 (143)	1000	4	LC_{80}	Rat		M
	Rat (105)	9.05	2.0				LC_{12}	Rat		
Isobutyl	Rat (75)	7.07	4.49 (75)	0.761 (143)	2000	4	LC_{LO}	Rat		M
2-Ethylbutyl	Rat	6.5	5.5						4 h	M
	Rat (105)	5.6	8.5[a] (105)	1.325 (143)					8 h	M tc
2-Ethylhexyl	Rat	5.66								
	Rat	6.4–								

		12.8							
Cyclohexyl	Rat	8.98	2.52					8 h	
2-Hydroxy	Rat	1.0	1.0	500	4	LC_{80}	Rat	1 h	S
	Rat	0.665	1.01 (97)			LC_{LO}	Rat (144)		
2-Ethoxyethyl	Rat (14)	1.07	1.0 (105)	500	4	LC_{80}	Rat	1 h	S
2-Ethoxypropyl	Rat (97)	0.82	1.401 (97)	250	4	LC_{16}	Rat	1 h	M

[b] Rabbit.
[a] Guinea pig.

Table 79.12. Summary of Toxicity Data for Some Methacrylates and Croto

Compound	Oral LD_{50}		Subcutaneous LC_{50}		Intraperitoneal LD_{50}		Inhalation				
	Species	g/kg	Species	g/kg	Species	g/kg	Species	ppm	mg/L	Exposure (h)	I
					Methacrylate						
Methyl	Rat (145)	8.4 12.7–18.14	Mouse (146)	6.3	Mouse (39)	1.0					
	Rabbit (145)	6.55	Rat (146)	7.5	Mouse (146)	1.1	Human (39)		0.150	Short	T
	Guinea pig (39)	6.3	Dog (146)	4.5	Rat (147)	1.33	Rat (105)	3750			I
	Dog (39)	5.0	Guinea pig (146)	6.3	Rat (39)	1.8	Rat (147)		15		I
	Rabbit (105)	>10.0[ab]			Guinea pig (39)	2.0	Mouse (39)		47.7[c]		I
							Mouse (39)		61.8[c]	3	I
							Rabbit (145)		17.5	4.5	I
							Guinea pig (145)		19.0[c]	5	I
Ethyl	Rat (145)	14.8	Rat (145)	25.0[e]	Rat (147)	1.22	Guinea pig		72.1[c]	4.5	I

					(39)				
	Rabbit (145)	3.63	Rat (147)	0.37[f]	Dog (39)		41.2	3	I
	Rabbit (105)	>10[ad]	Mouse (146)	1.25	Dog (39)		72.1	1.5	I
			Mouse (148)	1.37	Mouse (39)		41.2	0.5/day×15	I
n-Butyl	Rat (145)	>20	Rat (147)	2.3			41.2	1.5/day × 15	I
	Rabbit (145)	>6.3	Mouse (146)	1.49	Guinea pig (39)		39.3	3.0/day × 15	I
							65.5[c]	3.0/day × 3	I
Isobutyl	Rat (105)	>6.4	Rat (147)	1.4	Dog (39)		41.2	0.5/day × 15	I
							46.8	0.5/day × 15	I
			Mouse (145)	1.19			46.8	1.5/day × 8	I
					Crotonate				
Methyl	Rat (105)	>3.2			Rat (105)		15	3	I
	Mouse (105)	2.6–3.2			Rabbit (105)	3300		8	I
	Guinea pig (105)	10–20[a,d]			Rat (150)		6.0		
Ethyl	Rat (149)	3.0			Rat (105)	19,000		6	I
	Guinea pig (105)	>10[a,d]			Rat (149)	Saturated vapor		8	I
2-Ethylhexyl	Rat (105)	>3.2			Rat (105)	2500		6	I
	Guinea pig (105)	>20[a]			Rat (105)	Saturated vapor		6	I
Vinyl	Rat (105)	6.5			Rat (105)	4000		4	I
	Guinea pig (105)	>10[a]			Rat (105)	2000		4	I
					Rat (105)	Saturated vapor		1	I

[a] Dermal LD_{50}.

[b] mL/kg.

[c] Liver degeneration and focal necrosis.

[e] TD_{LO}.

[f] Teratogenic TD_{LO}.

[d] mL/kg.

Table 79.13. Summary of Physical and Chemical Properties of Some Lactates and

Compound	CAS Number	Molecular Formula	Molecular Weight	Boiling Point(° C)	Melting Point (° C)	Specific Gravity (at 25° C)	Solubility[a] in Water at (at 68° F)	Refractive Index (at 20°C)	Vap dens (Air =
Methyl lactate	[*547-64-8*]		104.1	35		1.092	s	1.414	
Ethyl lactate	[*97-64-3*]	$C_5H_{10}O_3$	118.13	153		1.033	s	1.413	
Isopropyl lactate	[*617-51-6*]		132.2	157		0.991	s	1.410	
n-Butyl lactate	[*138-22-7*]	$C_7H_{14}O_3$	146.19	188		0.984	s	1.422	
Amyl lactate	[*6382-06-5*]		160.2	207		0.964	s	1.424	
Methyl pyruvate		$C_4H_6O_3$	102.09	134–137			d	1.4046	
Ethyl pyruvate	[*617-35-6*]	$C_5H_8O_3$	116.12	144			d	1.4052	
Allyl acetate	[*591-87-7*]	$C_5H_8O_2$	100.13	103.5		0.928	d	1.4049	3.4
Geranyl acetate	[*105-87-3*]	$C_{12}H_{20}O_2$	196.28	242					
Linalyl acetate	[*115-95-7*]	$C_{12}H_{20}O_2$	196.29	220			i	1.4544	
Cyclohexyl acetate	[*622-45-7*]	$C_8H_{14}O_2$	142.20	173			i	1.4401	4.9
Phenyl acetate	[*122-79-2*]	$C_8H_8O_2$	136.16	195.7		1.073	d	1.5033	4.7
Methyl acetoacetate	[*105-45-3*]	$C_5H_8O_3$	116.12	171.7	–80	1.077	v	1.4184	4.0
Ethyl acetoacetate	[*141-97-9*]	$C_6H_{10}O_2$	130.14	–45.4	180.8	1.03	v	1.4194	4.4

[a] Solubility in water: v = very soluble; s = soluble; d = slightly soluble; i = insoluble.

Table 79.14. Summary of Acute Oral and Inhalation Toxicity of Some Lactates (202)

Compound	Parameter	Species	Dose	Observed Effects
Methyl	Oral LD_{50}	Rat	>2000 mg/kg	Pilorection ≤ 24 h; absence of gross necroscopy changes
	Inhalation $LC_{50/4\ h}$		>5030 mg/m^3	During exposure decreased breathing rates and wet nares; postexposure wet fur; gross necropsy showed 7/10 with grayish lungs and two lungs with irregular surfaces
Ethyl	Oral LD_{50}	Rat	>2000 mg/kg	Pilorection up to 24 h; absence of gross necropsy changes
	Inhalation $LC_{50/4\ h}$		>5400 mg/m^3	During exposure decreased breathing rates, pilorection, lachrymation, and wet nares; gross necropsy showed pale lungs with spots
Propyl	Oral LD_{50}	Rat	>2000 mg/kg	Sluggishness ≤4 h; absence of gross necropsy changes
Isoprophyl	Oral LD_{50}	Rat	>2000 mg/kg	Pilorection ≤24 h; absence of gross necropsy changes
Butyl	Oral LD_{50}	Rat	>2000 mg/kg	Pilorection ≤24 h and diarrhea; absence of gross necropsy changes
	Inhalation $LC_{50/4\ h}$		>5140 mg/m^3	During exposure decreased breathing rates and wet head and fur. absence of necropsy changes
Isobutyl	Inhalation $LC_{50/4\ h}$	Rat	>6160 mg/m^3	During exposure decreased breathing rates, pilorection, and hunched appearance; postexposure apnea; absence of gross necropsy changes

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Esters of Carbonic and Orthocarbonic Acid, Organic Phosphorous, Monocarboxylic Halogenated Acids, Haloalcohols, and Organic Silicon
Michael S. Bisesi, Ph.D., CIH

I. Introduction

Esters of Carbonic and Orthocarbonic Acid, Organic Phosphorous, Monocarboxylic Halogenated Acids, Haloalcohols, and Organic Silicon
Michael S. Bisesi, Ph.D., CIH

A. Overview

This chapter covers (*1*) esters of carbonic and orthocarbonic acid, (*2*) esters of organic phosphorous compounds, (*3*) esters of monocarboxylic halogenated acids, alkanols, or haloalcohols, and (*4*) organic silicon esters. Other classes of esters are summarized in Chapters 79 and 80. Refer to the Introduction in Chapter 79 for a more detailed overview of general properties of esters.

Unfortunately, as shown in the two prior chapters, mainly fragmented toxicological evaluations are available for esters. Most of these esters are characterized by low toxicity. Indeed, as expressed in Chapter 79, lethal dose (e.g., LD_{50}) values are frequently difficult or impractical to measure.

Localized dermal irritation is one common effect characteristic of exposures to most organic solvents. Few esters are readily absorbed, but there are exceptions, such as tri-*o*-cresyl phosphate (TOCP). Several of the halogenated derivatives, such as ethylchloro- and ethylbromo-, are potent lacrimators. Ethyl fluoroacetate and fluoroacetic acid exhibit about the same mode of action, which may indicate that the acetate is rapidly hydrolyzed and metabolized in the mammalian system. The unsaturated carbonates are also associated with high lacrimatory activity.

TOCP is an example of an ester that can cause neuropathy in a variety of animal species. The initial weakness and paralysis are normally reversible in early stages, but repeated or massive assaults result in demyelination of the nerve fibers. The mechanism of action is not yet certain, but it appears to involve phosphorylation of proteins. Only selected phosphates exhibit neuropathic effects, including diisopropyl fluorophosphorate and *N*,*N*'-diisopropyl phosphorodiamidic fluoride.

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B. Industrial Hygiene Evalution

As was expressed in Chapter 79, industrial hygiene evaluation of esters involves collecting and analyzing air samples to determine their airborne concentrations. Published industrial hygiene air sampling and analytical methods, however, are unavailable for most esters. In relation, there are few occupational exposure and biological limits. A list of ester compounds covered in this chapter that have industrial hygiene sampling and analytical methods are presented here in Table 81.1 along with their respective occupational exposure limits, established by the American Conference of Governmental Industrial Hygienists (ACGIH), the Occupational Safety and Health Administration (OSHA), and the National Institute for Occupational Safety and Health (NIOSH) (1–4). As stated in

Chapter 79, since sampling and analytical methods and occupational exposure limits are subject to periodic revision, the reader is encouraged to refer to current publications of ACGIH, OSHA, and NIOSH.

Table 81.1. Summary of Occupational Exposure Limits (OELs) and Monitoring Methods for Some Esters (1–4)

	OSHA		ACGIH			NIOSH		
Compound	**PEL**	**STEL**	**TLV**	**STEL**	**Notations**	**REL**	**IDLH**	**NIOSH Monitorin Method**
Triphenyl phosphate	3 mg/m^3	—	3 mg/m^3	—	ACGIH A4	3 mg/m^3	1000	Filter; diethyl ether; GC-FPD NIOSH #5038[a]
Methyl silicate	—	—	1 ppm	—	—	1 ppm	—	—
Ethyl silicate	100 ppm	700 ppm	10 ppm	—	—	10 ppm	700 ppm	XAD-2; CS_2; GC-FID NIOSH #5264[b]
Tri-*o*-cresyl phosphate	0.1 mg/m^3	—	0.1 mg/m^3	—	Skin; CNS cholinergic; ACGIH A4; BEI	0.1 mg/m^3	40 mg/m^3	Filter; diethyl ether; GC-FPD NIOSH #5037[a]
Trimethyl phosphite	—	—	2 ppm	—		2 ppm	—	—

[a] NIOSH MAM, 4th ed., 1994.
[b] NIOSH MAM, 2nd ed., vol. 3, 1977.

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II Esters of Carbonic and Orthocarbonic Acid

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A. Overview

The hypothetical hydration of carbon dioxide produces two compounds, carbonic acid, $C(O)(OH)_2$, and orthocarbonic acid, $C(OH)_4$. These acids have never been isolated, although they may be formed and exist in aqueous solution. However, numerous esterified derivatives have been prepared chemically. Only very few of them have been toxicologically investigated in great detail. The majority of toxicological data reported is limited range-finding studies. Organic carbonates are chemically RO(CO)OR, the ortho esters, $RC(OR')_3$, whereby R may equal R' or consist of alkyl, alkenyl, cyclane, or aromatic moieties. These di- and triortho esters have similar physical properties; however, the latter resemble acetals more than carboxylates. The general toxicological impacts are also expected to be similar but nonsignificant, owing to the esters' low stability in acid solutions and their resemblance to normal mammalian metabolites. A summary of physical and chemical properties is found in Table 81.2 (5), and a summary of toxicological data is shown in Table 81.3 (6, 7).

Table 81.2. Chemical and Physical Properties of Representative Esters of Carbonic and Ortho (5)

Compound	CAS No.	Molecular Formula	MW	Boiling Point (° C) (mmHg)	Melting Point (° C)	Density	Solubility[a] in Water	Refractive Index (20° C)	Vapor density (Air=1)
Dimethyl carbonate	[*616-38-6*]	$C_3H_6O_3$	90.08	89.7	3	1.0694	i/s/s	1.3687	
Diethyl carbonate	[*105-58-8*]	$C_5H_{10}O_3$	118.13	127	–43	0.9752	i/s/s	1.3845	4.1
Ethylene carbonate	[*96-49-1*]	$C_3H_4O_3$	88.06	243 (740)	36.4	1.3218	d/v/v	1.4158	3.04
Propylene carbonate	[*108-32-7*]	$C_4H_6O_3$	102.09	241.7	–55	1.2057	v/v/v	1.4189	
Triethyl orthoformate	[*122-51-0*]	$C_7H_{16}O_3$	148.20	146	–76	0.8909	d/s/s	1.3922	5.11
Triethyl orthoacetate	[*78-39-7*]	$C_8H_{18}O_3$	162.23	142		0.8847	i/v/v	1.3980	
Triethyl orthopropionate	[*115-80-0*]	$C_7H_{20}O_3$	176.26	155~160		0.886	-/v/v	1.4000	

[a] Solubility in water: v = very soluble; s = soluble; d = slightly soluble; i = insoluble d[b]: decomposes when dissolved; –68[c] and 84[c]: Freezing point (°C).

Table 81.3. Summary of Inhalation, Oral, Dermal, Subcutaneous, and Intraperitoneal Toxicity Data for Some Esters of Carbonic and

Orthocarbonic Acids

Compound	Chemical Formula	Mode or Route of Entry	Parameter	Species	Dose or Concentration	Ref.
Dimethyl carbonate	$C_3H_6O_3$	Oral	LD_{50}	Mouse; rat	6.4–12.8 g/kg	6
		IP	LD_{50}	Mouse; rat	0.8–1.6 g/kg	6
		Dermal	LD_{50}	Guinea pig	10 mL/kg	6
		Inhale	$LD_{100/2h}$	Rat	8000 ppm	6
Ethylene carbonate	$C_3H_4O_3$	Oral	LD_{50}	Rat	10.4 g/kg	7
		Dermal	LD_{50}	Rabbit	0.20 mL/kg	7
Propylene carbonate	$C_4H_6O_3$	Oral	LD_{50}	Rabbit	20 mL/kg	6
Triethyl orthoformate	$C_7H_{16}O_3$	Oral	LD_{50}	Rat	3.2–6.4 g/kg	6
		Dermal	LD_{50}	Guinea pig	>10 mL/kg	6
Triethyl orthoacetate	$C_8H_{18}O_3$	Oral	LD_{50}	Rat	6.4–12.8 g/kg	6
		IP	LD_{50}	Rat	12.8–25.6 g/kg	6
		Dermal	LD_{50}	Guinea pig	>10 mL/kg	6
Triethyl orthopropionate	$C_9H_{20}O_3$	Oral	LD_{50}	Rat; rabbit	6.4–12.8 g/kg	6
		IP	LD_{50}	Rat; rabbit	6.4–12.8 g/kg	6
		Dermal	LD_{50}	Rabbit	>10 mL/kg	6

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B. Carbonates
1.0a Dimethyl Carbonate
1.0.1a CAS Number: [*616-38-6*]

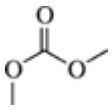
1.0.2a Synonyms: Carbonic acid dimethyl ester

1.0.3a Trade Names: NA

1.0.4a Molecular Weight: 90.08

1.0.5a Molecular Formula: $C_3H_6O_3$

1.0.6a Molecular Structure:



1.0b Diethyl Carbonate
1.0.1b CAS Number: [*105-58-8*]

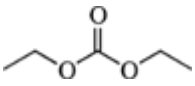
1.0.2b Synonyms: Carbonic acid diethyl ester

1.0.3b Trade Names: NA

1.0.4b Molecular Weight: 118.13

1.0.5b Molecular Formula: $C_5H_{10}O_3$

1.0.6b Molecular Structure:



1.1 Chemical and Physical Properties
1.1.1 General Dimethyl carbonate is miscible with most acids and alkalis, soluble in most organic solvents, but insoluble in water.

Diethyl carbonate is miscible with aromatic hydrocarbons, most organic solvents, and castor oil, but not with water.

1.1.2 Odor and Warning Properties Dimethyl carbonate has a pleasant odor. Diethyl carbonate has a weak odor resembling that of ethyl oxybutyrate.
1.2 Production and Use
The compound diethyl carbonate is manufactured via a reaction of phosgene and ethanol to produce ethyl chlorocarbonate, followed by reaction with anhydrous ethanol. It is used as a solvent for nitrocellulose, in the manufacture of radio tubes, and for fixing elements to cathodes.
1.3 Exposure Assessment
1.3.3 Workplace Methods: NA
1.4 Toxic Effects
1.4.1 Experimental Studies 1.4.1.1 Acute Toxicity The undiluted dimethyl carbonate liquid has an oral LD_{50} in the rat and the mouse between 6.4 and 12.8 g/kg and an intraperitoneal LD_{50} in the range of 800 to 1600 mg/kg (6). Symptoms were weakness, ataxia with gasping, and unconsciousness. A dermal LD_{50} in the guinea pig was found to be greater than 10 mL/kg. Some weight loss was noted, and minimal skin absorption was suspected. However, the degree of irritation was relatively slight (6). Exposure by inhalation appeared relatively hazardous, since 8000 ppm

caused rapid onset of gasping, loss of coordination, frothing from the mouth and nose, and pulmonary edema with death of all rats in a period of 2 h.

Diethyl carbonate is estimated to be moderately toxic via ingestion, dermal, and ocular contact. Intraperitoneally injected diethyl carbonate showed a slight neoplastic effect on the skin at the injection site in the mouse at about 11.4 mg, but not when administered orally at 12.5 mg (8).

1.4.1.2 Chronic and Subchronic Toxicity: NA

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Metabolically, the dimethyl and diethyl carbonates may possess alkylating properties similar to those of dimethyl and ethyl sulfate.

1.4.1.4 Reproductive and Developmental A teratogenic effect in 7.6–16.6% of 8-d pregnant hamsters was observed at a diethyl carbonate doses of 0.5–1.0 g/kg when injected intraperitoneally (9).

1.4.1.5 Carcinogenesis A study using male and female mice treated with 0, 50, 250, or 1000 ppm (0–140 mg/kg/d) diethyl carbonate in drinking water indicated no carcinogenic effects (10).

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C. Cyclic Carbonates
2.0a Ethylene Carbonate
2.0.1a CAS Number: [*96-49-1*]

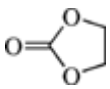
2.0.2a Synonyms: Ethylene carbonate, ethylene glycol carbonate, and 1,3-dioxolan- 2-one

2.0.3a Trade Names: NA

2.0.4a Molecular Weight: 88.06

2.0.5a Molecular Formula: $C_3H_4O_3$

2.0.6a Molecular Structure:



2.0b Propylene Carbonate
2.0.1b CAS Number: [*108-32-7*]

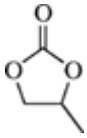
2.0.2b Synonyms: Propylene carbonate and 4-methyl-1,3-dioxolan-2-one

2.0.3b Trade Names: NA

2.0.4b Molecular Weight: 102.09

2.0.5b Molecular Formula: $C_4H_6O_3$

2.0.6b Molecular Structure:



2.2 Production and Use
Used as intermediates in plastic industry.
2.3 Exposure Assessment
2.3.3 Workplace Methods: NA
2.4 Toxic Effects
2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity A range-finding study using ethylene carbonate by Smyth et al. (7) has recorded an oral LD_{50} value of 10.4 g/kg in the rat and a dermal LD_{50} of .20 mL/kg for the rabbit. Inhalation of the concentrated vapor for 8 h caused no deaths in rats. It proved to be a very low irritant to the skin, but moderately irritating to the eye of the rabbit. From a range-finding study using propylene carbonate, an oral LD_{50} in the rabbit above 20 mL/kg was determined. Inhalation of the concentrated vapor for 8 h was not lethal to rats. The undiluted material was a slight irritant to the skin and a moderate irritant to the rabbit eye.

2.4.1.2 Chronic and Subchronic Toxicity: NA

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The mechanistic toxicity of ethylene carbonate was determined to be similar to the toxicity of ethylene glycol (11). Ethylene carbonate is enzymatically metabolized to ethylene glycol, and an enzyme has recently been isolated (12).

2.4.2 Human Experience 2.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms A dermal absorption study using living skin from human donors indicated that propylene carbonate had permeability constants of 0.7 > 0.4 $g/m^2/h$ and 0.6 > 0.3 $cm^3/m^2/h$ (13).

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D. Ortho Acid Esters

3.1 Chemical and Physical Properties
3.1.1 General Triethyl orthoformate is a stable liquid, even in sunlight.

Triethyl orthoacetate is liquid at ambient temperature.

Triethyl orthopropionate is a highly soluble liquid.
3.3 Exposure Assessment
3.3.3 Workplace Methods: NA
3.4 Toxic Effects
3.4.1 Experimental Studies 3.4.1.1 Acute Toxicity Oral LD_{50} values in the rat between 3.2 and 6.4 mg/kg of triethyl orthoformate have been recorded (6). Symptoms of toxicity included dyspnea

and weakness. Conversely, a dermal LD_{50} in the guinea pig was found to be above 10 mL/kg, indicating that the material was practically not absorbed. No skin irritation was noted.

The oral LD_{50} for triethyl orthoacetate has been documented (6) between 6.4 and 12.8 g/kg for the rat, the intraperitoneal LD_{50} even higher, as 12.8 to 25.6 g/kg. It is not absorbed through guinea pig skin, and a dermal LD_{50} was found to be above 10 mL/kg. A very low dermal irritation was observed.

Similar to triethyl orthoacetate, the LD_{50} for triethyl orthopropionate ranges in the rat and rabbit are 6.4 to 12.8 g/kg by oral and intraperitoneal administration, and >10 mL/kg in the rabbit when tested dermally (6).

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III Esters of Organic Phosphorus Compounds

Esters of Carbonic and Orthocarbonic Acid, Organic Phosphorous, Monocarboxylic Halogenated Acids, Haloalcohols, and Organic Silicon
Michael S. Bisesi, Ph.D., CIH

A. Overview

This class of esters includes phosphines, phosphinates, phosphonates, phosphites, and phosphates. The basic compound of the series is phosphine, PH_3, which then is successively alkylated, oxygenated, and esterified. The progressive series then contains phosphines, R_2PH or R_3P, phosphine oxide, $R_2P(O)H$ or $R_3P(O)$, phosphinic acid esters, phosphinates, $R_2P(O)OR$, phosphites, $(RO)_3P_7$, phosphonic acid esters, $RP(O)(OR')_2$, and phosphites $(RO)_3P(O)$, where R and R' can comprise alkyl or aryl groups for any of these compounds. Some physical and chemical properties and characteristics are listed in Table 81.4 and toxicological information in Tables 81.5 (14–45) and 81.6.

Table 81.4. Chemical and Physical Poperties of Selected Organic Phosphorous

Compound	CAS No.	Molecular Formula	MW	Boiling Point (° C) (mmHg)	Melting Point (° C)	Density	Solubility[a] in Water	Refractive Index (20° C)	(
Tributyl phosphine	[*998-40-3*]	$C_{12}H_{27}P$	202.32	240~242		0.812			

Triisooctyl phosphine	[*10138-88-2*]	$C_{24}H_{51}P$	370.64					
Triphenyl phosphine	[*603-35-0*]	$C_{18}H_{15}P$	262.29	377	80	1.132	i	1.6358
Octyl *O*-butyl phosphinate		$C_{12}H_{27}O_2P$	234.32					
Phenyl *O*-ethyl phosphinate	[*2511-09-3*]	$C_8H_{11}O_2P$	170.15					
Butyl phenyl *O*-allyl phosphinate		$C_{13}H_{19}O_2P$	238.29					
O-Dimethyl phosphonate	[*868-85-9*]	$C_2H_7O_3P$	110.05	170.5		1.1029	s	1.4128
Methane *O*-dimethyl phosphonate		$C_3H_9O_3P$	124.08			1.1507		1.4099
O-Ethyl propyl phosphonate	[*21921-96-0*]	$C_5H_{13}O_3P$	152.13	181				
Diisopropyl phosphonate	[1809-20-7]	$C_6H_{15}O_3P$	166.16	72~75 (10)		0.997		
Octyl *O*-dibutyl phosphonate	[*5929-67-9*]	$C_{16}H_{35}O_3P$	306.42					
Dibutyl phenyl phosphonate		$C_{14}H_{23}O_3P$	222.31					
Phenyl propyl 2-propynyl phosphonate	[*18705-22-1*]	$C_{12}H_{15}O_3P$	238.22					
Vinyl, bis(2-chloroethyl) phosphonate		$C_6H_{11}Cl_2O_3P$	233.03					
Methyl ethyl chlorophenyl phosphonate	[*033232-85-8*]	$C_9H_{12}ClO_3P$	234.62					
Diisopropyl fluoro phosphonate	[*33232-85-8*]	$C_6H_{14}FO_3P$	214.20					
Ethyl *O*-methyl *O*-*p*-nitrophenyl phosphonate	[*25536-01-3*]	$C_9H_{12}NO_5P$		245.19				
Ethyl *O*-ethyl *O*-*p*-nitrophenyl phosphonate	[*546-71-4*]	$C_{10}H_{14}NO_5P$	259.22					
Methyl *O*-isopropyl*O*-*p*-nitrophenyl phosphonate	[*15536-03-5*]	$C_{10}H_{14}NO_5P$	259.22					
Ethyl *O*-		$C_{11}H_{16}NO_5P$	273.25					

isopropyl *O-p*-nitrophenyl phosphonate							
Isopropyl *O*-ethyl *O-p*-nitrophenyl phosphonate		$C_{11}H_{16}NO_5P$	273.25				
Isopropyl *O*-isopropyl *O-p*-nitrophenyl phosphonate	[*7284-60-8*]	$C_{12}H_{18}NO_5P$	287.28				
Pentyl *O*-ethyl *O-p*-nitrophenyl phosphonate	[*3015-75-6*]	$C_{13}H_{20}NO_5P$	301.31				
Heptyl *O*-ethyl *O-p*-nitrophenyl phosphonate		$C_{15}H_{24}NO_5P$	329.37				
Octyl *O*-ethyl *O-p*-nitrophenyl phosphonate		$C_{16}H_{26}NO_5P$	343.40				
Ethyl *O*-phenyl *O-p*-nitrophenyl phosphonate		$C_{14}H_{14}NO_5P$	335.32				
Phenylpropyl *O*-ethyl *O-p*-nitrophenyl phosphonate		$C_{17}H_{20}NO_5P$	349.32				
Phenylbutyl *O*-ethyl *O-p*-nitrophenyl phosphonate		$C_{18}H_{22}NO_5P$	363.35				
Phenylvinyl *O*-ethyl *O-p*-nitrophenyl phosphonate		$C_{16}H_{16}NO_5P$	333.30				
O-ethyl propylphenyl *O-p*-nitrophenyl phosphonate		$C_{17}H_{20}NO_5P$	349.32				
Ethyl butylphenyl *O-p*-nitrophenyl Phosphonate		$C_{18}H_{22}NO_5P$	363.35				
Diethyl phosphite	[*762-04-9*]	$C_4H_{11}O_3P$	138.10	50~51 (2)	1.0720	d	1.4101
Cyclic		$C_2H_4O_3P$	107.72				

ethylene phosphite								
Dibutyl phosphite	[*1809-19-4*]	$C_8H_{19}O_3P$	194.21	118~119 (11)		0.995		
Trimethyl phosphite	[*121-45-9*]	$C_3H_9O_3P$	124.08	111–112	–78	1.046	d.i.	1.4095
Triethyl phosphite	[*122-52-1*]	$C_6H_{15}O_3P$	166.16	156		0.97	d[b]	1.4127
Tripropyl phosphite	[*923-99-9*]	$C_9H_{21}O_3P$	208.24	206–207		0.9417		1.4282
Triisopropyl phosphite	[*116-17-6*]	$C_{12}H_{21}O_3P$	208.24	63~64 (11)		0.844		1.4085
Tributyl phosphite	[*102-85-2*]	$C_{12}H_{27}O_3P$	250.32	118~125 (7)	–80	0.9259	d	1.4321
Triisosooctyl phosphite	[*25103-12-1*]	$C_{24}H_{51}O_3P$	418.64					
Tridecyl phosphite		$C_{30}H_{63}O_3P$	502.80		<0	0.892		
Triphenyl phosphite	[*101-02-0*]	$C_{18}H_{15}O_3P$	310.29	360	22~24	1.1844	i	1.5900
Tri-*o*-cresyl phosphite		$C_{21}H_{21}O_3P$	352.7	238 (11)		1.1423	d	1.5740
Tri-*p*-cresyl phosphite		$C_{21}H_{21}O_3P$	352.7	250–255 (10)		1.1313		1.5703
2-Ethylhexyl octylphenyl phosphite	[*7346-61-4*]	$C_{22}H_{39}O_3P$						
Nonyl diphenyl phosphite		$C_{21}H_{29}O_3P$	360.43					
Tris(2-chloroethyl) phosphite	[*140-08-9*]	$C_6H_{12}Cl_{l3}O_3P$	269.50	125~135 (7)		1.3348	d[c]	1.5174
Trimethyl phosphate	[*512-56-1*]	$C_3H_9O_4P$	140.08	197.2	–46	1.197	v	1.3967
Triethyl phosphate	[*78-40-0*]	$C_6H_{15}O_4P$	182.16	215	–56.4	1.072	s	1.4053
Tributyl phosphate	[*126-73-8*]	$C_{12}H_{27}O_4P$	266.32	289	–80	0.976	s	1.4224
Trioctyl phosphate	[*1806-54-8*]	$C_{24}H_{51}O_4P$	434.64	220~230	–74		i	
Di(2-ethylhexyl) phosphate	[*298-07-7*]	$C_{16}H_{35}O_4P$	322.42	48 (12)	–60			
Tri(2-ethylhexyl) phosphate	[*78-42-2*]	$C_{24}H_{51}O_4P$	434.64	190~233	–70	0.9262	d	
3,5,5-Trimethylhexyl		$C_9H_{21}O_4P$	518.80					

phosphate								
Diundecyl phosphate		$C_{22}H_{47}O_4P$	406.60					
Triallyl phosphate	[*1623-19-4*]	$C_9H_{15}O_4P$	218.19					
Triphenyl phosphate	[*115-86-6*]	$C_{18}H_{15}O_4P$	326.28	245 (11)	49	1.2055	i	
Tri-*o*-cresyl phosphate	[*78-30-8*]	$C_{21}H_{21}O_4P$	368.37	420	–33	1.1955	i	1.5575
Tri-*m*-cresyl phosphate	[*563-04-2*]	$C_{21}H_{21}O_4P$	368.37	275(17)	25.6	1.150	i	1.5575
Tri-cresyl phosphate	[*1330-78-5*]	$C_{21}H_{21}O_4P$	368.37	420	–33	1.247		
Tri-*p*-cresyl phosphate	[*78-32-0*]	$C_{21}H_{21}O_4P$	368.37	244 (3.5)	77–78	1.16	i	
Dimethyl benzyl phosphate		$C_9H_{13}O_4P$	216.17					
2-Ethylhexyl diphenyl phosphate	[*1241-94-7*]	$C_{20}H_{27}O_4P$	362.44	330	–80	1.0884	i	
Cresyl diphenyl phosphate	[*26444-49-5*]	$C_{19}H_{17}O_4P$	340.31	235~255	–38	1.2		
Di(2-chloroethyl) phosphate		$C_4H_9Cl_2O_4P$						
Tri(2-chloroethyl) phosphate	[*115-96-8*]	$C_6H_{12}Cl_3O_4P$	285.49	330	–55	1.39	i	
2,2-Dichlorovinyl dimethyl phosphate	[*62-73-7*]	$C_4H_7Cl_2O_4P$	220.98	140 (20)	–60	1.415	d	
2-Chlorovinyl diethyl phosphate	[*311-47-7*]	$C_6H_{12}ClO_4P$	214.85					

[a] Solubility in water: v = very soluble; s = soluble; d = slightly soluble; i = insoluble

[b] Decomposes when dissolved.

[c] Freezing point (°C)

B. Alkyl and Aryl Phosphines

4.1 Chemical and Physical Properties
4.1.1 General

4.1.2 Odor and Warning Properties
4.2 Production and Use
Tributylphosphine is used as a gasoline additive.
4.4 Toxic Effects
4.4.1 Experimental Studies 4.4.1.1 Acute Toxicity The overall toxicity is expected to be relatively high (58); however, a moderate degree of toxic effects for triphenylphosphine and low toxicity for triisooctylphosphine has been demonstrated (6). This is also confirmed by an oral LD_{50} of 4.29 mL/kg (14). Conversely, according to Carpenter et al. (14), an inhalation exposure of rats to saturated vapor required 8 h for lethal effects. A dermal LD_{50} in the rabbit was greater than 5 mL/kg. Triisooctylphosphine appears to be less toxic by the oral route at 21.4 mL/kg, but is more readily absorbed through the skin, showing an LD_{50} of 3.97 mL/kg (7). It is also more of an irritant to the skin, but less so to the eye (7).

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C. Phosphinates
Alkyl aryl phosphinic acid esters bear the chemical structure $R_2P(O)OR'$. A paucity of toxicological data were found. Some data are summarized in Table 81.5 for the following phosphinates: octylphosphinic acid *O*-butyl ester, $C_8H_{17}PH(O)OC_4H_9$, phenylphosphinic acid *O*-ethylester, $C_6H_5PH(O)OC_2H_5$, allylphenylphosphinic acid *O*-butyl ester, $(CH_2{:}CHCH_2)(C_6H_5)P(OH)OC_4H_9$, and butylphenylphosphinic acid *O*-allyl ester, $(C_4H_9)(C_6H_5)P(O)OCH_2CH{:}CH_2$.

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D. Phosphonates
Phosphonates are esters of phosphoric acid of the type $RP(O)(OR')_2$, whereby R and R' can constitute alkyl, aryl, cyclic, or heterocyclic groups. They are less acidic and hydrolyze with less ease than the corresponding phosphates (51). The phosphonates often occur as mixed products, unless they are prepared through their ester anhydrides (51). Some derivatives, especially the halogenated types, are used as pesticides.

Various aliphatic, aromatic, and substituted phosphonates appear to be moderately to highly toxic. The toxicity appears to be lowest for the alkyl derivatives, but rises with increasing aromatization and even further with halogen or nitro group substitution. Diisopropyl fluorophosphonate, $FP(O)[OCH(CH_3)_2]_2$, is neurotoxic against the housefly (59).

51). Such esters in the presence of allyl halides tend to convert easily from the trivalent to the pentavalent form, the thermodynamically more stable phosphonates.

The biologic properties of the organic phosphites resemble closely those of the phosphonates, possibly owing to their chemical similarity or transformation possibilities. Most animal experiments have been carried out with rats or rabbits, which are not particularly sensitive to neurotoxic stimuli. Thus no definite toxicologic conclusions can be drawn from these experiments. The differential irritancy characteristics may be due to the hydrolyzability of the individual esters.
5.1 Chemical and Physical Properties
5.1.1 General Organic phosphites are esters of phosphorous acid and alkyl or aryl alcohols, of the type $(RO)_3P$. Chemically, they can undergo transesterification with alcohols (51). The biologic properties of the organic phosphites resemble closely those of the phosphonates, possibly owing to their chemical similarity or transformation possibilities.
5.3 Exposure Assessment
5.3.3 Workplace Methods: NA
5.4 Toxic Effects
5.4.1 Experimental Studies 5.4.1.1 Acute Toxicity The oral acute toxicity of trimethyl phosphite was found to be comparatively low and the material was not appreciably absorbed through the rabbit skin (23); however, it caused moderately severe irritation lasting several days. Introduction into the rabbit eye caused severe irritation and edema that persisted for several days. In vapor inhalation experiments, rats survived a 6 h exposure to saturated air. However, the material produced considerable discomfort, restlessness, and severe irritation of the eyes and respiratory tract (23).

According to Deichmann and Gerarde (23), the dermal LD_{50} of tridecyl phosphite in the rat is greater than 10 mL/kg. This indicates that the material is not absorbed through the skin, but still may cause irritation. It may also indicate that it has similar physical properties to those of tri(2-ethylhexyl) phosphite.

Triphenyl phosphite appears to be more toxic than the aliphatic derivatives. In addition, its neurotoxic properties, first described by Smith et al. (26), it was used for a convulsive model in experimental epilepsy (60). In addition, the authors studied the phosphite blood distribution and the motor cortex, diencephalon, and brain activity with radioactive triphenyl phosphite (60).

Aird et al. (60) using 0.3 mL/kg ^{32}P-labeled triphenyl phosphite intraperitoneally in the cat, observed considerable hydrolysis of the phosphite and only a very small quantity of original material in the central nervous system. The authors concluded that even this small quantity could have degenerative effects (60). The cresyl derivatives, similar to the phenyl, are charactersitically more toxic than the aliphatic equivalents. Nonetheless, triphenyl phosphite causes a delayed neuropathy with related ataxia and degeneration of the spinal cord in animals (61). The chemical inhibits neurotoxic esterase activity, but the structurally related compounds triphenyl phosphate, triphenyl phosphine, and trimethyl phosphite did not at the experimental doses (61). Animal studies have demonstrated that triphenyl phosphite causes potent neurotoxic effects due to cellular and axonal degeneration in the spinal cord, medulla, cerebellum, thalmus, and cerebral cortex (62).

Mixed alkyl–aryl phosphites tend to have lower toxicities than the aryl phosphites, as might be predicted. An oral LD_{50} in the rat for 2-ethylhexyl octylphenyl phosphite was7–10 g/kg (23), and an oral LD_{50} in the mouse for diphenylnonyl phosphite was 0.1 g/kg (27).

Chlorination of alkyl phosphites increases the toxicity, as demonstrated with bis(2-chloroethyl) phosphite with an intraperitoneal LD_{50} in the mouse of 250 mg/kg (17).

5.5 Standards, Regulations, or Guidelines of Exposure
Both the ACGIH TLV and the NIOSH REL for trimethyl phosphite is 2 ppm.

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F. Alkyl Phosphates
Organic phosphates constitute a highly hazardous class of compounds. The materials most extensively investigated concern the organophosphate insecticides that are discussed in a separate chapter. The summary here is limited to the alkyl, aryl, and their lower-molecular-weight derivatives. The phosphates are chemically the most stable, and thus the most persistent phosphorus esters in biologic systems.
6.1 Chemical and Physical Properties
6.1.1 General

6.1.2 Odor and Warning Properties
6.2 Production and Use
The aryl phosphates are used widely in industry as plasticizers, as motor lubricants and gasoline additives (63), and as part of fire-resistant hydraulic fluid (63). Certain types of organic phosphates have found application as military defense agents (64). For the treatment of aryl phosphates poisoning, see Mieth and Beier (65). Zech et al. (64) reported that the oximes, which had raised great hopes in the field of medicine, however, do not always act as antidotes, but as synergists in certain cases. Trimethyl phosphate is used as an ethylating agent and as raw material to prepare insecticides, such as tetraethyl pyrophosphate (23). Triethyl phosphate is used as a plasticizer for cellulose esters, lacquers, plastics, especially vinyl resins, and as an antifoaming agent. The di(2-ethylhexyl) phosphate has wide industrial use.
6.3 Exposure Assessment
6.3.3 Workplace Methods NIOSH Method 5034 is recommended for determining workplace exposures to tributyl phosphate (3a).
6.4 Toxic Effects
6.4.1 Experimental Studies Male rats fed 0.5% of trimethyl phosphate, triethyl phosphate, tri-*n*-butyl phosphate, trioctyl phosphate, or tricresyl phosphate for 9 wk exhibited decreased body weight relative to controls (66). To date, it has been the only alkyl phosphate with documented flaccid paralytic effects (28). Orally, it is in the toxicity range of the phenyl phosphates. According to Jones and Jackson (67), trimethyl phosphate is not a teratogen. However, subtoxic oral or parenteral administration caused mutagenic effects in mice (68). Incubation experiments of TMP and DNA solutions have shown decreased sedimentation coefficients of the biopolymers. This is presumably the result of DNA alkylation, followed by depurination and scission of the phosphodiester's backbone. Gas chromatographic analysis yielded a compound, 7-methyldeoxyguanosine.

6.4.1.1 Acute Toxicity Toxicological data in Table 81.5 show a somewhat higher degree of toxicity. Fassett and Roudabush conducted a subacute study by injecting rats intraperitoneally with 400 mg/kg TEP five times a wk for 4–6 wk (69). The animals still gained weight, and no side effects were noted. Experimental work with triethyl phosphate has so far failed to show neurotoxic effects. This is partially confirmed by the *in vitro* studies with the neurotoxin antidote pyridine-2-aldoxime methylchloride (PAM), whereby TEP was not hyrolyzed *in vitro* (70).

The acute oral toxicity of tributyl phosphate is relatively low, although it is a weak inhibitor in rats and *in vitro* human red blood cells (25). It also is a CNS stimulant. Affected rats show muscle twitching, general weakness, dyspnea, coma, and pulmonary edema. No latent paralysis has been observed. The material is a respiratory, eye, and primary skin irritant, and may be dermally absorbed (30, 55). Intraperitoneally, the dose with the lowest effect in the mouse was 63 mg/kg (30). The same toxicological properties are expected to hold for triisobutyl phosphate. Male rats exposed to the compound exhibited decreased body weight, alteration of brain cholinesterase, and increased blood coagulation rates (71).

An oral LD_{50} in the rat has been recorded as 4940 mg/kg (7), a dermal LD_{50} in the rabbit as 1250 mg/kg (7), and a lowest-effect level intraperitoneally in the mouse of 63 mg/kg (17).
6.5 Standards, Regulations, or Guidelines of Exposure
The ACGIH TLV for tributyl phosphate is 0.2 ppm.

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G. Aryl Phosphates
Aryl phosphates contain an aromatic (benzene) ring and have the wide application in industry.
7.0a Triphenyl Phosphate
7.0.1a CAS Number: [*115-86-6*]

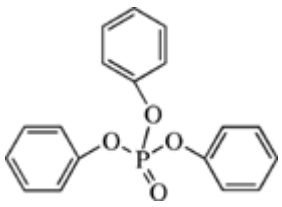
7.0.2a Synonyms: Phosphoric acid triphenyl ester; phenyl phosphate; TPP; triphenyl phosphoric acid ester; celluflex tpp

7.0.3a Trade Names: NA

7.0.4a Molecular Weight: 326.28

7.0.5a Molecular Formula: $C_{18}H_{15}O_4P$

7. Molecular Structure:



7.0b Tri-***o***-cresyl Phosphate
7.0.1b CAS Number: [*78-30-8*]

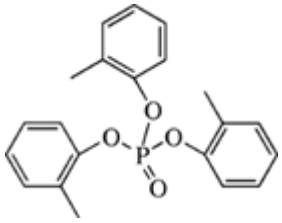
7.0.2b Synonyms: Tricresylphosphate; *o*-trioyl phosphate; TCP; TOCP; phosphoric acid tris(2-methylphenyl) ester; *o*-cresyl phosphate; phosflex 179-c; phosphoric acid, tri-*o*-cresyl ether; TOFK; *o*-tolyl phosphate; TOTP; tris(*o*-methylphenyl) phosphate; tris(*o*-tolyl) phosphate; phosphoric acid, tri-*o*-tolyl ester; triothocresyl phosphate

7.0.3b Trade Names: NA

7.0.4b Molecular Weight: 368.37

7.0.5b Molecular Formula: $C_{21}H_{21}O_4P$

7.0.6b Molecular Structure:



7.1 Chemical and Physical Properties
7.1.1 General Triphenyl phosphate (TPP) is crystalline solid with a faint, aromatic odor.

Tri-*ortho*-cresyl phosphate (TOCP) is a liquid, also available as triaryl phosphate oil containing a mixture of the three isomers, the *ortho*, *meta*, and *para* forms. However, whenever possible, the portion of the *ortho* isomer is reduced or eliminated because of its paralytic properties.

7.1.2 Odor and Warning Properties
7.2 Production and Use
Triphenyl phosphate serves as a noncombustible substitute for camphor in celluloid, as a fire retardant in acetylcellulose, nitrocellulose, and airplane glue, as a plasticizer for lacquers and varnishes, and to impregnate roofing paper.

The tri-*o*-, *m*-, or *p*-cresyl phosphates, also named *o*-, *m*-, or *p*-tritolyl phosphates, phosphoric acid tri-2-, 3-, or 4-tolyl or methylphenyl phosphate esters, are widely used industrial additives. Tri-*o*-cresyl phosphate is used widely as a gasoline additive, plasticizer, fire retardant, solvent, extreme pressure additive, and as a lead scavenger in gasoline.
7.3 Exposure Assessment
7.3.3 Workplace Methods Table 81.1 describes the method recommended for determining workplace exposures to TPP and TOCP.
7.4 Toxic Effects
7.4.1 Experimental Studies 7.4.1.1 Acute Toxicity The basic animal experiments were carried out by Smith et al. (72) in 1930, who observed low acute toxicity in the commonly used laboratory species, and no effects in rats and mice when administered 1/10 to 1/20 of the oral LD_{50} for 3 mo. It caused generalized delayed illness and paralysis in cats and primates. The observed demyelination of the spinal cord resembled that obtained with tri-*o*-cresyl phosphate (72). Neuromuscular signs were observed above 0.2 g/kg in the cat. *In vitro* studies showed a 50 mg/kg no-effect level on whole blood cholinesterase, but a 20% decrease at the 100 mg/kg level (32). The material is poorly absorbed through the intact skin (23) and had no irritant effects in the rat skin (33). Dermal sensitization has been reported (73).

The compound studied most extensively has been tri-*o*-cresyl phosphate, since it has proved to be the causative agent in most epidemics. Some experiments by Hine et al. (58), using White Leghorn cockerels as test animals, were carried out in order to test the neurotoxic properties of a series of substituted aromatic phosphorus and related compounds for anticholinesterase activity. The authors demonstrated that in the fowl, only the *o*-tolyl phosphate produced paralytic properties either as a tri-*ortho* derivative or mono- and disubstituted compounds mixed with phenyl or *p*-tolyl phosphates. The *o*-tolyl and other substituted aryl and arylalkyl phosphates caused cholinesterase inhibition *in vivo* but not *in vitro* (58).

Of the aryl phosphates, only the tri-*o*-cresyl, the mono- and di-*o*-cresyl, and di- or monophenyl derivatives cause paralysis in the cockerel, and also have anticholinesterase activity. The fact that a series of aryl phosphates possess only anticholinesterase activity indicates that these pathological signs are due to different, nonrelated mechanisms (58). TOCP was also found to inhibit true erythrocyte cholinesterase in rats (77). This has been studied by Bleiberg and Johnson (78), who confirmed that TOCP, when administered orally, was toxic to mice and chickens and produced cholinesterase inhibition in red blood cells of the dog and the chicken. TOCP is a low dermal irritant and has been documented as the causative agent in a dermatitis case (73). *In vitro* studies with whole blood, using about 10 mg/kg TTP, depressed the acetyl cholinesterase level approximately 30% (32). Mechanistically, it appears that TOCP causes biochemical changes in the sciatic nerve of hens, marked by evidence of phosphorylation of proteins (79, 80).

Pathological effects observed in the human have been reproduced in various experimental animals, such as the cat, chicken, rabbit, dog, primate, and calf. The rat, the mouse, and the guinea pig are more resistant. Smith et al. (46, 81) report some minor fatty changes in animal liver and some degenerative deviations in the kidney. Barnes and Denz (82) studied the histopathology of the nervous fibers produced by TOCP and other phosphates. They determined that the demyelination did not appear to be directly related to anticholinesterase activity. Rayner et al. (83) have noted hyporeflexia in some workers chronically exposed to more complex organophosphate insecticides.

The chicken appears somewhat more resistant to tri-*o*-cresyl phosphate (26). The *o*-cresyl phosphate reduces the cholinesterase activity of whole blood in mice, accompanied by symptoms of tremor and diarrhea, resembling other cholinesterase inhibitory agents in the rat. A study revealed that tributyl, tributoxyethyl, and dibutylphenyl phosphate inhibited brain neurotoxic esterase activity as high as 70% (84). Rats were exposed to a fire-resistant hydraulic fluid containing dibutyl phenyl phosphate and tributyl phosphate at airborne levels ranging from 5 to 300 mg/m^3 6 h/d, 5 d/wk for 6–13 wk (85). The data revealed observations of a reddish nasal discharge and simultaneous oral salivation, and, at high exposures reduced body weights, increased liver weights, decreased number of erythrocytes, decreased hemoglobin levels, and decreased hematocrit values (85).

Injection into the yolk sac of fertile eggs prior to incubation has shown TOCP to cause reductions in survival rates with 100% deaths at 0.02 mL of undiluted material. At a concentration of 0.01 mL, 40% of the chicks hatched, but showed growth retardation and developed paralysis in 2–6 wk after hatching (86). The typical paralysis in the majority of the chicks is associated with demyelination in the spinal cord, cerebellum, and peripheral nerves (81), as observed in humans. Investigators of another study involving hens exposed to oral doses of solutions containing triphenyl phosphate, tricresyl phosphate, or butylated triphenyl phosphate additives in synthetic polyol-based lubricating oils concluded that there was low neurotoxicity and hazard under realistic conditions of exposure (87). A study by Barrett et al. in 1994 showed decreased acetylcholine esterase activity in red blood cells and plasma and decreased neurotoxic esterase activity in leukocytes due to single oral exposures of swine tri-*o*-cresyl phosphate (88).

An *in vitro* study involving use of immunocompetent cells (peritoneal cells and splenocytes) isolated from mice and subsequently exposed to triphenyl phosphate and triphenylphosphine oxide (TPPO) revealed signs of altered immune functions (89). Another study conducted *in vivo* and involving rats exposed to oral doses of TPP indicated no significant immunotoxicity (90). Another study showed that TOCP caused inhibition of several cytoplasmic enzymes (proteases) that are important in processes of intracellular protein turnover, processing hormonal peptides, and processing immune system antigenic proteins (91). Accordingly, the investigators suggest that the data may represent a previosuly unrecognized toxicity hazard.

7.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Some studies have shown that TOCP is readily absorbed, transported by the vascular and central nervous system, and distributed into the

brain, cord, and cerebellar tissue within 24 h of oral administration (58). Of 17 compounds tested, tri-*o*-cresyl phosphate is one of the most active inducers of drug-metabolizing enzymes. The compounds had in common low systemic toxicity, but high lipid solubility (92). Cohen and Murphy have shown that TOCP is capable of potentiating malathion activity (93). A study published by Wu and Leng (94) using white Leghorn hens suggested that TOCP causes phosphorylation of brain membrane proteins leading to organophosphate-induced delayed neuropathy, but treatment with the drug Verapamil, a calcium channel blocker, eliminated enhancement and caused some inhibition of the adverse effects. Saligenin cyclic *o*-tolyl phosphate (SCOTP) is thought to be an active metabolite of TOCP and is more neurotoxic (95). Hodge and Sterner demonstrated with radioactive materials that TOCP was absorbed through the intact human palm and the abdominal skin of the dog (35). About 0.10% of the quantities administered were excreted in the urine within a few hours. Experimentally, a dermal LD_{50} of 2.8 cm^2/kg was determined for the mouse, 1/5 to 1/25 as toxic for the cat, dog, or rabbit (35). Paralysis of hind legs, however, was observed in mice (35). It also was reported that TOCP was found in the blood of the dog at 8 mg/100 cm^3 within 24 h of application and was found distributed throughout the visceral organs, muscle, brain, and bone in the dog (35).

7.4.1.4 Reproductive and Developmental TOCP is toxic to the male reproductive system due to damage caused to the testes (96). Rats exposed to 135 d of oral doses of TCP and butylated triphenyl phosphate (BTP)-based hydraulic fluids were studied to evaluate reproductive toxicity (97). The results showed decreased fertility and number of litters born for BTP-exposed groups and decreased fertility and litter sizes in TCP-exposed groups. Rat studies also have shown that both BTP and TCP appear to be associated with endocrine toxicity (98). A study involving rats fed a diet containing various levels of triphenyl phosphate for a period from 4 wk postweaning for 91 d, through mating and gestation, indicated that there was no significant impact to the mothers or their offspring (99).

7.4.1.5 Carcinogenesis TOCP was shown in a study by Mentzshel et al. (100) to be associated with detection of DNA adducts in tissues harvested from rats treated with the chemical. The authors concluded that a metabolite formed from biotransformation of TOCP may be associated with initiation of carcinogenesis.

7.4.2 Human Experience 7.4.2.1 General Information Of the three isomers, the toxicities and neurotoxic character increase *para* < *meta* < *ortho* (54). The lethal oral dose for adults is 1–10 g for the *ortho* isomer; *meta* and *para* isomers are practically nontoxic and do not cause demyelination (27). Most human intoxications have involved accidental ingestion of adulterated alcoholic beverages, cooking oils (48, 50), or, as an unusual case, industrial inhalation of heated vapors (76).

Reviews of human incidents have been presented by Hunter et al. (76), Susser and Stein (50), Smith et al. (72), and Smith and Lillie (81). The minimum paralytic dose in humans is unknown, but from studies by Smith et al. (26, 72), it can be estimated as about 10–30 mg/kg of tri-*o*-cresyl phosphate for an adult. The clinical picture after ingestion has been similar in all reported cases. Immediately post ingestion usually no symptoms occur or occasionally there may be gastrointestinal disturbances lasting from a few hours to 2 d; sharp cramplike pains may occur in the calves with some numbness in the hands and feet. A few hours later weakness in legs and feet may progress to bilateral foot drop, but the cramping pain may disappear. Within another few days, weakness of fingers and wrists may develop, but not extending above elbows and thighs. There is a dispute over the extent of sensory loss; however, it is agreed that it may run parallel to the extent of dysfunction of the motor system. In mild cases, sensory changes regress rapidly (50). The progress of affected cases varies considerably, but in general, the muscular weakness may increase over a period of several weeks or even months, and then become more or less stationary. The extent to which the paralysis may be permanent depends mainly on the quantities involved, intake rates, and cumulative effects. Fatalities are quite rare and occur mainly in response to the ingestion of very large phosphate quantities in a short time.

Due to the lack of human autopsy material of the rarely fatal cases, little is known of the progressive

microbiological changes. The pathology described by Smith and Lillie (81) in six human cases was characterized by some involvement of the anterior horn cells, fatty degeneration of the white substance of the cord, tigrolysis of nerve cells, displacement of the nucleus to the periphery, and particularly demyelination with marked fragmentation and fatty degeneration of the myelin sheath. Exposure of personnel for various time periods to TCP, a preparation that contains several aryl derivatives, including tri-*o*-cresyl phosphate, handled as a component of hydraulic oil on an aircraft carrier, showed no physiological effects. Exposed and control personnel were checked intensively for neurological signs, hematologic effects, and blood cholinesterase levels (74).

7.4.2.2 Clinical Studies Tabershaw and Kleinfeld (101) have described a monitoring study of a chemical TOCP manufacturing plant. Results revealed TOCP air concentrations ranging from 0.27 to 3.40 mg/m^3, depending on the type of operation. The effect on the worker population (101) indicated some plasmic cholinesterase depression. However, no evidence of neuromuscular difficulties attributable to the industrial exposure was found.Tabershaw et al. (102) have described a triphenyl and tricresyl phosphate manufacturing plant with air concentration measurements ranging from 0.27 to 3.4 mg/m^3. The authors found no correlation between results from cholinesterase determinations and minor gastrointestinal or neuromuscular symptoms and the degree and duration of exposure (102). Occupational exposures have occurred on various occasions. Sutton et al. (32) have published a study covering the chemical, toxicological, and industrial aspects of triphenyl phosphate exposure. Fourteen employees were exposed to triphenyl phosphate vapor, mist, or dust over a period of 8–10 yr. The particle sizes of the dusts measured < 1 mm in diameter for 90%, and the average air concentration was determined as 3.5 mg/m^3 with occasional excursions to 40 mg/m^3. Results showed no signs of illnesses, but a slight statistically significant reduction in red blood cell cholinesterase activity. The human data were confirmed by Smith et al. (46, 81).

A similar report of men handling lubricating oils containing some cresyl phosphates on an aircraft carrier showed no signs of illnesses or chemical changes (74). One report by Hunter et al. (76) describes three cases of polyneuritis from the manufacture of various aryl phosphates, with the suspicion that exposure to TOCP was the causative factor. One case of permanent paralysis in a worker has been reported by Bidstrup and Bonnell (103). He had been engaged in the manufacturing of *m*- and *p*-tricresyl phosphate isomers, where the final product contained only 1% of the *ortho* form (TOCP), but 6–10% appeared during the processing. Large quantities of TPP inhibit human cholinesterase *in vitro* and *in vivo*; however, it is not considered a potent anticholinesterase agent. No adverse clinical effects were found in men exposed to TPP vapor mist and dust for 10 yr at a concentration of 3.5 mg/m^3 (23). Another study reported polyneuropathy in a mechanic exposed to hydraulic fluids containing isopropylated tricresyl phosphate (ITP) (104). The investigators concluded that this observation and results from a related cross-sectional study of eight other exposed men and eight controls suggest a possible relationship between heavy exposure to ITP and polyneuropathy. A report indicated a case of allergic contact dermatitis associated with exposure to TPP that was contained in plastic eyeglass frames (105). In relation to the observed dermatitis associated with wearing the plastic eyeglass frames, the investigators reported positive dermal patch test results for TPP and tri-*m*-cresyl phosphate, but not for tri-*p*-cresyl phosphate.

Triaryl or tricresyl phosphate (TCP) is a mixture of various aryl phosphates, including tri-*o*-cresyl phosphate. One study indicated that personnel exhibited no toxicological effects when exposed for various durations to TCP, a preparation handled as a component of hydraulic oil on an aircraft carrier and that contained several aryl derivatives including (74). Exposed and control personnel were checked intensively for neurological signs, hematologic effects, and blood cholinesterase levels (74). An epidemiological study in Italy of workers handling rubber-base materials and cements containing triaryl phosphate revealed 47 cases of motor polyneuritis (75). However, in addition, the workers had also handled a variety of other neurotoxic chemicals when previously employed in the shoe, tire, rubber, or adhesive tape industry.

7.4.2.3 Epidemiology Studies An epidemiological study in Italy of workers handling rubber-base

materials and cements revealed 47 cases of motor polyneuritis (75). One of the causative agents was suspected to be triaryl phosphate (75). However, in addition, the workers had also handled a variety of other neurotoxic chemicals when previously employed in the shoe, tire, rubber, or adhesive tape industry.

7.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV, NIOSH REL and OSHA PEL for triphenyl phosphate are all 3 mg/m^3.

The ACGIH TLV, NIOSH REL and OSHA PEL for triorthocresyl phosphate are all 0.1 mg/m^3 for tri-*o*-ethylphosphate.

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Michael S. Bisesi, Ph.D., CIH

I. Halogenated Phosphate Esters

In contrast to the previously discussed phosphate esters, the chlorinated derivatives possess anesthetic-like and muscle-relaxant properties, even at relatively high doses, without pathological side effects.

8.0 Trichloroethyl Phosphate

8.0.2 Synonyms: Trichloroethyl phosphate, also known as trichloroethyl phosphate (TCEP; trichloroethyl phosphoric acid mono ester; Triclofos), $P(O)(OH)_2(OCH_2CCl_3)$ and tris(b-chloroethyl) phosphate, (tri(2-chloroethyl) phosphoric acid ethyl ester; TRCP), $P(O)(OCH_2CH_2Cl)_3$

8.4 Toxic Effects

Triclofos is a sedative or hypnotic. Tri-2-chloroethyl phosphate produces prolonged epileptiform convulsions in the rat intraperitoneally at levels of 0.28 g/kg (38). At higher doses, convulsions occur, but only weak cholinesterase inhibition (6). The material does not appear to be absorbed through the skin, nor is it a dermal irritant. A subacute study comparing triethyl phosphate and trichloroethyl phosphate by Fassett and Roudabush (69) showed a definite hemorrhagic tendency by the trichloroethyl phosphate. A variety of chlorovinyl phosphates are available, which serve as pesticides and insecticides. For example, an acute human poisoning by 2-chloro-1-(2,4-dichlorophenyl) vinyl diethyl phosphate, chlorfenvinphos, has been reported. The clinical picture was dominated by the nicotinic, mascarinic, and central nervous syndromes with severe respiratory difficulties, accompanied by acidosis and by initial hyperglycemia, which converted into hypoglycemia (106). Siggins et al. have tested a series of 2-chloroethanol esters of a-keto acids and similarly found some to possess hypoglycemic properties (107).

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IV Esters of Monocarboxylic Halogenated acids, Alkanols, or Haloalcohols

Esters of Carbonic and Orthocarbonic Acid, Organic Phosphorous, Monocarboxylic Halogenated Acids, Haloalcohols, and Organic Silicon
Michael S. Bisesi, Ph.D., CIH

A. Overview

The halogenated acid esters are discussed in the order of prevalence of the halogen, that is, the chlorine, the fluorine, bromine, and iodine derivatives. The esters are listed with increasing molecular weight or complexity. Halogenation of hydrocarbons increases their toxicity considerably. The halogen formates are highly irritating and are used as lacrimators. The halogenated acetates serve chiefly as intermediates in various organic syntheses. They are generally colorless liquids with relatively high densities, soluble in water, and more stable toward hydrolysis than the chloroformates, although ethyl iodoacetate may release iodine on extensive heating. Physiologically, the halogenated acetates behave similarly, such as producing pulmonary edema. Especially, their lacrimatory and irritant properties can be classified in the order of potency I > Br > Cl > F. According to Dixon (108), the lacrimatory mechanism may involve specific reactions of the halogen with certain enzyme-sulfhydryl groups. The ester groups appear to enhance this activity. The reaction appears to occur rapidly, is reversible at low and irreversible at very high concentrations in some tissues (109, 110). Some physical and chemical properties and characteristics are listed in Table 81.7 and toxicological information in Tables 81.8, 81.9, 81.10 (111–117) (118, 119).

Table 81.7. Chemical and Physical Properties of Representative Esters of Monocarboxylic Ha Haloalcohols (5)

Compound	CAS No.	Molecular Formula	MW	Boiling Point (° C) (mm Hg)	Melting Point (° C)	Density	Solubility[a] in Water	Refractive Index (20° C)	I (
Methyl chloroformate	[*79-22-1*]	$C_2H_3ClO_2$	94.50	70.4–70.9 (752)	–61	1.223	d[b]	1.3868	
Ethyl chloroformate	[*541-41-3*]	$C_3H_5ClO_2$	108.52	93	–81	1.135	d[b]	1.3947	
Propyl chloroformate	[*109-61-5*]	$C_4H_7ClO_2$	122.55	105		1.0901	d[b]	1.4035	
Isopropyl chloroformate	[*108-23-6*]	$C_4H_7ClO_2$	122.55	104.6–104.9		1.08	i	1.4013	
Allyl chloroformate	[*2937-50-0*]	$C_4H_5ClO_2$	120.54	110		1.14	i		
Benzyl chloroformate	[*501-53-1*]	$C_8H_7ClO_2$	170.60	103 (20)		1.20	d[b]	1.5160	
Trichloromethyl chloroformate	[*503-38-8*]	$C_2Cl_4O_2$	197.83	128	–57	1.64	i	1.4566	
Chloroethyl chloroformate	[*627-11-2*]	$C_3H_4Cl_2O_2$	142.97	155.7–156.0		1.3847	i	1.4465	
Methyl chloroacetate	[*96-34-4*]	$C_3H_5ClO_2$	108.52	131	–33	1.238	d[b]	1.4218	
Ethyl chloroacetate		$C_4H_7ClO_2$	122.55	144 (740)	–27	1.145	i	1.4125	

Butyl chloroacetate	[*590-02-3*]	$C_6H_{11}ClO_2$	150.60	183		1.0704	i	1.4297
2,4,5-Trichlorophenyl chloroacetate		$C_8H_4Cl_4O_2$	273.93					
2-Chloroallylidene 3,3-diacetate chloroacetate	[*5459-90-5*]	$C_7H_9ClO_4$	192.60					
Methyl chloropropionate	[*17639-93-9*]	$C_4H_7ClO_2$	122.55					
Ethyl chloropropionate	[*535-13-7*]	$C_5H_9ClO_2$	136.58	146–149		1.072	i	
2-Chloro-3-(4-chlorophenyl) propionic acid methyl ester		$C_{10}H_{10}Cl_2O_2$	233.09					
2-Chloroethyl acrylate	[*2206-89-5*]	$C_5H_7ClO_2$	134.56	51–53			i	
Methyl fluoroformate		$C_2H_3FO_2$	78.04	40		1.06		
Ethyl fluoroformate		$C_3H_5FO_2$	92.07	53–54	–80	0.917	s	1.3597
Methyl fluoroacetate	[*453-18-9*]	$C_3H_5FO_2$	92.07					
Ethyl fluoroacetate	[*459-72-3*]	$C_4H_7FO_2$	106.10	119.2 (753)		1.098		
Propyl fluoroacetate		$C_5H_9FO_2$	120.12					
Isopropyl fluoroacetate		$C_5H_9FO_2$	120.12					
Allyl fluoroacetate		$C_5H_7FO_2$	118.12					
2-Chloroethyl fluoroacetate		$C_4H_6ClFO_2$	140.54					
2-Fluoroethyl acetate		$C_4H_7FO_2$	106.10					
Ethyl bromoacetate	[*105-36-2*]	$C_4H_7BrO_2$	167.00	159	–38[c]	1.5059	i	1.4489
Ethyl 2-bromo-propionate	[*535-11-5*]	$C_5H_9BrO_2$	181.03	156~160		1.394	i	1.4490
Ethyl 2-bromo-butyrate	[*533-68-6*]	$C_6H_{11}BrO_2$	195.06	177.5 (765)		1.321	i	1.4475
Ethyl iodoacetate	[*623-48-3*]	$C_4H_7IO_2$	214.00	178–180		1.808		1.5079

[a] Solubility in water: v = very soluble; s = soluble; d = slightly soluble; i = insoluble.

[b] Decomposes when dissolved.

[c] Freezing point (°C).

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B. Chloroesters

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V. Organic Silicon Esters

Esters of Carbonic and Orthocarbonic Acid, Organic Phosphorous, Monocarboxylic Halogenated Acids, Haloalcohols, and Organic Silicon
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A. Overview

The alkyl silicon esters can be classified into several categories, namely, the silanes, which are alkyl-substituted silicon tetrahydrides (R_4S) and the next more highly oxygenated derivatives only, silanols (R_3SiOR' $R_2Si(OR')_3$). Some silanols can be polymerized to form silicones of the type $[R_xSiO_{(4-x/2)}]_n$. The most highly oxygenated compound is silicic acid and its esters, the silicates, which are chemically $Si(OR)_4$.

Some of these compounds are important industrial raw materials used to produce a variety of widely used end products, such as the silicones that serve as lubricating fluids, oil baths, resins, and plastic copolymers. The toxicological effects vary from inert to caustic, depending on the oxidation potential and the molecular size. Some chemical and physical properties and characteristics are listed in Table 81.11 and toxicological information in Table 81.12 (127–130).

Table 81.11. Chemical and Physical Properties of Representative Esters of Organi

Compound	CAS No.	Molecular Formula	MW	Boiling Point (° C) (mmHg)	Melting Point (° C)	Density	Solubility[a] in Water	Refractive Index (20° C)

Tetrachloro silane	[*10026-04-7*]	Cl_4Si	169.90	57.6	–70	1.483	d[b]	
Methyltrichloro silane	[*75-79-6*]	CH_3Cl_3Si	149.48	66	–77[c]	1.27	d[b]	
Dimethyldichloro silane	[*75-78-5*]	$C_2H_6Cl_2Si$	129.06	70.0	–16	1.07	d[b]	
Ethyltrichloro silane	[*115-21-9*]	$C_2H_5Cl_3Si$	163.51	168	–105.6	1.2381	d	1.4257
Diethyldichloro silane	[*1719-52-5*]	$C_4H_{10}Cl_2Si$	157.12	128–130	–96.5	1.0504	d[b]	
Dimethyldiethoxy silane	[*78-62-6*]	$C_6H_{16}O_2Si$	148.28	114		0.865		
Methyltriethoxy silane	[*2031-67-6*]	$C_7H_{18}O_3Si$	178.30	141–143		0.8925		1.3835
Ethyltriethoxy silane	[*78-07-9*]	$C_8H_{20}O_3Si$	192.33	158.9		0.8594	i	1.3955
Amyltriethoxy silane	[*2761-24-2*]	$C_{11}H_{26}O_3Si$	234.41	198		0.889		
Vinyltriethoxy silane	[*78-08-0*]	$C_8H_{18}O_3Si$	190.31	160–161		0.903		
Tri(2-chloroethoxy) silane		$C_6H_{13}Cl_3O_3Si$	267.61					
Methyl silicate	[*681-84-5*]	$C_4H_{12}O_4Si$	152.22	121–122	–2°[c]	1.0232		
Ethyl silicate	[*78-10-4*]	$C_8H_{20}O_4Si$	208.30	168	–85	0.933	i, d[b]	
Hexamethyl disiloxane	[*107-46-0*]	$C_6H_{18}OSi_2$	162.38	101	–59	0.764	i	1.3818
Dodecamethyl pentasiloxane	[*141-63-9*]	$C_{12}H_{36}O_4Si_5$	384.84	229 (710)	–84[c]	0.8755	i	1.3925

[a] Solubility in water: v = very soluble; s = soluble; d = slightly soluble; i = insoluble.

[b] Decomposes when dissolved.

[c] Freezing point (°C).

Table 81.12. Summary of Oral, Inhalation, and Contact Toxicity Data for Some Or

	Oral LC_{50}		LD_{50}		LD_{50}		Inhalation (Rat)		
Compound	**Species**	**g/kg**	**Species**	**g/kg**	**Species**	**g/kg**	**Con (ppm)**	**Exposure (h)**	**Mortality or Effects**
Silane									
Methyltrichloro	Rat	0.8			Rat	~0.06			
Dimethyldichloro	Rat	0.8			Rat	~0.06			

Ethyltrichloro	Rat	0.8			Rat	~1.0			
Diethyldichloro	Rat	2.0			Rat	~0.6			
Trimethylethoxy	Rat	9.33							
Methyltrimethoxy	Rat	12.5	Rabbit	10					
Trimethylethoxy	Rat	12.5	Rabbit	10			2000	8	0/5 LC_{00}
							4000	8	4/5 LC_{80}
Dimethyldiethoxy	Rat	2.5					500	10 × 7	Sl. inc. heart wt.
							4000	8	0/5 LC_{00}
						2000	7	0/5 LC_{00}	
Methyltriethoxy	Rat	5.0					4000	8	4/5 LC_{80}
Tetraethoxy							125	5–30 × 7	Sl. effects
							250	4–10	Wt. loss, renal and lung damage
							500	3–5 × 5 d	Decr. wt., renal effects, lung irrit.
							1000	3 × 7	Decr. wt., other signs
Amyltrimethoxy	Rat	4.92	Rabbit	10.0					
Amyltriethoxy	Rat	19.6	Rabbit	7.13					
Vinyltrimethoxy	Rat	11.3	Rabbit	3.54			4000	4	1/6
Vinyltriethoxy	Rat	22.5	Rabbit	10.0					
Tri(2-chloroethoxy) Silicate	Rat	0.19	Rabbit	0.089 mL/kg					
Tetramethoxy	Rat	0.7[a]					1000	8	4/5
Tetraethoxy	Rat	0.2–0.4[b]			Rat	0.9–3.5	2000	4	3/5
							4000	4	5/5
							23–88[c]		None
							500[d]	Several	None
							2000[d]	1	None
2-Ethylbutyl	Rat	19.7	Rabbit	>10					
Silicones									
Siloxane									
Hexamethyldi-	Guinea	>50[e]							

Dodecamethylpenta-	pig Guinea pig	40[f]

[a] Minimal lethal dose with renal damage.
[b] No-effect level.
[c] Guinea pig and rat.
[d] Guinea pig.
[e] No symptoms.
[f] 10–30 mL/kg have laxative effect 8 h post administration.

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B. Silanes

For comparative purposes, some physical properties and range-finding toxicological data are presented in Tables 81.11 and 81.12. Toxicological data show high oral and intraperitoneal toxicities for the methyl and ethyl chlorosilanes. Tetrachlorosilane, $SiCl_4$, an irritant gas, has been used as a warfare agent and to prepare smoke screens (128). The chlorinated derivatives appear to be most toxic of this series, as shown with tri(2-chloroethoxy)silane, $HSI(OCH_2CH_2Cl)_3$.

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C. Silanol Esters

The silanol esters are commonly called silanes, but should more correctly be called silanates. They represent the basic raw materials for the commercial production of silicones. Range-finding toxicological data are shown in Table 81.12. Trimethylethoxysilane (ethoxytrimethylsilane), $(CH_3)_3SiOC_2H_5$, is a liquid at ambient temperatures. Intraperitoneal injections of 1000 mg/kg tetramethoxysilane (TMOS), tetraethoxysilane (TEOS), tetrapropoxysilane (TPOS), and tetrabutoxysilane (TBOS) caused renal toxicologic effects in mice. TMOS and TEOS caused acute tubular necrosis; TEOS, TPOS, and TBOS caused elevated creatinine and blood urea nitrogen; and TMOS exposed mice died exhibiting cytolysis suggestive of spleen damage (131). Mice exposed via inhalation to 100 ppm TEOS 6 h/d, 5 d/wk, for 2–4 wk developed tubulo-interstitial nephritis (132). The mice exposed to 50 ppm TEOS for the same period did not develop nephritis; however, histopathological changes developed in their nasal mucosa. Dimethyldiethoxysilane (diethoxydimethylsilane), $(CH_3)_2Si(OC_2H_5)_2$, is a liquid at ambient temperatures. A mixture of dimethyldiethoxysilane and glycerol has successfully been applied in the rabbit as a model for the

prevention of arterial wall and metabolic disorders (133). Amyltriethoxysilane (amyltriethoxysilanate), $C_5H_{11}Si(OC_2H_5)_3$, is of relatively low toxicity.The vinyl triethoxy derivative appears in the same toxicity range.

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D. Silicates
16.0a Methyl Silicate
16.0.1a CAS Number: [*681-84-5*]

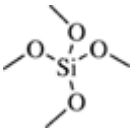
16.0.2a Synonyms: Tetramethyl orthosilicate, silicic acid tetramethyl ester; methyl orthosilicate, Tetramethoxysilane, tetramethyl silicate, and TMOS

16.0.3a Trade Names: Dynasil M

16.0.4a Molecular Weight: 155.22

16.0.5a Molecular Formula: $C_4H_{12}O_4Si$

16.0.6a Molecular Structure:



16.0b Ethyl Silicate
16.0.1b CAS Number: [*78-10-4*]

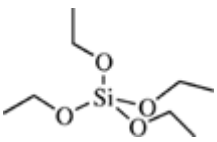
16.0.2b Synonyms: Silicic acid tetraethyl ester

16.0.3b Trade Names: NA

16.0.4b Molecular Weight: 208.30

16.0.5b Molecular Formula: $C_8H_{20}O_4Si$

16.0.6b Molecular Structure:



16.3 Exposure Assessment
16.3.3 Workplace Methods NIOSH Method S264 is recommended for determining workplace exposures to ethyl silicate.

Alkyl silicates, tetraalkyloxysilanes, are organic derivatives of hydrocarbons esterified with silicic acid of the type $Si(OR)_4$. The methyl and ethyl silicates have industrial uses in protective coatings and as preservatives or waterproofing agents for stone and concrete. Range-finding toxicological data are shown in Table 81.12.

Methyl silicate (tetramethyl orthosilicate; silicic acid tetramethyl ester), $Si(OCH_3)_4$, is a liquid under ambient conditions. Methyl silicate has been used in the ceramic industry for closing pores, including those in concrete and cement, for coating metal surfaces and as a bonding agent in paints and lacquers. It is of moderate toxicity, and under certain humid conditions effects progressive necrosis of the cornea.

Ethyl silicate (silicic acid tetraethyl ester), $Si(OC_2H_5)_2$, is a high-boiling liquid. Ethyl silicate is used as a preservative for stone, brick, concrete, and plaster. It is used in water, weather- and acid-proofing processes, heat- and chemical-resistant paints, and protective coatings. Orally, the ethyl silicate is moderately toxic, but may be narcotic in high concentrations. Injected into the skin of the rabbit, it produced transient erythema, edema, and slight necrosis at the injection site (128). In the rabbit eye, it produced transient irritation (128). Inhalation of 400 ppm by rats for 7 h/d for 30 d caused mortalities and lung, liver, and kidney pathological effects. Under similar conditions, 88 ppm caused no effects. Inhalation exposure of the guinea pig to ethyl silicate revealed that humid air was related to more severe effects than dry air (130).
6.5 Standards, Regulations, or Guidelines of Exposure
Both the ACGIH TLV and the NIOSH REL are 1 ppm for methyl silicate. The ACGIH TLV and the NIOSH REL for ethyl silicate is 10 ppm while the OSHA PEL is 100 ppm for ethyl silicate.

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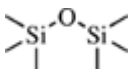
E. Silicones (Siloxanes)
17.0a Hexamethyl Disiloxane (HMS)
17.0.1a CAS Number: [*107-46-0*]

17.0.5a Molecular Formula: $C_6H_{18}OSi_2$

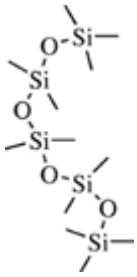
17.0.6a Molecular Structure:



17.0b Dodecamethylpentasiloxane
17.0.1b CAS Number: [*141-63-9*]

17.0.5b Molecular Formula: $C_{12}H_{36}O_4Si_5$

17.0.6b Molecular Structure:



The silicones, organopolysiloxanes, may be divided into the commercial materials, the fluids, and the resins, structurally $R_2[R_2SiO_{n-1}]_n$ for the linear compounds. The final products are water repellent, insoluble in most solvents, and resistant toward oxidation and chemical attack (128). Silicones are used medically and for cosmetic prosthetic devices.

In chronic feeding experiments, rats on HMS showed widespread systemic irritation. Rabbits injected intradermally with HMS showed irritation with edema and necrosis at the injection site (128). Siloxanes injected into the rabbit eye resulted in transient irritation with complete clearing after 48 h (128). When inhaled at 4400 ppm for 19–26 d, HMS caused slight depression in the rat and the guinea pig, with a very slight increase in rat liver and kidney weights (128).

Silicone resins had no influence on health when fed for 94 d to rats, and did not result in irritation to the rabbit skin or eye or when injected into rats intraperitoneally (128). It has been postulated and reported in the literature, however, that implanted silicone prostheses may cause granulomas, lymphadenopathy, cancer, and various autoimmune diseases in humans (134–136). Other reports indicate, however, that a definite correlation has not yet been confirmed by scientific data (137, 138).

Esters of Carbonic and Orthocarbonic Acid, Organic Phosphorous, Monocarboxylic Halogenated Acids, Haloalcohols, and Organic Silicon

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Epoxy Compounds—Olefin Oxides, Aliphatic Glycidyl Ethers and Aromatic Monoglycidyl Ethers

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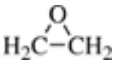
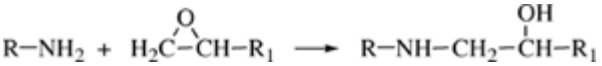
Introduction

An epoxy compound is defined as any compound containing one or more oxirane rings. An oxirane ring (epoxide) consists of an oxygen atom linked to two adjacent (vicinal) carbon atoms as follows for the example compound, ethylene oxide:



The term alpha-epoxide is sometimes used for this structure to distinguish it from rings containing more carbon atoms. The alpha does not indicate where in a carbon chain the oxirane ring occurs.

The oxirane ring is highly strained and is thus the most reactive ring of the oxacyclic carbon compounds. The strain is sufficient to force the four carbon atoms nearest the oxygen atom in 1,2-epoxycyclohexane into a common plane, whereas in cyclohexane the carbon atoms are in a zigzag arrangement or boat structure (1). As a result of this strain, epoxy compounds are attacked by almost all nucleophilic substances to open the ring and form addition compounds. For example,



Among agents reacting with epoxy compounds are halogen acids, thiosulfate, carboxylic acids, hydrogen cyanide, water, amines, aldehydes, and alcohols.

A major portion of this chapter presents information on the two olefin oxides, ethylene oxide and propylene oxide, which are produced in high volume and are largely used as intermediates in the production of the glycol ethers. In addition, these compounds are used in the production of several other important products (e.g., polyethylene glycols, ethanolamines, and hydroxypropylcellulose) and have minor uses as fumigants for furs and spices and as medical sterilants. The other olefin oxides discussed are used as chemical intermediates (e.g., vinylcyclohexene mono- and dioxide), as gasoline additives, acid scavengers, and stabilizing agents in chlorinated solvents (butylene oxide) or in limited quantities as reactive diluents for epoxy resins. The discussion of the toxicology of certain olefinic oxides may be pertinent to their respective olefin precursors. However, it must be pointed out that the olefinic precursors of these different oxides demonstrate widely varying degrees of toxicity in mammalian models, mostly attributable to pharmacokinetic/metabolism differences in metabolic conversion of olefins to their respective oxide metabolites. For example, chronic bioassay results range from repeated negatives (ethylene, propylene) to clear positives (butadiene). A major use of the glycidyl ethers discussed in this chapter are as reactive diluents in epoxy resin mixtures. However, some of these materials are also used as intermediates in chemical synthesis as well as in other industrial applications.

The concept that epoxides, through their binding to nucleophilic biopolymers such as DNA, RNA, and protein, can produce toxic effects is well established. However, the magnitude and nature of physiological disruption depend on the reactivity of the particular epoxide (2–4), its molecular weight, and its solubility (5), all of which may control its access to critical molecular targets. In addition, the number of epoxide groups present, the dose and dose rate, the route of administration, and the affinity for the enzymes that can detoxify or activate the compound may affect the degree and nature of the physiologic response. A key enzyme for epoxide detoxification is microsomal epoxide hydrolase (EH), which is widely distributed throughout the body, but it is organ, species, and even strain variant (6). It should be noted that mouse tissues have a much lower level of EH activity than human tissue; in fact, at least two strains of mice, C57BL/6N and DBA/2N, have no EH activity in their skins (7). Hence, the relevance of risk assessment based on the toxicity findings from studies of epoxides in mice is moot. Epoxy compounds may also be metabolized by the cytoplasmic enzyme glutathione-*S*-transferase (GST), which conjugates epoxides with its co-substrate, glutathione (GSH), leading to formation of 2-alkylmercapturic acids. This enzyme, because it is in the aqueous phase, may play a minor role in the detoxification of larger more lipophilic epoxides but is active against low-molecular-weight epoxides (8, 9). GST also exhibits organ, species, and strain differences in expression and activity as well as genetic polymorphisms.

Acute toxic effects most commonly observed in animals have been dermatitis (either primary irritation or secondary to induction of sensitization), eye irritation, pulmonary irritation, and gastric irritation, which are found in these tissues after direct contact with the epoxy compound. Skin irritation is usually manifested by more or less sharply localized lesions that develop rapidly on contact, more frequently on the arms and hands. Signs and symptoms usually include redness, swelling, and intense itching. In severe cases, secondary infections may occur. Workers show marked differences in sensitivity.

Most of the glycidyl ethers in this chapter have shown evidence of delayed contact skin sensitization, in either animals or humans. The animal and human data available on skin sensitization of epoxy compounds do not assist in determining the structural requirements necessary to produce sensitization, but do provide some practical guidance for industrial hygiene purposes. Specifically, of the alkyl glycidyl ethers, only the C8–C10 alkyl glycidyl ether appears to be a human sensitizer. Despite equivocal results in tests for delayed contact sensitization in guinea pigs, *n*-butyl glycidyl ether and cresyl glycidyl ether do produce dermal sensitization in some humans. Skin sensitization reactions can be elicited from much less agent than is required for an irritative response. Because this condition is difficult to treat, sensitized individuals may require transfer to other working areas.

Animals exposed to vapors of gaseous or volatile epoxy compounds, primarily ethylene oxide and propylene oxide, have shown pulmonary irritation. Sequelae of this effect may include pulmonary edema, cardiovascular collapse, and pneumonia. However, this route of exposure is unlikely for some of the other epoxy compounds owing to their lower volatility.

For those epoxy compounds for which repeat exposures have been conducted, respiratory epithelium or nasal mucosa (when inhalation was the route of exposure) and stomach (when given by gavage) appear to be the major target organs. In some cases liver and kidney have been target organs. These effects on the liver and kidney have been relatively nonspecific or adaptive, as indicated by an increased organ weight without accompanying histopathology. Exceptions include ethylene oxide, which caused renal tubular degeneration and necrosis in mice; vinylcyclohexene dioxide, which produced kidney tubule cell necrosis; *n*-butyl glycidyl ether, which produced liver necrosis; and phenyl glycidyl ether, which produced atrophic liver and kidney effects in rats. Ovarian toxicity and depression of hematopoesis have also been observed in laboratory animals for butadiene dioxide and vinylcyclohexene dioxide. Respiratory epithelium and nasal mucosa effects have been responses typical of irritation, such as flattening or destruction of epithelial cells.

Although all of the compounds described in this chapter were mutagenic to bacteria (excluding

epoxidized glycerides) as well as positive in other *in vitro* genotoxicity assays, not all have produced genotoxicity in *in vivo* studies. Ethylene oxide was positive in the mouse micronucleus assay and mouse dominant lethal assay. In contrast, propylene oxide, although positive in all the *in vitro* assays in which it was tested, was negative in all of the *in vivo* mammalian assays where propylene oxide was administered via the relevant inhalation route. These negative mammalian studies include a mouse micronucleus assay (although positive by IP injection of high doses), mouse sperm cell analysis, and a rat dominant lethal assay. In addition, propylene oxide failed to cause chromosomal changes (SCE and chromosomal aberrations) in monkey lymphocytes following chronic exposures to 300 ppm. Other compounds showing positive or equivocal effects *in vitro* but negative effects *in vivo* are styrene oxide, and many of the glycidyloxy compounds used in epoxy resin formulations.

There has been no evidence of teratogenicity for glycidyl ethers or olefin oxides, except ethylene oxide (EO), when tested by oral or inhalation exposure in conventional developmental toxicity studies. Fetal toxicity has been observed at maternally toxic doses for ethylene oxide, propylene oxide by inhalation in rats, and 1,2-epoxybutane by inhalation in rabbits. No evidence for fetal toxicity, in some instances even at maternally toxic doses, has been observed for phenyl glycidyl ether by inhalation in rats, 1,2-epoxybutane by inhalation in rats, or propylene oxide or styrene oxide by inhalation in rabbits. Additionally, repeated intravenous infusion of ethylene oxide was teratogenic in mice. Inhalation of extremely high levels of EO (600–1200 ppm compared to the ACGIH-recommended 8-h TWA–TLV of 1 ppm) in mice at the time of fertilization or early zygote development has led to fetal deaths or malformations in some survivors. However, no teratological effects have been demonstrated by inhalation exposures up to 150 ppm in rats or rabbits.

A number of these epoxide compounds have been found to be carcinogenic in rodents, although there has been no clear epidemiologic evidence for cancer in the workplace. In rats and/or mice, many epoxy compounds produce a carcinogenic response in the tissues of first contact. These compounds include ethylene oxide, butylene oxide, propylene oxide, styrene oxide allyl glycidyl ether, phenyl glycidyl ether, and neopentyl glycol diglycidyl ether. A few of them, such as ethylene oxide, butadiene dioxide, and vinylcyclohexene dioxide, have produced tumors at sites other than the "portal of entry."

Epoxy Compounds—Olefin Oxides, Aliphatic Glycidyl Ethers and Aromatic Monoglycidyl Ethers
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B. Glycidyl Ethers

Epoxy Compounds—Olefin Oxides, Aliphatic Glycidyl Ethers and Aromatic Monoglycidyl Ethers

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Epoxy Compounds—Aromatic Diglycidyl Ethers, Polyglycidyl Ethers, Glycidyl Esters, and Miscellaneous Epoxy Compounds

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Introduction

The principal focus of this chapter is on the epoxy compounds frequently encountered in industrial use as uncured epoxy resins. These resins are marketed in a variety of physical forms from low-viscosity liquids to tack-free solids and require admixture with curing agents to form hard and nonreactive cross-linked polymers. They are in demand because of their toughness, high adhesive properties (polarity), low shrinkage in molds, and chemical inertness.

It is the uncured resins that are of main interest to toxicologists, for a well-cured resin should have few or no unreacted epoxide groups remaining in it. The toxicology of the curing agents is not treated in this chapter. They are most frequently bi- or trifunctional amines, di- or tricarboxylic acids

and their anhydrides, polyols, and compounds containing mixed functional groups, such as aminols and amino acids, as well as other resins containing such groups (1).

Some of the other epoxide compounds described in this chapter are used as reactive diluents in epoxy resin mixtures; others are of commercial importance for their multiple uses in the synthesis of other compounds (specifically, epichlorohydrin). As reactive diluents, monomeric epoxides are added to epoxy resins to reduce viscosity and modify the handling characteristics of the uncured materials. The epoxide functionalities of these diluents react with the resin curing agents in the same manner as the resin to become part of the finished polymer. Epoxy resins have found application as protective coatings, adhesives for most substrates (metals included), caulking compounds, flooring and special road paving, potting and encapsulation resins, low-pressure molding mixtures, and binding agents for fiber glass products. Uncured, they are used as plasticizers and stabilizers for vinyl resins.

Epoxy resin coating formulations can generally be limited to one of three forms: solution coatings, high-solids formulations, and epoxy powder coatings. Solid epoxies are used in coating applications, as solid solutions or heat-converted coating. Solution coatings are often room-temperature applications, and typically there is little potential for vapor exposure. The potential clearly exists for skin contact during application of coatings of this type. Heat-converted coatings are usually applied and cured by mechanical means and exposure to vapors or contact with skin is minimal.

Solid resins are used for other applications such as electrical molding powders and decorative or industrial powder coatings. For applications of this kind, exposure to vapors and dust can occur and is greatest during formulating and grinding.

Considering that epoxides can react with nucleophiles, particularly basic nitrogens, one might expect the epoxides to react with cellular biomolecules such as glutathione, proteins, and nucleic acids, and indeed this has been demonstrated for some of these epoxide compounds. The nature and magnitude of these interactions with these biomolecules is most likely related to the toxicity and observed for any given molecule in this class of compounds. However, the potential for any epoxide to react with cellular nucleophilic biomolecules is dependent on several factors, including the reactivity of the particular epoxide, the dose and dose rate, as well as the molecular weight, and solubility, these latter two influencing access to molecular targets within the cell. In addition, the efficiency of metabolism via epoxide hydrolase or other metabolic routes of detoxication may significantly influence the toxicologic potential and potency of these materials.

Epoxide hydrolase activity is widely distributed throughout the body, but it is organ, species, and even strain variant (2). The liver, testes, lung, and kidney have considerable epoxide hydrolase activity; the activities in the skin and gut, however, are considerably lower. In this regard it should be noted that mouse tissues have a much lower level of EH activity than does human tissue; in fact, at least two strains of mice, C57BL/6N and DBA/2N, have no EH activity in their skins (3). Therefore, it may be questioned if toxicity or treatment-related effects observed in dermal mouse studies are relevant for hazard evaluation. Epoxy compounds may also be metabolized by the cytoplasmic enzyme glutathione-*S*-transferase, which converts epoxides to 2-alkylmercapturic acids. This enzyme because it is in the aqueous phase, may play a minor role in the detoxification of large lipophilic epoxides, but is active against low-molecular-weight epoxides (4, 5). Due to differences in physio-chemical properties and the effectiveness and nature of the detoxification of these materials through metabolism, the toxicity of these compounds ranges from the highly active, electrophilic, low-molecular-weight mono- and diepoxides to the nontoxic and inert cured materials, which possess only a few epoxy groups per molecule.

In general, the acute toxicity of epoxy resin compounds as observed in laboratory animals can be considered low; oral and dermal LD_{50} values generally range from about 2000 to greater than 10,000 mg/kg in rodents; there are not marked differences in acute toxicity among the structurally

diverse categories of epoxy resin compounds. The acute toxicity of low-molecular-weight epoxides such as epichlorohydrin and glycidol is significantly greater (oral LD_{50} values range from 90 to about 500 mg/kg). Lung irritation following inhalation or gastrointestinal irritation following gavage has also been observed in animals. It is generally difficult to achieve acutely toxic levels of epoxy compounds by dermal exposure. Usually the irritating properties of epoxy liquids or vapors limit significant exposure to produce systemic toxicity.

Effects most commonly observed in animals have been dermatitis (either primary irritation or secondary to induction of sensitization), eye irritation, pulmonary irritation, and gastric irritation, which are typically found in the tissues that are the first to come into contact with the epoxy compound. In general, it appears that epoxy compounds of higher molecular weight (e.g., epoxy novolac resins and diglycidyl ether of bisphenol A) produce less dermal irritation than those of lower molecular weight. In some instances, liquid epoxy compounds splashed directly into the eye may cause pain and, in severe cases, corneal damage. Skin irritation is usually manifested by more or less sharply localized lesions that develop rapidly on contact, more frequently on the arms and hands. Signs and symptoms usually include redness, swelling, and intense itching. In severe cases, secondary infections may occur.

Workers show marked differences in sensitivity. Devices made from epoxy resins have produced severe dermatitis when not properly cured and when in prolonged contact with the skin (6). Skin irritation also has been reported from exposure to epoxy vapors (7). Most of the epoxy compounds have the ability to produce delayed contact skin sensitization, although there are notable exceptions, such as the advanced bisphenol A/epichlorohydrin resins. The higher molecular weight of these resins may be responsible for the absence of dermal sensitization (8, 9). Skin sensitization reactions can be elicited from much less agent than is required for a primary irritation response. Because this condition is difficult to treat, sensitized individuals may require transfer to other working areas. Particular attention should be paid to vapors and fine airborne dusts.

Animals exposed to vapors of epichlorohydrin have shown pulmonary irritation. Sequelae of this effect may include pulmonary edema, cardiovascular collapse, and pneumonia. However, this route of exposure is unlikely for many of these epoxy compounds owing to their low volatility. For the glycidyloxy compounds for which LC_{50}s have been determined, it appears that none of these compounds can be considered highly acutely toxic by the inhalation route.

For those epoxy compounds for which repeat dosing studies have been conducted, generally the liver, kidneys, respiratory epithelium or nasal mucosa (when inhalation was the route of exposure), and stomach (when given by gavage) appear to be the major target organs. Respiratory epithelium and nasal mucosa effects have been responses typical of irritation, such as flattening or destruction of epithelial cells. Disruption of hematopoesis, primarily leukopenia, has also been demonstrated in laboratory animals with a polyglycidyl ether of substituted glycerin and resorcinol diglycidyl ether, but similar changes have not been observed in workers as a result of occupational exposures. The testes have been found to a target organ for glycidol and epichlorohydrin. Glycidol was also embryotoxic in laboratory animals when administered by a route not relevant to occupational exposure (intra-amniotic injection). However, no developmental toxicity has been observed for any other compounds in this chapter where there are data available. In addition, a two-generation reproduction study in rats on the diglycidyl ether of bisphenol A also indicated that this material did not produce adverse effects on either male or female reproduction.

There is evidence in rats from a National Toxicology Program study that glycidol produces neurotoxicity (10), and this finding suggests that glycidyl esters, if metabolized to glycidol, could have this effect. However, glycidyl ethers have shown no evidence of neurotoxic effects in numerous acute or repeated dosing subchronic studies in rodents. A recently completed neurotoxicity study of diglycidyl ether of bisphenol found no evidence of neurotoxic effects in rats dosed dermally.

Generally, *in vitro* genetic toxicity testing of the epoxide compounds has resulted in positive (genotoxic) responses; the majority of the studies of genotoxic potential have been carried out using bacteria. These results are not surprising because many of these compounds have been tested in strains TA1535 and TA100 of *S. typhimurium* or in other gene mutation assays that are specifically sensitive to base-pair substitution, Metabolic activation was not required for most of the epoxides, which showed mutagenic in these tests. Many other *in vitro* assays examining both gene mutation and chromosomal effects have been employed to test the epoxy compounds, including assays in *E. coli*, yeast, Chinese hamster ovary cells (CHO/HPGRT), mouse lymphoma cells, and cultured human lymphocytes; the results have usually been mixed or positive. Fewer epoxy compounds have been tested using *in vivo* assays for genotoxic effects, although some have been extensively studied. Glycidol was positive in the *Drosophila* sex-linked recessive lethal assay and mouse micronucleus assay and produced chromosomal aberrations in the bone marrow of mice dosed orally or intraperitoneally. Glycidaldehyde was positive in the *Drosophila* sex-linked recessive lethal assay. In contrast, epichlorohydrin, also a low-molecular-weight epoxy compound, was negative in both the mouse micronucleus test following intraperitoneal administration and the mouse dominant lethal assay following oral or intraperitoneal administration, although it was positive in many of the *in vitro* assays. Another compound showing positive or equivocal effects *in vitro* but negative effects *in vivo* is the diglycidyl ether of bisphenol A.

Of the compounds in this chapter, four (resorcinol diglycidyl ether, epichlorohydrin, glycidaldehyde, and glycidol) were the subject of studies in which there was clear evidence of tumorigenic effects in rodents. Larger-molecular-weight glycidyloxy compounds such as castor oil glycidyl ether, the diglycidyl ether of bisphenol A, and advanced bisphenol A/epichlorohydrin epoxy resins have been negative in dermal bioassays. Epidemiology studies have not provided any evidence for an association between workplace exposure and cancer to any of the materials in this chapter.

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Aromatic Diglycidyl Ethers

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Polyglycidyl Ethers

Table 83.1. Effects on the Hematopoietic System of Exposure to the Polyglycidyl Ether of Substituted Glycerin (161)

Route	Species	Dose (g/kg)	No. of Doses	Response[a]

Respiratory	Rat	Saturated vapors	50 (8 h each)	No effect noted
Intramuscular	Rat	0.10	6	No effect
		0.20	6	Depression of WBC count and bone marrow nucleated cell count
Intramuscular	Dog	0.2	2 (1/week)	Marked depression of WBC count; neutropenia; leukocytosis; ulceration and abscess of injection site.
Intravenous	Dog	0.2	1	Progressive decline in WBC count
				Death from overwhelming infection
Intravenous	Rabbit	0.1	2	Decrease in total WBC
Percutaneous	Rat	1.0	20	No effect
		2.0	20	No effect
		4.0	20	Depression of bone marrow nucleated cell count (only)

[a] WBC, white blood cells.

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Glycidyl Esters

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Miscellaneous Epoxy Compounds

Table 83.2. Summary of Acute Toxicity Data on Epichlorohydrin

Route	Species	Dose	Parameter of Toxicity
Oral	Rats	0.09 g/kg	LD_{50}

Oral	Guinea pigs	0.178 g/kg	LD_{50}
Oral	Mice	0.238 g/kg	LD_{50}
Intravenous	Rats	0.154 g/kg	LD_{50}
Intravenous	Mice	0.178 g/kg	LD_{50}
Percutaneous	Rabbits	0.88 ml/kg	LD_{50}
Percutaneous	Rats (3 applications)	0.5 mL/kg	LD_{50}
Inhalation	Mice	2370 ppm	0/30[a]
Inhalation	Mice	8300 ppm	20/20[a]
Inhalation	Rats	250 ppm (8 h)	LC_{50}
Inhalation	Rats	500 ppm (4 h)	LC_{50}
Inhalation	Guinea pigs	561 ppm (4 h)	LC_{50}
Inhalation	Rabbits	445 ppm (4 h)	LC_{50}
Inhalation	Rats (males)	3617 ppm (1 h)	LC_{50}
Inhalation	Rats (females)	2165 ppm (1 h)	LC_{50}

[a] Number of deaths over the number of animals exposed.

Epoxy Compounds—Aromatic Diglycidyl Ethers, Polyglycidyl Ethers, Glycidyl Esters, and Miscellaneous Epoxy Compounds

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Introduction
A review of the literature for these compounds has resulted in very little new information. Consequently, the content of this chapter is drawn heavily from the previous authors, including the tables. The only compounds where there has been publishing activity are: dibenzoyl peroxide,

methyl ethyl ketone peroxide, *t*-butyl hydroperoxide, isopropylbenzene hydroperoxide, and peroxyacetic acid. A recent review compared the skin tumor promoting activity of different organic peroxides in SENCAR mice (especially *t*-butyl peroxide, dicumyl peroxide, and also dibenzoyl peroxide) (1). Much of this literature is, however, irrelevant to health. The introduction presented in the previous edition is entirely correct and relevant.

Peroxides are highly reactive molecules due to the presence of an oxygen–oxygen linkage. Under activating conditions, the oxygen–oxygen bond may be cleaved to form highly reactive free radicals. These highly reactive radicals can be used to initiate polymerization or curing. Consequently, organic peroxides are used as initiators for free-radical polymerization, curing agents for thermoset resins, and cross-linking agents for elastomers and polyethylene. In some cases they can be used as antiseptic agents.

These materials must be handled and stored with caution. If free radicals are formed during storage in concentrated form, an accelerated decomposition could result, leading to the release of considerable heat and energy. It has been determined that decompositions of commercially available peroxides are generally low-order deflagrations rather than detonations (2).

There have been several investigations into the types of physical hazards represented by organic peroxides (2–5). These compounds may possess the combination of thermal instability, sensitivity to shock, and/or friction, as well as flammability. Organic peroxides tend to be unstable, with the instability increasing with greater concentrations. Because of their instability, many peroxides are stored/handled in inert vehicles (6). It has been shown by Tamura (3) that the ignition sensitivity and the violence of deflagration for each organic peroxide may have a tendency to increase with increasing active oxygen content among the same type of organic peroxide, with a few exceptions. The ignition sensitivity and the violence of deflagration for each type of organic peroxide may decrease in the following order, given the same active oxygen content: diacyl peroxides > peroxyesters > dialkyl peroxides > hydroperoxides (3).

Basically only acute health testing has been performed on organic peroxides. Exposures should be well controlled, primarily owing to the decomposition or deflagration hazard of the organic peroxide. The health data presented in Tables 84.1–84.9 were collected and furnished by the Organic Peroxide Producers Safety Division of the Society of the Plastics Industry to the previous authors of this chapter and are presented again in this edition. This represents an effort by industry to evaluate their products and provide that information to the public. Most of the information in the table has been previously published (7) in an industry bulletin.

The analytic method should also be specific for each organic peroxide. NIOSH has fully validated a high-performance liquid chromatography/ultraviolet light method for benzoyl peroxide (8). Very few of the other organic peroxides have fully validated analytic methods. One of the first conventional methods to determine concentrations of organic peroxides was the titration of iodine from sodium iodide. However, it was not specific for organic peroxides. The polarographic method came into use with the visible-recording polarograph because hydroperoxides could be distinguished from other peroxides. This method could identify the functional groups and also quantify mixtures. Di-*t*-butyl peroxide is an exception because it is not reduced polarographically (9).

Many analytical methods that have not been subjected to review by consensus standard organizations or regulatory agencies are in use. Some examples include gas chromatography (dialkyl peroxides such as di-*t*-butyl peroxide), high-pressure liquid chromatography (peroxyketals), and iodometric titration (peroxyesters, diacyl peroxides, hydroperoxides, and peroxydicarbonates). Some degree of selectivity in iodometric titrations may be obtained by variation of the reducing agent employed and the reaction conditions.

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A. Peroxydicarbonates

Table 84.1. Toxic Properties of Peroxydicarbonates (7)[*]

Peroxydicarbonate	CAS No.	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Primary Skin Irritation[a]	Eye Irritation[a]	LC_{50}, ppm (mg/L)[b]	*Salmonella typhimurium* Assay
Diisopropyl peroxydicarbonate	[*105-64-6*]						
100%		2140		Mod. irritant	Ext. irritating		
30% in toluene		3720	2025	Ext. irritating	Mod. irritating		
45% in Soltrol 130		8500	1.7[c]	V. severe irritant	Irritant	Irritant gas	
45% in cyclohexane--benzene		6500	4.0[c]	V. severe irritant	Irritant		
Di-*n*-propyl peroxydicarbonate	[*16066-38-9*]						
100%		3400	>6800	Ext. irritating	Ext. irritating	>22.7 (>0.19) 1 h	
85% in methylcyclohexane		4600	3500	Ext. irritating	Ext. irritating	>1433 (>12) 1 h	
Di-*sec*-butyl peroxydicarbonate	[*19910-65-7*]						
100%		7600				172 ppm—no adverse effects (1 h)	
75% in odorless mineral spirits		>4640	Not toxic at 2000[d]		Irritant		
75% in Soltrol 130		9300	1200				
Di-(2-ethylhexyl) peroxydicarbonate	[*16111-62-9*]						
97% min			Not toxic at 2000[d]		Irritant		
75% in Soltrol 130		1020					
40% in Soltrol		20,800					

130						
40% in dimethyl phthalate		3690				
Di-(4-*t*-butylcyclohexyl) peroxydicarbonate	[*15520-11-3*]	>5000	Not an irritant	Not an irritant		Negative
Di-*n*-butyl peroxydicarbonate	[*16215-49-9*]					
50% in aromatic-free mineral spirits		10[c]	V. servere irritant	Slight irritant		
Di-(3-methylbutyl) peroxydicarbonate	[*4113-14-8*]					
20% in white spirits					1.7 ppm—no toxic signs; slight nose irritation	
Diacetyl peroxydicarbonate	[*26322-14-5*]	5000	Not an irritant	Not an irritant		Negative
75% wet						
Di-(2-phenoxyethyl) peroxydicarbonate	[*41935-39-1*]	>20,000	>20,000	Mild irritant		Negative
Di-(2-chloroethyl) peroxydicarbonate	[*6410-72-6*]	4000400				
Di-(3-chloropropyl) peroxydicarbonate	[*34037-78-0*]	1500				
Di-(4-chlorobutyl) peroxidicarbonate	[*14245-74-0*]	5200				
Di-(2-butoxyethyl) peroxidicarbonate	[*6410-72-6*]	4000				

[*] *All studies used rats.

[a] V = Very; ext = extremly; mod = moderately.

[b] All LC_{50} tests lasted 4 h unless noted otherwise.

[c] LD_{50} reported in ml/kg.

[d] According to the Federal Hazardous Substances Act.

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B. Diacyl Peroxides

Table 84.2. Toxic Properties of Diacyl Peroxides (7)[*]

Diacyl peroxide	CAS No.	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Primarry Skin Irritation	Eye Irritation	LC_{50} (mg/L)[a]	*Salmonella typhimurium* Assay (Unless Specified)
Dibenzoyl proxide 78% wet	[*94-36-0*]	Not toxic at 5000[b]		Not an irritant	Not irritanting (5 min wash)	>24.3	Negative
					Strongly irritating, but not corrosive (24 h wash)		Negative[c]
Di-(2,4-dichlorobenzoyl) peroxide	[*133-14-2*]						
50% in silicone fluid		>12.918	>8000		Not an irritant		
Di-*p*-chlorobenzoyl peroxide	[*94-17-7*]	500(IP)					Negative[c]
Di-(2-methylbenzoyl) peroxide	[*3034-79-5*]						
78% wet		>5000		Severe irritant	Irritant (unwashed)		Negative
Didecanoyl peroxide	[*762-12-9*]	>5000		Mod. irritating	Slight irritation		Negative
Dilauroyl peroxide	[*105-74-8*]	>5000[b]		Not an irritant	Not an irritant RTECS-moderate[f]	Toxic at 200	NegativeNega
Diacetyl peroxide	[*110-22-5*]				Severe		
Diproprionyl peroxide22.7% in white spirits	[*3248-28-0*]					Saturated—1.5 h—all animals died; 100 ppm—nose and eye irritation, respiratory difficulty, 1 death	Negative
Di-*n*-octanoyl peroxide	[*762-16-3*]			Severe irritation	Slight irritation		Negative

50% in Shellsol T		>5000					
Di-(3,5,5-trimethylhexanoyl) peroxide	[*3851-87-4*]						
75% in isododecane		12.7[e]		Very sereve irritation	Irritant		Negative

[*] All studies used rats.

[a] All LC_{50} tests lasted 4 h unless noted otherwise.

[b] According to the Federal Hazardous Substances Act.

[c] Tumor cell growth assay.

[f] Registry of Toxic Effects of Chemical Substances Classified it as moderate irritant.

[d] Mouse lymphoma forward mutation assay, with/without metabolic activation.

[e] LD_{50} reported in mL/kg.

Table 84.3. Toxic Properties of Peroxyesters (7)[*]

Peroxyester	CAS No.	Oral LD_{50} (mg/kg)	Dermal LD_{50}	Primary Skin Irritation	Eye Irritation	LD_{50} (mg/L)[a]	*Salm* Assay
t-Butyl peroxyacetate	[*107-71-1*]						
75% in OMS[c]		2562	4757	Slight irritant	Irritant	6.1	
70% in benzene (mice)		1900					
50% in Shellsol T					450 (8 hr)		
t-Butyl peroxypivalate	[*927-07-1*]						
75% in OMS[c]		4169–4640	2500	Mod to severe	Not an irritant	7.79	
t-Amyl perioxypivalate	[*29240-17-3*]						
75% in OMS[c]		4270	>2000	Not an irritant	Not an irritant	>9.5	
t-Butyl peroxybenzoate	[*614-45-9*]	3639–4838	3817	Not an irritant or sensitizer	Slight irritation	>.26	Slightl positiv
Mice		914–2500					
t-Butyl peroxy-2-ethylhexonate	[*3006-82-4*]	>10,000	16,818	Not an irritant	Not an irritant	42.2	
t-Amyl peroxy-2-ethylhexonoate	[*686-31-7*]	>5000	>2000	Slightly irritating	Not an irritant		
t-Butyl peroxy-3,5,5-trimethylhexanoate	[*13122-18-4*]	17.4[d]		Mod. to severe	Not an irritant	>0.8	Negati

t-Butyl peroxyneodecanoate	[*26748-41-4*]						
50% Shellosol T		>12,918	>8000	Mod. to severe	Not an irritant	50.0	
t-Butyl peroxy-2-ethylhexylcarbonate	[*34443-12-4*]	>5,000	>2000	Mildly irritating	Not an irritant		
t-Butyl peroxycronate	[*23474-91-1*]	4100		Moderate irritant			
t-Amyl peroxybenzoste	[*4511-39-1*]						Negati
Cumyl peroxyneodecanoate	[*26748-47-0*]						
90%		5126	>7940 <19,800	Not an irritant		20.2	
75% in OMS[c]						>20.4 slight dyspnea, eye squint and wt. loss	
2.5-dimethyl-2,5-di-(2-ethylhexonoylperoxy) hexane	[*13052-09-0*]	>12,918	>8000	Not an irritant	Not an irritant	>800	
Di-*t*-butyl diperoxyazelate	[*16580-06-6*]						
75% in OMS[c]		>5000	>2000	Severe irritant	Not an irritant		
1,1,3,3-Tetramethylbutyl peroxyphenoxyacetate	[*59382-51-3*]						
30% in Shellosol T (OMS[c])		>12.0[d]		Severe irritant	Not an irritant	>24 ppm	
t-Butylperoxyisopropyl carbonate	[*2372-21-6*]	5.0[d]	>10,000	Not an irritant	Conjunctivitis		
t-Butyl monoperoxymaleate	[*1931-62-0*]	16(Ip)					
Di-*t*-butyl diproxyphylate	[*15042-77-0*]	128 (Ip)					
Cumyl peroxyneoheptanoate	[*130097-36-8*] [*104852-44-0*]	~5000		Mildly irritating			
75% in OMS[c]							

[*] All studies used rats unless otherwise specified.

[a] All LC_{50} test lasted 4 h unless noted otherwise.

[b] ±CHO indicates a positive or negative finding in Chinese hamster ovary cells. The following +/– indicating with/without metabolic activation. ±ML indicates a positive or negative finding in the mouse lymphoma forward mutation assay.

[c] Odorless mineral spirits.

[d] LD_{50} reported in mL/kg.

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C ketone peroxides

Table 84.4. Toxic Properties of Ketone Peroxides (7)*

Ketone Peroxide	CAS No.	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Primary Skin Irritation	Eye Irritation	LC_{50} (mg/L)[a]	*Salmon typhimu* Ass
Methyl ethyl ketone peroxide	[*1338-23-4*]						Positive
OPPSD composite		>500 <5000		Moderate irritant	Corrosive	>200	Negativ
Lupersol DDM		681					
Lucidol & Cadet		484		Irritant	Irritant	200 ppm	
Noury(40% in DMP[b])		1017	4000		Corrosive	17	
Noury & Lucidol						33	
Methyl isobutyl Ketone peroxides	[*37206-20-5*]	1.77[d]		Very severe irritant	Sereve irritant	1.5	Negativ
Acetyl acetone peroxide	[*37187-22-7*]	2870		Not an irritant	Severe irritant	Not a hazard at 13.1 mg/L for 1 h	
Diacetone alcohol peroxide	[*54693-46-8*]	2.68[d]		Very severe irritant	Severe irritant	0.54	Negativ
1,1-Dihydroperoxycyclohexane	[*2699-11-9*]						
21% in DMP[b]		1.08[d]		Very severe irritant	Very severe irritant		Slightly positive
Cyclohexanone peroxide	[*12262-58-7*]				Severe irritant		

Di-(1-hydroxycyclohexyl) peroxide	[*2699-12-9*]				
100% (mice)		900	Irritating	Irritating	
60% in DBP[c] (mice)		850			
1-Hydroperoxy-1-hydroxydiclohexyl peroxide	[*78-18-2*]				
100% (mice)		880	Irritating	Irritating	
60% in DBP[c](mice)		740			

[*] All studies used rats unless otherwise specified.
[a] All LC_{50} tests lasted 4 h unless noted otherwise.
[b] DMP dimethyl phthalate.
[d] LD_{50} reported in ml/kg.
[c] DBP dibutyl phthalate.

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D. Dialkyl Peroxides

Table 84.5. Toxic Properties of Dialkyl Peroxides (7)[*]

Dialkyl Peroxide	CAS. No	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Primary Skin Irritation	Eye Irritation	LC_{50}[a]	*Sa typ*
Di-*t*-butyl peroxide	[*110-05-4*]	>25,000		Not an irritant	Not an irritant	>4103 ppm	Ne
Mice		>20.0[b]	>10,000				
Mice		>50.0[b]					
2,5-Dimethyl-2,5-di-(*t*-butylperoxy) hexane	[*78-63-7*]	>32,000	4100				
2,5-Dimethyl-2,5-di-(*t*-butylperoxy) hexyne-3	[*1068-27-5*]						
In dodecane		>7680		Moderate irritatant		Nontoxic[c]	
90%				Not an irritant			

Dicumyl peroxide	[*80-43-3*]						
96% min		4100		Mild irritation, no sensitizer			Ne
Dust from 40% on Filter						2.24 mg/L no effect (6 h)	
20% in corn oil		~4000					
50% in corn oil					Mild (unwahed) conjuctivities		
a,a'-*Bis*(*t*-butylperoxy) diisopropylbenzenes	[*25155-25-3*] [*2781-00-2*]						
96% min		>23,100		Slight irritation, not a sensitizer	Minimal irritation	>6000 ppm—vapor >180 mg/m^3—dust	Ne
Mice		>4500				>180 mg/m^3—dust	
t-Butyl cumyl peroxide 92%	[*3457-61-2*]	5.18[b]		Severe irritant	Not an irritant	>140 ppm (1.2 mg/L)	Ne
4-(*t*-Butylperoxy)-4-methyl-2-pentanone	[*26394-04-7*]	3949	>20,000		Slight irritation (unwashed)	>2.3 mg/L (1 h)	

[*] All studies used rats unless rats unless otherwise specified.

[a] All LC_{50} tests lasted 4 hr unless noted otherwise.

[b] LD_{50} reported in ml/kg.

[c] According to the Fedral Hazardous Substances Act.

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E. Peroxyketals

Table 84.6. Toxic Properties of Peroxyketals (7)[*]

Peroxyketal	CAS No.	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Primary Skin Irritation	Eye Irritation	LC_{50} (mg/L) [a]	*Salmonella typhimurium* Assay

1,1-Di-(*t*-butylperoxy)-3,3,5-Trimethylcyclohexane	[*6731-36-8*]					
75% in DBP[b]		>12,918	>8000	Not an irritant	~800	
1,1-Di(*t*-butylperoxy) cyclohexane	[*3006-86-8*]					
65% in DBP[b]		16,653	Not an irritant	Not an irrtation	>207.2	
2,2-Di(*t*-butylperoxy) butane	[*2167-23-9*]					
50% in DBP[b]		23.2[c]	Mod. irritating	Slight irritation	>2.42	Negative
50% in mineral oil		>30.0[c]		Slight irritation		
n-Butyl 4,4-di-(*t*-butylperoxy)valerate	[*995-33-5*]					
40% in chalk		>5000	Not an irritant	Slight irrtation		
2,2-Di-(cumylperoxy) propane	[*4202-02-2*]					
50% in odorless mineral spirits		11.5[c]	Severe irritant	Not an irritant		Negative

[*] All studies used rats.
[a] All LC_{50} tests lasted 4 h unless noted otherwise.
[b] Dibutyl phthalate.
[c] LD_{50} reporterd in mL/kg.

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F. Hydroperoxides

Table 84.7. Toxic Properties of Hydroperoxides (7)[*]

Hydroperoxide	CAS No.	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Primary Skin Irritation	Eye Irritation	LC_{50}, ppm (mg/L)[a]	*Salmone typhimur* Assay
t-Butyl	[*75-91-2*]						

Hydroperoxide							
70%		560	0.5[b]	Extreme irritant	Extreme irritant	502 (1.85)	Positive (text)
80% 20% di-*t*-butyl peroxide		406	>10,000	Irritating	Irritant	500	
a-Cumyl hydroperoxide	[*80-15-9*]						
80–83% in corn oil		800–1600	>200	Severe irritation corrosive (DOT)	Irritant	700 (4.3) (6 h)	
73%		382		Irritating	Irritating	220	Inconclus
1-Phenylethyl hydroperoxide	[*3071-32-7*]						
30% in ethylbenzene		800	1700	Severe irritant	Severe irritant	20–33 mg/L	
1,1,3,3-Tetramethylbutyl hydroperoxide	[*5809-08-5*]	0.92[b]		Very severe irritant	Very severe irritant	>480 (2.85)	Negative
1,2,3,4-Tetrahydro-1-naphthyl hydroperoxide	[*771-29-9*]	250 (unk.route in mice)					
1-Vinyl-3-cyclohexen-1-yl hydroperoxide	[*3736-26-3*]		1440				
Diisopropylbenzene hydroperoxide	[*26762-93-6*]						
53%		6200		Severe irritation (immidiate) corrosive (DOT)	Severe irritant	4.5 mg/L (6 h)	
p-Menthyl Hydroperoxide	[*26762-92-5*]						
55%		3700		Severe irritation (immediate) corrosive (DOT)	Severe irritation	9.2 mg/L (6 h)	Positive

[*] All studies used rats.

[a] All LC_{50} tests lasted 4 h unless noted otherwise.

[b] LD_{50} reported in mL/kg.

Table 84.8. Toxic Properties of Peroxyacids (7)[*]

Peroxyacids	CAS No.	Oral LD_{50} (mg/kg)	Dermal LD_{50}	Primary Skin Irritation	Eye Irritation	LC_{50} (ppm)	*typhimurium* Assay (Unless Specified)
Peroxyacetic acid	[*79-21-0*]						
100%		1540	1410 mg/kg				Negative
40% in acetic acid		1230	0.71 mL/kg	Severe irritant	Severe irritant	>500<1000 (4 h)	
p-Nitroperoxybenzoic acid	[*943-39-5*]						Subcutaneous sarcomas

* All studies used rats.

Table 84.9. Toxic Properties of Silyl Peroxides (7)*

Silyl Peroxide	CAS No.	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Primary Skin irritation	Eye Irritation	LC_{50} (ppm)[a]
Vinyltri-(*t*-butylperoxy)silane	[*15188-09-7*]					
100%		>100<250	>10,000	No toxic signs	Inflammation	0.68 (9 mg/L)
40% in *n*-hexane		~2.5	>10,000	No toxic signs	Slight irritation	
5% in odorless mineral spirits						0.006–0.009 mg/L
Cumylperoxytrimethyl silane	[*18057-16-4*]					>22.3

* All studies used rats.
[a] All LC_{50} tests lasted 4 h unless noted otherwise.

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G. Sulfonyl Peroxides
75.0 Acetyl Cyclohexanesulfonyl Peroxide
75.0.1 CAS Number: [*3179-56-4*]

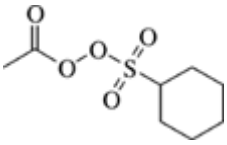
75.0.2 Synonyms: NA

75.0.3 Trade Names: NA

75.0.4 Molecular Weight: 222.2

75.0.5 Molecular Formula: $C_8H_{14}O_5S$

75.0.6 Molecular Structure:



75.1 Chemical and Physical Properties
75.1.1 General No information was located for this compound.
75.2 Production and Use
No information was located for this compound.
75.3 Exposure Assessment
75.3.1 Air No air collection method or analytic method was located for this compound.
75.4 Toxic Effects
The only toxicity data found for acetyl cyclohexanesulfonyl peroxide were as follows (7): It had an oral LD_{50} of >4640 mg/kg, a dermal LD_{50} of >2000 mg/kg, and was classified as an eye irritant. At a concentration of 29% in dimethyl phthalate, its oral LD_{50} was 1710 mg/kg.

An acute inhalation study was performed exposing 40 rats to 25, 50, 100, and 200 mg/L of this chemical. At the lowest concentration, 25 mg/L, bloody nasal discharge and congested lungs were noted. One death was noted. The LC_{50} was judged to be 58.3 mg/L with 95% confidence limits of 46–74 mg/L (159).

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H. Silyl Peroxides

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Glycols

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1 Introduction to Class of Chemicals

The glycols are hydrocarbons that have two hydroxyl groups attached to separate carbons in an aliphatic chain or alicyclic ring. They are used as antifreeze agents, cryoprotectants, solvent carriers, chemical intermediates, and vehicles in a number of chemical formulations. They vary from slightly viscous liquids to waxy solids, are soluble in water, alcohols, and ketones, and are insoluble in hydrocarbons (1–10).

They have low vapor pressures; therefore inhalation of vapors and aerosols is of little concern unless they are heated, agitated, or sprayed. They have little or no odor; thus only their irritancy at high concentrations is a warning property (11–15).

Because of the irritant properties and the potential for central nervous system (CNS) depression at high concentrations, the threshold limit value (TLV) for glycols is generally set as a ceiling limit. The chemical and physical properties of several of the more common glycols are given in Table 85.1 (1–15).

Table 85.1. Physical and Chemical Properties of Common Glycols (Diols)

Property	Ethylene Glycol	Diethylene Glycol	Triethylene Glycol	Propylene Glycol
CAS Number	[*107-21-1*]	[*111-46-6*]	[*112-27-6*]	[*57-55-6*]

Molecular formula	$C_2H_6O_2$	$C_4H_{10}O_3$	$C_6H_{14}O_4$	$C_3H_8O_2$
Molecular weight	62.07	106.12	150.1	76.1
Specific gravity (25/4°C)	1.11	1.12	1.125 (20/20° C)	1.033
Boiling point, °C (760 mmHg)	197.4	245	287.4	187.9
Freezing point, °C	–13.4	–8.0	–4.3	–31.0
Vapor pressure, mmHg (25°C)	0.06 (20°C)	<0.01	0.001	0.13
Refractive index (25° C)	1.432		1.456	1.431
Flash point, °F (o.c.)	240	290	330	215–225
Percent in saturated air (25°C)	0.017	0.0013 (20° C)	0.00013 (20° C)	0.038
1 ppm ⇔ mg/m^3 at 25°C and 760 mmHg	2.54	4.35	6.14	3.11
1 mg/l ⇔ ppm at 25°C and 760 mmHg	365.0	230.7	162.8	321.6

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Ethers of Ethylene Glycol and Derivatives
Rodney J. Boatman, Ph.D., DABT, James B. Knaak, Ph.D.

Introduction
A. Background
There are currently seven U.S. manufacturers of ethers and other derivatives of ethylene glycol (EG), diethylene glycol (DEG), and higher glycols. Five of them are members of the American Chemistry Council (ACC) Glycol Ethers' Panel (Table 86.1).

Table 86.1. U.S. Manufacturers of Ethylene Glycol Ethers and Derivatives

Manufacturing Company	Trade Name
The Dow Chemical Company[a]	Dowanol® solvent
Eastman Chemical Company[a]	Eastman® solvent
Ferro Corporation	
Olin Chemical Corporation	Poly-solv® solvent
Equistar Chemical Company[a]	
Shell Chemical Company[a]	Oxitol solvent® (ethers of EG) Dioxitol® solvent (ethers of DG)
Union Carbide Corporation[a]	Cellosolve® solvent (ethers of EG) Carbitol® solvent (ethers of DEG)

[a] Member of the American Chemistry Council, Ethylene Glycol Ethers Panel.

B. Production and Use
The glycol ethers most commonly encountered industrially are colorless liquids that have mild ethereal odors. Alkyl glycol ethers are manufactured in a closed, continuous process by reacting ethylene oxide with an anhydrous alcohol in the presence of a suitable catalyst. Depending on the

molar ratios of the reactants and other process parameters, the product mixtures obtained contain varying amounts of the monoethylene-, diethylene-, triethylene-, and higher glycol ethers. Typically, the products in these mixtures are separated and purified by fractional distillation. Ethylene-based glycol ether production capacity in 1996 was about 1500 million lb. In 1995, output of the butyl ether of ethylene glycol, the most widely produced glycol ether was about 413 million lb (1).

The miscibility of most of these ethers with water and with a large number of organic solvents makes them especially useful as solvents in oil–water compositions. Their relatively slow rate of evaporation also makes them useful as solvents and coalescing agents in paints (2). Other uses include inks, cleaners, chemical intermediates, process solvents, brake fluids, and deicers (2). The ethers of the higher glycols are used as hydraulic fluids. An estimate of the U.S. production and use of representative ethylene glycol ethers is presented in Table 86.2. Production of ethylene glycol ethers (total) in Western Europe amounted to 245 thousand metric tons in 1995 (1). Japanese production of ethylene glycol ethers (total) amounted to 59.5 thousand metric tons in 1995 (1). Lesser amounts of glycol ethers are also produced in Brazil, Canada, and Eastern Europe (1).

Table 86.2. Ethylene Glycol Ethers and Ether Acetates: Production Volumes and Uses i

Chemical	Company Trade Name	CAS Number	Production Volume (10^6 lbs)	Type of Consumer End Products	Consumer Products Volume (10^6 lbs)	Consumer Products (% of Production)	Consu Prod (App Wei %
Ethylene glycol monomethyl ether (EGME)	Methyl Cellosolve® Solvent Glycol Ether EM	[*109-86-4*]	15	None			
Ethylene glycol monoethyl ether (EGEE)	Cellosolve® Solvent Glycol Ether EE	[*110-80-5*]	32	None			
Ethylene glycol monoethyl ether acetate (EGEEA)	Glycol Ether EE Acetate	[*111-15-9*]	< 30	None			
Ethylene glycol monobutyl ether (EGBE)	Eastman® EB Solvent	[*111-76-2*]	408.5	Paints/coatings	51	12.5	2–25
	Butyl Cellosolve® Solvent			Cleaners	74	18.1	0.1–2
	Dowanol® EB			Solvent	34.3	8.4	—
	Butyl Oxitol® EB			Polishes	0.1	0.2	5–10
	Glycol Ether EB						
Ethylene glycol monobutyl	Eastman EB Acetate Butyl	[*112-07-2*]	15.6	Paints/coatings	0.1	0.6	5–25

ether acetate (EGBEA)	Cellosolve® Acetate Glycol Ether EB Acetate		Solvent	0.3	1.9	—
Ethylene glycol monopropyl ether (EGPE)	Eastman® EP Solvent	[*2807-30-9*] <15	Paints/coatings	< 1	0.7	10–20
	Propyl Cellosolve® Solvent *n*-Propyl Oxitol		Solvents	< 1	4.0	—
			Cleaners	< 1	2.0	1–10
Ethylene glycol monophenyl ether (EGPhE)	Dowanol® EPH	[*122-99-6*] <20	Paints/coatings	< 10	37.5	5–15
			Cleaners	< 5	19.0	5–15
			Dyes	< 1	6.5	5–15
Ethylene glycol monohexyl ether (EGHE)	Hexyl Cellosolve® Solvent	[*112-25-4*] <10	Cleaners	< 5	50.0	0.1–3
Diethylene glycol mono-methyl ether (DGME)	Eastman® DM Solvent	[*111-77-3*] 69.5	Paints/coatings	5.6	8.0	0.1–2(
	Methyl Carbitol® Solvent Dowanol® DM Glycol Ether DM		Solvents	0.1	0.1	—
Diethylene glycol monoethyl ether (DGEE)	Eastman® DE Solvent	[*111-90-0*] 33	Hair colorant	1.3	3.9	1–10
	Carbitol® Solvent-low gravity		Floor polish	4.7	14.2	2–10
			Paints/coatings	0.1	0.3	10–20
	Glycol Ether DE		Cleaners	0.2	0.6	1–10
			Solvents	0.2	0.6	—
Diethylene glycol monoethyl ether acetate (DGEEA)	Eastman® DE Acetate	[*112-15-2*] <5	Solvents	< 1	7.0	—
Diethylene glycol monobutyl ether (DGBE)	Eastman® DB Solvent	[*112-34-5*] 101.5	Paints/coatings	26	25.6	2–20
	Butyl Carbitol® Solvent		Cleaners	18.5	18.2	1–20
	Dowanol® DB		Solvents	1.8	1.8	—
	Butyl Dioxitol®		Brake fluids	5.5	5.4	10–65
	Glycol Ether DB					
Diethylene glycol	Eastman® DB Acetate	[*124-17-4*] 9.9	Paints/coatings	0.9	9.1	1–75

monobutyl ether acetate (DGBEA)	Butyl Carbitol® Acetate Glycol Ether DB Acetate			Solvents	0.6	6.1	—
Diethylene glycol monopropyl ether (DGPE)	Eastman® DP Solvent	[*6881-94-3*]	<5	Floor polish	< 1	10.0	2–10
				Brake fluids	< 5	60.0	10–65
Diethylene glycol monohexyl ether (DGHE)	*n*-Hexyl Carbitol® Solvent	[*112-59-4*]	<5	Cleaners	< 5	30.0	0.1–3
Triethylene glycol methyl ether (TGME)	Methoxytriglycol Glycol Ether TM	[*112-35-6*]	27	Brake fluids	19.8	73.3	20–70
Triethylene glycol ethyl ether (TGEE)	Ethoxytriglycol Glycol Ether TE	[*112-50-5*]	7.2	Brake fluids	2.2	30.6	10–65
Triethylene glycol butyl ether (TGBE)	Butoxytriglycol Glycol Ether TB	[*143-22-6*]	38.9	Brake fluids	31.4	80.7	10–65
Triethylene glycol monopropyl ether (TGPE)		[*23305-64-8*]	<5	Brake fluids	< 5	100.0	10–65

[a] This information was compiled by the Chemical Manufacturers Association, Ethylene Glycol Ethers Panel.

C. Occupational Exposure

Occupational exposure to glycol ethers occurs dermally and by inhalation. Ingestion is not a concern in industrial exposure, although some cases of intentional ingestion of consumer products containing ethylene glycol ethers have been reported. Several review articles were recently published dealing with house painters' exposure to glycol ethers in water-based paints (3) and exposure of workers in the semiconductor industry to glycol ethers during manufacturing (4–12).

Analytical Methods

A number of analytical methods have been published that are suitable for detecting glycol ethers in environmental air samples (13). These methods rely principally on adsorption onto activated charcoal or other suitable material followed by desorption and gas chromatographic analysis. Lower limits of detection generally range from 0.1 to 2 ppm in air depending on the specific analytical method employed and on the gas sampling procedure used. Typical methods include NIOSH method 1403 (14) and OSHA method 83 (15). A typical example is an industrial hygiene monitoring method developed by Dow Chemical Company (16) that can analyze for nine airborne glycol ethers: ethylene glycol methyl ether (EGME), ethylene glycol ethyl ether (EGEE), ethylene glycol phenyl ether (EGPhE), ethylene glycol butyl ether (EGBE), diethylene glycol methyl ether (DGME), diethylene glycol ethyl ether (DGEE), diethylene glycol phenyl ether (DGPhE), diethylene glycol

butyl ether (DGBE), triethylene glycol methyl ether (TGME), and triethylene glycol phenyl ether (TGPhE), collected on charcoal or silica gel using an air pump. The procedure involves pulling air that contains the volatile glycol ethers through charcoal or silica gel adsorbent tubes for periods of time up to 8 h. The adsorbed glycol ethers are desorbed from charcoal using water/CS_2 and from silica gel using a 25/75% mixture of methanol/water. The aqueous layer is analyzed for glycol ethers by gas chromatography using a flame-ionization detector (GC-FID). A 3.3 ft × 2 mm i.d., glass column, packed with 5% SP-1000 on 60/80 mesh Carbopack B may be used for the analysis or the packed column may be substituted with a SPB-1000 (Supelco, Inc., Bellefonte, PA) capillary column (30 m × 0.53 mm i.d., 0.5 mm film thickness). Supelco (17) recommends using a Nukol® fused silica capillary column for glycols (15 m × 0.53 mm i.d., 0.5 mm film). Water can be directly injected into this column. The column may be used to separate free acids, phenols, glycol ethers, and glycols dissolved in water. Several other similar capillary columns would also be suitable for this analysis.

Eckel et al. (18) reported the presence of glycol ethers in groundwater samples from hazardous waste sites. These authors point out that the general-purpose USEPA methods (GC/MS) used for either volatile or semivolatile pollutants may underestimate the true amounts of glycol ethers in environmental samples. This is due to the inefficiency of either the common purge-and-trap or solvent extraction methods for isolating glycol ethers. These authors suggest that more appropriate techniques would involve direct aqueous injection, extractive alkylation or salting-out extraction with derivatization.

D. Pharmacokinetics, Metabolism, and Mechanism of Action

Pharmacokinetics—Absorption

Inhalation Glycol ethers as a class are polar solvents that have generally low volatility and higher boiling points than most comparable solvents. Respiratory retention of glycol ethers is high and accounts for 50 to 80% of inhaled amounts due to high blood/air partition coefficients (i.e., 34913 for EGME) in lungs. Inhalation of 5.13 ppm EGME at the Occupational Exposure Limit (OEL) concentration of 16 mg/m^3 for 8 h resulted in an uptake of 57 mg in human volunteers at rest (19). Work (50 W, 100 W, 150 W) results in an increase in respiratory volume and the inhalation and retention of substantially larger amounts of volatile glycol ethers (EGME, EGEE, and EGBE).

Dermal—Liquid Glycol ethers (neat) are absorbed by the dermal route, and 0.2 to 3% of topically applied EGME is absorbed by humans under occlusive conditions (area (27 cm^2) × concentration (1.0 g/cm^3) × K_p (28.9×10^{-4} cm/h) × time (10 h) = 780 mg absorbed; 780 mg/27000 mg applied × 100 = 2.9%) (19). The amount absorbed is determined by the exposed area, applied concentration, permeation constant (K_p), and total contact time. Microgram quantities are absorbed per cm^2 of skin per h from concentrations (mg/cm^3) normally encountered in the work place. For those glycol ethers that have been adequately tested, dermal administrations generally result in toxicities that are similar to those following oral administrations, but require higher equivalent dermal doses and longer periods of exposure. Skin penetration is determined primarily by the stratum corneum. The *in vitro* rates of permeability of a homologous series of glycol ethers through human stratum corneum have been summarized in Table 86.3. The methyl, ethyl, and butyl ethers of diethylene and triethylene glycol are absorbed to a lesser extent than the corresponding ethers in the ethylene glycol series (20, 21). An increase in either the chain length of the alkyl substituent or in the number of ethylene glycol moieties (ethylene oxide adducts) results in a decreased rate of percutaneous absorption. It can be seen that EGME is absorbed 131 times more rapidly than the triethylene glycol butyl derivative. Increased absorption of the lower molecular weight homologues is offset by an increased rate of evaporation from the skin, as indicated by the lower boiling points for these derivatives.

Table 86.3. Permeation of Glycol Ethers Through Human Epidermis *In Vitro*[a]

Glycol Ether	Mol. Wt.	Vapor Pressure (mmHg)	Boiling Pt. (°C)	Permeation Constant (cm/h × 10^4)	Relative Rate
Ethylene glycol series:					
Methyl ether	76	9.7	124	28.9	131
Ethyl ether	90	5.75	135	8.42	38
Butyl ether	118	0.88	171	2.14	9.7
Diethylene glycol series:					
Methyl ether	120	0.18	194	2.06	9.4
Ethyl ether	134	0.14	202	1.32	6.0
Butyl ether	162	0.043	230	0.357	1.6
Triethylene glycol series:					
Methyl ether	164	<0.01	249	0.34	1.5
Ethyl ether	178	<0.01	256	0.24	1.1
Butyl ether	206	<0.01	279	0.22	1.0

[a] Taken from Refs. 20 and 21.

Dermal-Vapor Glycol ethers are absorbed through skin in accordance with the following rate equation:

[TEXnical Error]

where C is the concentration gradient of the chemical in skin (g/cm^3), l is the thickness of the skin (cm), k_m is the partition coefficient of the chemical in skin (unitless), D is the diffusion coefficient (cm^2/h), and K_p is the permeability constant (cm/h). In the case of glycol ether vapors, skin/air partition coefficients need to be determined and used in the absorption equation to account for higher concentrations in skin due to partitioning. The equation is as follows for whole body exposure at the OEL for EGME of 16 mg/m^3 (5.13 ppm): area (18,000 cm^2) × concentration (16.0 × 10^{-6} mg/cm^3) × PC (11,734) × K_p (28.9 × 10^{-4} cm/h) × time (8 h) = 78 mg absorbed (19). The combined amount (135 mg) results in a dose of 1.9 mg/kg for a 70-kg person during an 8-h workday, assuming total body contact with vapors.

Pharmacokinetics—Distribution to Tissues

Regardless of the route of administration, glycol ethers are absorbed and distributed to tissues when administered to animals whose blood/air and skin/air partition coefficients for EGME are of the order of 34,900 and 11,700. Except for adipose tissue, measured tissue to blood partition coefficients

for glycol ethers and alkoxyacetic acid metabolites are generally near unity (11700/34900 = 0.335 for EGME skin/blood). See Table 86.4. Notable exceptions include EGME and methoxyacetic acid (MAA), which attain greater concentrations in developing embryos and embryonic fluids than in plasma, and EGBE, which has an increased affinity for lung and gastrointestinal tissue (22, 23).

Table 86.4. Tissue Partition Coefficients for EGME, EGEE, and EGBE and Alkoxyacetic Acid Metabolites

	Tissue Partition Coefficients					
	EGME[a]	MAA[a]	EGEE[b]	EAA[b]	EGBE[c]	BAA[c]
Blood/air	34,913	0.99	22,093	NA	7,965	NA
Liver/blood	1.02	1.26	1.0	1.1	1.46	1.30
Fat/blood	0.05	—	0.04	0.32	2.03	0.77
Poorly perfused/blood	0.93	—	0.94	0.05	0.64	1.31
Richly perfused/blood			1.1	1.06	1.46	1.30
Placenta/blood	1.20	1.05				
Extraembryonic fluid/blood	1.48	1.33				
Embryo/blood	1.52	0.94				

[a] Clarke et al. (41).
[b] Hayes et al. (42).
[c] Corley et al. (23).

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Metabolism and Elimination
A general metabolic scheme for ethylene glycol monoalkyl ethers is summarized in Figure 86.1. Glycol ether acetates are rapidly hydrolyzed to their corresponding glycol ethers by carboxylesterases. This occurs in a variety of tissues, including blood and olfactory mucosa and as a result, both the toxicity as well as patterns of metabolic elimination are nearly identical for glycol ethers and their acetates. The parent glycol ethers are substrates for alcohol dehydrogenase (ADH) which catalyzes the conversion of their terminal alcohols to aldehydes. Further conversion by aldehyde dehydrogenase produces alkoxyacetic acids. The conversion by ADH and the resulting toxicity of the glycol ether can be blocked by pyrazole and other ADH inhibitors. Alcohol also inhibits this conversion. The higher molecular weight glycol ethers, (di- and triethylene glycol ethers), are believed to be poor substrates for ADH and are partially cleaved by the action of P-450 isozymes. Alkoxyacetic acids are significant if not major urinary metabolites of glycol ethers in both animals and humans and are the only toxicologically significant metabolites that have been detected *in vivo*. Although indirect evidence suggests that the aldehydes form under *in vivo* conditions, these have not yet been detected in whole animal studies. In animal studies, ethylene glycol has been

identified as a minor metabolite of glycol ethers. Sulfate and glucuronide conjugation of the parent glycol ethers has been reported as have the glycine (rodents) and glutamine (humans) conjugates of the alkoxyacetic acid metabolites. The formation of ethylene glycol under normal conditions of exposure is unlikely to contribute to the toxicity of glycol ethers. None of the other conjugates that have been identified has been associated with a toxicological response, and the formation of these is presumed to represent detoxification (24–26).

Ethers of Ethylene Glycol and Derivatives

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A. Ethers of Propylene Glycol

A.1 Background

There are currently five U.S. manufacturers of propylene glycol ether derivatives as shown in Table 87.1 (1). This table also contains a listing of the trade names used by these manufacturers for these materials.

Table 87.1. U.S. Manufacturers of Propylene Glycol Ethers and Tradenames

Manufacturer	Trade Name
Lyondell Chemical Company[a]	Arcosolv®
The Dow Chemical Company[a]	Dowanol®
Eastman Chemical Company[a]	Eastman®
Olin Chemical Corporation	Poly-Solv®
Union Carbide Corporation	Propasol®

[a] Members of the Chemical Manufacturers Association, Propylene Glycol Ethers Panel.

A.2 Production and Use

The ethers of mono-, di-, tri-, and polypropylene glycol are prepared commercially by reacting propylene oxide with the alcohol of choice in the presence of a catalyst. They also may be prepared by direct alkylation of the selected glycol with an appropriate alkylating agent such as a dialkyl sulfate in the presence of an alkali. When propylene oxide is used as the starting material, which is the case for most propylene glycol ethers, preparation under commercial conditions yields products that are mixtures of the a and b isomers. The a isomer consists of the ether linkage on the terminal hydroxyl group of propylene glycol; while the b isomer has the ether linkage on the secondary hydroxyl group, with the primary hydroxyl group unsubstituted. The a isomer is thermodynamically favored during synthesis from propylene oxide and the desired alcohol; thus, it constitutes the bulk of the resulting ether. By further manipulating the conditions of synthesis, the proportion of a isomer may be enhanced to constitute >99% of the end product. As explained later, this distinction is important regarding the toxicity of the propylene glycol ethers. The a and b isomers are shown below, where “R” represents the desired alcohol portion of the propylene glycol ether.

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B. Ethers of Butylene Glycol

B.1 Source, Uses, and Industrial Exposure
The methyl, ethyl, and *n*-butyl ethers of butylene glycol considered herein are prepared by reacting the appropriate alcohol with so-called straight-chain butylene oxide, consisting of about 80% 1,2 isomer and about 20% 2,3 isomer in the presence of a catalyst. They are colorless liquids with slight, pleasant odors. The methyl and ethyl ethers are miscible with water, but the butyl ether has limited solubility. All are miscible with many organic solvents and oils; thus they are useful as mutual solvents, dispersing agents, and solvents for inks, resins, lacquers, oils, and greases. Industrial exposure may occr by any of the common routes.

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C. Esters, Diesters, and Ether Esters of Glycols
C.1 Sources, Uses, and Industrial Exposure
The common esters and diesters of the polyols are prepared commercially by esterifying the particular polyol with the acid, acid anhydride, or acid chloride of choice in the presence of a catalyst. Mono- or diesters result, depending on the proportions of each reactant employed. The ether esters are prepared by esterifying the glycol ether in a similar manner. Other methods can also be used (142).

The acetic acid esters have remarkable solvent properties for oils, greases, inks, adhesives, and resins. They are widely used in lacquers, enamels, dopes, and adhesives to dissolve the plastics or resins. They are also used in lacquer, paint, and varnish removers.
C.2 Physical and Chemical Properties
All the esters and ether esters of organic acids are colorless volatile liquids. Generally the odors are mild, sometimes fruity, and they all have a bitter taste. See Tables 87.10 and 87.11 for additional properties.

Table 87.10. Physical and Chemical Properties of Esters of Various Glyc

Property	**Ethylene Glycol**		**Triethylene Glycol Diacetate**	**2-Methyl-2-propene-1,1-diol Diacetate**	**2,2-Dimethyl-1,3-propanediol Diacrylate**	**2-Methyl-2,4-pentanediol Diacetate**	**2,2,4-T 1,3-pe Monoi**
	Acetate	**Diacetate**					
CAS no.	[*542-59-6*]	[*111-55-7*]	[*111-21-7*]	[*10476-95-6*]	[*2223-82-7*]	[*1637-24-7*]	[*252*
Molecular formula	$C_4H_8O_3$	$C_6H_{10}O_4$	$C_{10}H_{18}O_6$	$C_8H_{12}O_4$	$C_{11}H_{16}O_4$	$C_{10}H_{18}O_4$	C_{12}
Molecular weight	104.11	146.14	234.25	172.18	212.25	202.2	2
Specific gravity 25/4°C	1.108	1.128	1.117 (20/20°C)	1.051 (20/20°C)	1.030 (20/20°C)	1.000 (20/20°C)	0.95 (
Boiling point (°C) (760 mmHg)	181–182	187	300				
Freezing point (°C)		–41	<–50				
Vapor pressure		0.25	<0.01			0.07 (20°C)	

(mmHg) (25°C)							
Refractive index (25°C)	1.422	1.416	1.439 (20° C)			1.423 (20° C)	
Flash point (°F) (open cup)	215	82°C (closed cup)	174	215	253	235	
Vapor density (air = 1)	3.6	5.0	8.1				
Percent in saturated air (25°C)		0.044	10^{-6}				
1 ppm ≈ mg/m^3 at 25°C, 760 mmHg	4.25	5.98	9.58	7.03	8.68	8.25	
1 mg/L ≈ ppm at 25°C, 760 mmHg	235	168	104.3	142.0	115.2	121.0	1

Table 87.11. Physical and Chemical Properties of Acetate Esters of Certain Propylene Glycol Ethers

Property	Propylene Glycol, Methyl	Propylene Glycol, Ethyl	Dipropylene Glycol, Methyl	Tripropylene Glycol, Methyl
CAS no.	[*108-65-6*]	[*54839-24-6*]	[*88917-22-0*]	None found
Molecular formula	$C_6H_{12}O_3$	$C_7H_{14}O_3$	$C_9H_{18}O_4$	$C_{12}H_{24}O_5$
Molecular weight	132.16	146.19	190.24	248.2
Melting point (°C)		–89		
Specific gravity 25/4°C	0.969			
Boiling point (°C) (760 mmHg)	145.8	158–160	209	258
Vapor pressure (mmHg) (25°C)	1.8	2.03 (20°C)		
Refractive index (25°C)	1.400			
1 ppm ≈ mg/m^3 at 25°C, 760 mmHg	5.40	6.09 (at 20°C)	7.77	10.15
1 mg/L ≈ ppm at 25°C, 760 mmHg	185		128.6	98.5

C.3 Determination in the Atmosphere

The choice of methods for the determination of esters, diesters, and ether esters of various glycols vary with existing conditions. Gas chromatography would seem to offer the best means not only of resolving mixtures of vapors but also of identifying components. Mass spectrometry may also be used. Chemical methods such as proposed by Morgan (143) for esters or ether esters may be useful where spectroscopic equipment is not available.

C.4 Summary of Toxicology

Generally speaking, the fatty-acid esters of the glycols and glycol ethers, in either the liquid or vapor state, are more irritating to the mucous membranes than those of the parent glycol or glycol ethers. However, once absorbed into the body, the esters are hydrolyzed and the systemic effect is quite typical of the parent glycol or glycol ethers. Lepkovski et al. (144), in studies with higher fatty acids of glycols, concluded that the fatty acids were liberated and used nutritionally. Furthermore, they observed in rats that severe injury to the tubular epithelium of the kidneys occurred when the esters of ethylene glycol and diethylene glycol were administered, but not when equivalent amounts of fatty esters of propylene glycol, glycerol, ethyl alcohol, methyl alcohol, or the free fatty acids themselves were given. Shaffer and Critchfield (145), in studies with polyethylene glycol 400 monostearate, concluded that it was low in toxicity and also could be utilized nutritionally.

It should be noted that the nitric acid esters of glycols are highly toxic and exert a physiological action quite different from that of the parent polyols. These materials are covered in Section D of this chapter.

Table 87.12. Occupational Exposure Guidelines for Propylene Glycol Monoacrylate[a]

Regulatory or Expert Authority (Date)	Exposure Value	Comment/Notation
ACGIH (TLV) (1997)	TWA = 0.5 ppm	Skin
NIOSH (REL) (1994)	TWA = 0.5 ppm	Skin
Australia (OEL) (1993)	TWA = 0.5 ppm	Skin
Belgium (OEL) (1993)	TWA = 0.5 ppm	Skin
Denmark (OEL) (1993)	TWA = 0.5 ppm	Skin
France (OEL) (1993)	TWA = 0.5 ppm	Skin
Netherlands (OEL) (Oct-1997)	TWA = 0.5 ppm	Skin
Russia (OEL) (1993)	STEL = 1 mg/m^3	Skin
Switzerland (OEL)	TWA = 0.5 ppm	Skin

(1993)		
United Kingdom (OEL) (1993)	TWA = 0.5 ppm	Skin

[a] The OEL values set by Bulgaria, Colombia, Jordan, Korea, New Zealand, Singapore, and Vietnam are based on the ACGIH value.

D. Nitrate Esters of Ethylene and Propylene Glycols

The nitric acid esters of glycols are not typical of the esters or ether esters of organic acids and are considered separately in this chapter. They are used as explosives, usually in combination with nitroglycerin, to reduce the freezing point.

Industrial exposures of consequence are most likely to occur through the inhalation of vapors, but may also occur through contact with the eyes and skin. With the dinitrate, a serious hazard exists from absorption through the skin.

Table 87.13. Physical and Chemical Properties of Sone Glycol Dinitrates

Property	Ethylene Glycol Dinitrate	Diethylene Glycol Dinitrate	Triethylene Glycol Dinitrate	Propyl Glycol Dinitrate
CAS no.	[*628-96-6*]	[*693-21-0*]	[*111-22-8*]	[*6423-43-4*]
Common designation	EGDN, EGN	DEGDN	TEGDN	PGDN
Molecular formula	$C_2H_4N_2O_6$	$C_4H_8N_2O_7$	$C_6H_{12}N_2O_8$	$C_3H_6N_2O_6$
Molecular weight	152.1	196.1	240	166
Specific gravity (25/4°C)	1.491	—	—	1.4
Boiling point, °C (760 mm Hg)	Explodes	—	—	92 (10 mm Hg)
Vapor pressure, mm Hg (25°C)	0.072	—	—	0.07 (22.5°C)

Vapor density (air = 1	5.24	—	—	—
Percent in saturated air (25° C)	0.0095	—	—	—
1 ppm ~ mg/m^3 at 25°C, 760 mm Hg	6.24	8.02	9.82	6.79
1 mg/L ~ ppm at 25°C, 760 mm Hg	160.9	124.7	101.9	147.3

Table 87.14. Occupational Exposure Guidelines of EGDN[a]

Regulatory or Expert Authority (Date)	Exposure Value	Comment/Notation
ACGIH (TLV) (1997)	TWA = 0.05 ppm	Skin
NIOSH (1994)	STEL = 0.1 mg/m^3	Skin
OSHA (1994)	PEL = 0.2 ppm	Skin
Australia (OEL) (1993)	TWA = 0.05 ppm	Skin
Belgium (OEL) (1993)	TWA = 0.05 ppm	Skin
Denmark (OEL/TWA) (1993)	STEL = 0.02 ppm	Skin
Finland (OEL) (1993)	TWA = 0.1 ppm STEL = 0.3 ppm	Skin
France (OEL/TWA) (1993)	0.25 ppm	Skin
Germany (MAK/TWA) (1993)	0.05 ppm	Skin
Japan (JSOH) (1998)	TWA = 0.05 ppm	Skin
Netherlands (OEL/TWA) (Oct. 1997)	TWA = 0.05 ppm	Skin
Philippines (OEL) (1993)	TWA = 0.2 ppm	Skin
Russia (OEL) (1993)	TWA = 0.05 mg/m^3	
Sweden (OEL) (1993)	TWA = 0.1 ppm STEL = 0.3 ppm	Skin
Switzerland (OEL) (1993)	TWA = 0.05 ppm STEL = 0.1 ppm	Skin
Thailand (OEL) (1993)	TWA = 0.2 ppm	
Turkey (OEL) (1993)	TWA = 0.2 ppm	Skin
United Kingdom (OEL) (1993)	TWA = 0.2 ppm STEL = 0.2 ppm	Skin

[a] The OEL values set by Bulgaria, Colombia, Jordan, Korea, New Zealand, Singapore, and Vietnam are based on the ACGIH value.

Table 87.15. Acute Toxicity of Triethylene Glycol Dinitrate in Laboratory Animals

Species	Sex	Administration Route	LD_{50} (mg/kg)
Mouse	M	IP	945
Guinea pig	M	IP	700
Rat	M	IP	796
Rat	M	SC	2520
Rat	M	Oral	1000

Table 87.16. Acute Toxicity of Propylene Glycol Dinitrate in Laboratory Animals Following Injection

Species	Sex	Route of Injection	LD_{50} (g/kg)	Ref.
Rat	F	SC	0.463	232
	M	SC	0.524	232
	M	SC	0.53	228
Mouse	F	SC	1.21	232
Cat	F	SC	0.2–0.3	232
Mouse		IP	0.93	232
Mouse	M	IP	1.05	228
Guinea pig	M	IP	0.40	228
Rat	M	IP	0.48	228

Table 87.17. Occupational Exposure Guidelines for Exposure to PGDN[a]

Regulatory or Expert Authority	Exposure Value	Comment/Notation
ACGIH (TLV) (1997)	TWA = 0.05 ppm	Skin
NIOSH (1994)	TWA = 0.05 ppm	Skin
Australia (OEL) (1993)	TWA = 0.05 ppm	Skin
Belgium (OEL) (1993)	TWA = 0.05 ppm	Skin

Denmark (OEL) (1993)	TWA = 0.02 ppm	Skin
Finland (OEL) (1993)	TWA = 0.02 ppm	Skin
	STEL = 0.06 ppm	
France (OEL/TWA) (1993)	0.05 ppm	Skin
Germany (MAK/TWA) (1993)	0.05 ppm	Skin
Netherlands (OEL/TWA) (1993)	TWA = 0.05 ppm	Skin
Sweden (OEL) (1993)	TWA = 0.1 ppm	Skin
	STEL = 0.3 ppm	
Switzerland (OEL) (1993)	TWA = 0.05 ppm	Skin
United Kingdom (OEL) (1993)	TWA = 0.2 ppm	Skin
	STEL = 0.2 ppm	

[a] The OEL values set by Bulgaria, Colombia, Jordan, Korea, New Zealand, Singapore, and Vietnam are based on the ACGIH value.

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Synthetic Polymers

Bailus Walker, Jr., Ph.D., MPH, Laureen Burton, MPH

Introduction

Polymers are among the oldest chemicals known to humans. Since ancient times, natural polymers, including silk, wool, rubber, and cellulose, have been known and exploited. For a century and a half now, synthetic fibers, plastics, and modified natural polymers have been part of everyday life. The

early history of these materials is being documented, and new generations are being taught about their production and fabrication. In the United States, a number of institutions have been established to preserve and transmit knowledge of polymer technology. Natural polymers such as proteins occupy a central position in the architecture and function of living matter. Nucleic acid polymer, called deoxyribonucleic acid (DNA), automatically controls the formation of another nucleic acid, ribonucleic acid (RNA), that controls the formation of a specific protein. These natural polymers are increasingly important, especially in agriculture and medicine, and much has been written about them. They are not considered here.

Many of the general considerations discussed in the chapters on synthetic polymers in the fourth edition of *Patty's Industrial Hygiene and Toxicology* are still applicable. To update those portions that need alteration, literature since 1994 when the fourth edition was published has been searched using primarily the National Library of Medicine's Hazardous Substances Data Bank (HSDB) and ToxLine. Other sources including the polymer science literature were reviewed for useful information. However, there has been no intent to compile an exhaustive bibliography. References to the multiple dimensions of synthetic polymers are so numerous that it has been necessary to limit citations to those that are most useful to understanding and controlling the toxicological problems of polymers in the occupational environment.

The Polymer Industry

Perhaps no other aspect of the chemical industry has grown as rapidly as synthetic polymers. Each year since 1868 when cellulose nitrate was first introduced, new commercial polymers have been produced for a broad range of industrial and nonindustrial applications. Prominent examples include polyvinyl chloride which was introduced in 1927, ethyl cellulose in 1931, fluoropolymers in 1943, acrylonitrile-butadiene-styrene (ABS) in 1948, polypropylene in 1957, and polyisoprene in 1962.

In the 1970s and 1980s, engineering polymers made their mark by replacing traditional materials such as metals, rubber, automotive glass, electronics, and other materials. During the decade of the 1980s, the polymer industry's focus shifted to developing blends and alloys of existing polymers. In the 1990s, new products were rapidly developed, as manufacturers capitalized on developments in metallocene catalysis and other new chemistry. A manufacturer using metallocene catalysis transformed polystyrene—an amorphous, low melting point, relatively brittle plastic—into a tough crystalline material that has a melting point of 270°C, and employs the same styrene monomer. Medical and diagnostic containers are expected to benefit from another promising new cycloolefin copolymer, which is expected to be produced in large quantities by mid-2000. The copolymer's clarity, stiffness, and moisture and shatter resistance should make it attractive for pharmaceutical packaging, where moisture resistance is needed. It will also be useful in cut-produce packaging where the copolymer's high oxygen permeability is a desirable property.

Synthetic Polymers

Bailus Walker, Jr., Ph.D., MPH, Laureen Burton, MPH

Introduction to class of chemicals

Olefin Resins

Olefin is a class of unsaturated hydrocarbon, obtained by cracking naphtha or other petroleum fractions at high temperatures. The simplest members are ethylene, propylene, and butylene which are the starting points for certain resins.

The commercial development of polyethylene began in the 1930s and was followed by full-scale production of the major olefin resins during the 1940s and through the 1960s. Polyethylene and other olefins are closely related to paraffins. As a class, these resins have very low water absorption, moderate to high gas permeability, good toughness and flexibility at low temperatures, and relatively

low heat resistance. Environmental stress cracking is greater with polyethylene, whereas polypropylene is more susceptible to oxidation. Polyethylene cross-links on oxidation, whereas polypropylene degrades to form lower molecular weight products. Typical properties are given in Table 88.1.

Table 88.1. Physical Constants of Selected Polymers

Compound	CAS	Molecular Formula	Molecular Weight	Boiling Point (°C)	Specific Gravity	Melting Pt (°C)	Sol in Water (at 68F) mg/ml	Refractive Index (20° c)	V Pı (n
Polyethylene	[*9002-88-4*]	$(C_2H_4)_n$	28.054	—	0.92	130–145	—	1.51–1.54	
Polypropylene	[*9003-07-0*]	$(C_3H_6)_n$	42.080	—	0.89–0.94	160–171	—	1.49	
Polybutylene	[*9003-29-6*]	$(C_4H_8)_n$	56.107	—	0.87–0.95	124–135	—	—	

Toxicological Potential
Monomer residue has not been considered a problem. Ethylene, propylene, and 1-butene monomers act toxicologically as asphyxiant gases. Ethylene is a natural constituent of apples and other fruit and is used commercially to accelerate ripening of fruit. Low molecular weight additives or impurities may be of concern if significant migration of these materials into food or water is possible.

Synthetic Polymers

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Synthetic Polymers—Olefin, Diene Elastomers, and Vinyl Halides
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Introduction
Elastomers, also called rubber, can withstand considerably greater deformation than other materials and uniquely return essentially to their original shape even after substantial deformation. A familiar example is the behavior of a stretched rubber band after its release. All elastomers are composed of long macromolecular chains that assume a random coil conformation when undeformed (1). Deformation causes these coils to straighten out. Upon being allowed to relax, an elastomer returns essentially to its original shape because the chains reassume their random conformation.

The first elastomer identified, natural rubber, was described by Columbus as a ball that bounced. More practical early applications included primitive waterproof clothing and the rubber tires made for the carriage of Queen Victoria in 1846. Although the first specialty elastomers, polysulfides and polychloroprene, were commercialized in the 1930s, natural rubber was the major industry product until World War II, when styrene-butadiene rubber (SBR) and acrylonitrile-butadiene rubber (NBR) were established as important synthetic rubbers.

From these early beginnings, the elastomer industry grew rapidly to a global elastomer demand of 15 million metric tons in 1990 (2). The range and diversity of synthetic rubber becomes evident upon reviewing the Synthetic Rubber Manual (3) that describes both thermosetting elastomers (TSE) and thermoplastic elastomers (TPE).

TSE and TPE exhibit important similarities. The most useful properties are the result of their long molecular chains linking to one another to form a three-dimensional network. In TSE this network is linked together with essentially irreversible cross-links. Vulcanization is the process of forming these cross-links, most typically using sulfur as the cross-linking agent.

In contrast, the attachments between chains in TPE can be reversibly broken and re-formed by heating the TPE. This feature permits the direct recycling of scrap TPE by molding and other shaping processes. This is the principal difference in properties between TSE and TPE; the

irreversible sulfur links of TSE cause the polymer to break down when sufficiently heated, whereas the TPE can be reliably reprocessed.

TPEs are generally provided as pellets to rubber product manufacturers. Although additives might be incorporated into the pellets by the manufacturer (a process called compounding) of the final product, the TPE pellets are usually converted directly into products. This differs from typical practice with TSE.

TSE generally arrives at the rubber fabricators in bales. Ten or more ingredients might be added to the bale in heavy mixers before the compounded elastomer is shaped into a product and vulcanized. Schunk (4) has characterized the health hazards of many of these ingredients, including carbon blacks, mineral fillers, plasticizers, protective and cross-linking agents, and accelerators. Broadly considered, these health hazards can be considered in terms of the following:

1. monomers, solvents, and other materials used to prepare elastomers
2. storage and handling of elastomer (bales, pellets, and powder)
3. processing of elastomers, generally at high temperatures
4. finished rubber product

Health hazards in processing, and storage and handling elastomers are the dominant focus of this section; limited references will be made to the other two areas where appropriate.

Certain portions of the material refer to monomer toxicology and epidemiology because some of the monomers used in manufacturing elastomers remain at low levels in the polymer. A full discussion of the toxicity of monomers is beyond the scope of this chapter.

Table 89.1 lists some typical basic properties of certain elastomers. Properties within a given class of elastomers can vary significantly. For example, increasing acrylonitrile content in NBR reduces swelling of the NBR caused by some oils and solvents. Figure 89.1 gives comparative properties of various elastomers.

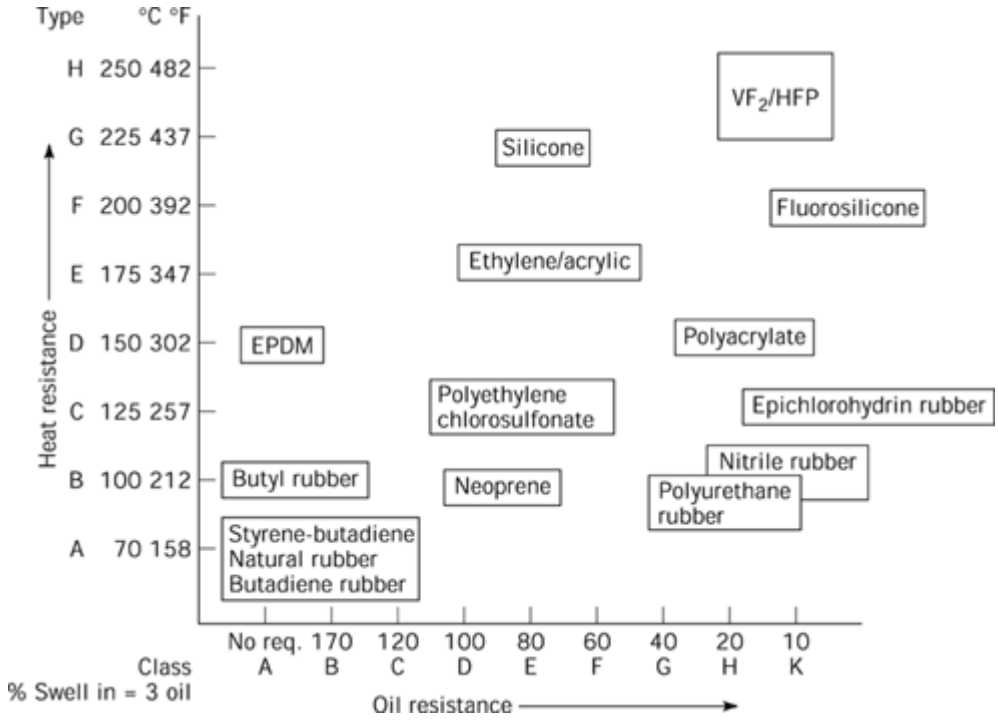

Figure 89.1. Heat and oil resistance of various elastomers (courtesy of D. H. Geschwind, DuPont Company, Inc., Polymer Products Department, Wilmington, Delaware.

Compound	CAS	Molecular Formula	Molecular Weight 68.118	Boiling Point (°C)	Specific Gravity
Polyisoprene	[*9003-31-0*]	$(C_5H_8)_n$	NR<100,000–4,000,000 IR 700,000–>1,600,000	—	0.90–0.93
Styrene-butadiene	[*9003-55-8*]	$(C_{12}H_{14})_n$	158.24	—	0.94
cis-Polybutadiene	[*9003-17-2*]	—	420,000	—	0.89–0.94
Ethylene propylene copolymer	[*9010-79-1*]	$[(C_2H_4)_x—(C_3H_6)_y]_n$	100,000–500,000	—	—
Acrylonitrile butadiene copolymer	[*9003-18-3*]	$[(CNC_2H_3)_x—(C_4H_6)_y]_n$	20,000–10^6	—	—
Vinylidene fluoride-hexafluoro propylene	[*9011-17-0*]	$[(CH_2CF_2)_x—(CF_2CF\text{-}CF_3)_y]_n$	—	—	1.8
Chlorosulfonated polyethylene	[*68037-39-8*]	$[(C_5H_9ClC_2H_4)_x—(CH_2CHSO_2—Cl)]_n$	—	—	1.28
Butyl rubber	[*9010-85-9*]	$[(C_4H_8)_x—(C_5H_8)_y]_n$	400,000–600,000	—	0.92
Perfluoro rubber	—	$[(C_2F_4)_x—(CF_2CF—OCF_3)_y—(CF_2CF—ORx)_z]_a$ Rx=$(CF_2)_nCN$; CO_2H; SO_2F;$CF_2(CFO—CF_3)—C_6F_5$	—	—	2.02
Acrylic elastomer	[*9003-32-1*]	$[(C_2H_4)_x—(CH_2CHO—OR)_y]_n$	95,000	—	—
Chlorinated polyethylene	—	$(C_2H_3—Cl—C_2H_4)_n$	—	—	—
Epichlorohydrin	[*106-89-8*]	$(C_3H_5ClO)_n$	92.525	117.9	1.181–1.183
Silicone	[*63148-62-9*]	$(C_4H_{12}O_3Si_3)$	—	—	0.963
Polyurethane elastomers	[*9009-54-5*]	$[C_3H_8N_2O]_n$	88.1	—	—
Polyvinyl chloride	[*9002-86-2*]	$(C_2H_3Cl)_n$	62,499	—	1.4
Polyvinylidene chloride	[*9002-85-1*]	$(C_2H_3Cl_2)_n$	20,000–50,000	—	—

Vinylidene chloride vinyl chloride	[*9011-06-7*]	$(C_4H_5Cl_3)_n$	—159.44	—	—
Vinylidene chloride-methyl acrylate	[*25038-72-6*]	—	—	—	—
Vinylidene chloride acrylonitrile	[*9010-76-8*]	—	—	—	—
Polyvinyl fluoride	[*24981-14-4*]	$(C_2H_3F)_n$	46.044	—	1.38–1.44
Polytetrafluoroethylene	[*9002-84-0*]	$(C_2F_4)_n$	—, 100.02	—	2
Fluorinated ethylene propylene copolymer	[*25067-11-2*]	$[(C_2F_4)_x—(C_2H_4)_y]_n$	—	—	—
Perfluoroalkoxy copolymer	[*26655-00-5*]	$[(CF\{OR_f\}CF_2)_x—(C_2F_4)_y]_n$ OR_f = perfluoroalkoxy group	—	—	—
Ethylene tetrafluoro-ethylene copolymer	[*54302-05-5*]	$[(C_2F_4)_x—(C_2H_4)_y]_n$	—	—	1.70
Polyvinylidene fluoride	[*24937-79-9*]	—	300,000–600,000	—	1.75–2.02
Polychloro-trifluoro-ethylene	[*9002-83-9*]	$(CF_2—CFCl)_n$	—	—	—
Ethylene chloro-tri-fluorethylene copolymer	[*25101-45-5*]	—	—	—	—

Most rubber is sold raw or uncured as a solid or liquid latex. The basic steps in the manufacture of some types of dry synthetic rubber are polymerization, coagulation, washing, and drying. The basic steps in producing a latex are polymerization, stabilization, and usually, concentration. A latex is defined as a stable aqueous dispersion that contains discrete polymer particles about 0.05 to 5 mm in diameter (5).

Emulsion polymerization systems contain water, monomer(s), initiator, and anionic or cationic surfactants. Solution polymerization with stereospecific catalysts involves reacting one or more monomers in an inert solvent; system conditions can be controlled to maximize a desired isomer arrangement in the polymer.

Antioxidants are generally added for shelf, processing, and in-service stability. Unsaturation of the components in the polymer chain correlates with sensitivity to oxidation. For example, among synthetic rubbers, butadiene and isoprene polymers are much more sensitive to oxidation than ethylene-propylene polymers. Natural rubber contains some natural antioxidants from rubber trees.

Vulcanization is usually done with sulfur, sulfur-containing compounds, or peroxides, but it may also be accomplished with other compounds that yield free radicals at curing temperature or by radiation. Various supplementary materials such as cure accelerators, cure retarders, or reinforcing agents are commonly part of the compounding recipe. Vulcanization ideally begins when the elastomer assumes its final shape in a mold. The elastomer type and its viscosity significantly affect molding behavior (6).

Analysis and Specifications

Measurements to determine the amounts of residual monomer have been of particular interest (7–9). Residual butadiene, acrylonitrile, and styrene can be determined in solid rubber to <1 ppm (by

weight, w/w) by headspace gas chromatography (9). Butadiene monomer in 0.1 g samples of latex can be measured by gas chromatography with a detection limit of 50 ppm (10). A gas chromatographic/mass spectrometric method to identify volatile materials released during simulated vulcanization at 160 to 200°C has been reported (11); the polymers tested were *cis*-polybutadiene, styrene-butadiene, and a blend of these two. Pyrolysis/mass spectrometry (samples <5 mg) has been used to distinguish among adhesives based on natural rubber, styrene-butadiene, and polychloroprene (12). More recent work has helped to unravel some of the complexities of ingredient–emission relationships through computerized analysis of emissions from vulcanized rubber (13).

Residual acrylonitrile in nitrile rubber reportedly varies from "nondetectable to something less than 100 ppm" (14). The concentration of chloroprene monomer is less than 1 ppm (w/w) in solid polychloroprene, but amounts as high as 5000 ppm have been reported in some latex samples (8).

Accepted practice in raw rubber manufacturing calls for quality control of the polymer within various specifications (usually +10%). Standards for these measurements are generally formulated by ASTM (15) or product-oriented organizations such as the Society of Automotive Engineers (16).

Elastomers that meet certain specifications are permitted in specific food-additive applications (17). Both natural rubber and polyisoprene are specifically identified among the elastomers permitted in rubber articles intended for repeated use. Natural rubber, natural latex, *cis*-1,4-polyisoprene, synthetic rubber, and rubber hydrochloride are specifically identified among the elastomers permitted in adhesives, sealing gaskets, paper, paperboards, and coatings. Styrene-butadiene, ethylene-propylene copolymer (and certain diene-containing terpolymers), acrylonitrile-butadiene copolymer, and chloroprene polymers are similarly permitted in specific applications. The components permitted in rubber articles intended for repeated use also include vinylidene fluoride-hexafluoropropylene copolymer that has a minimum number-average molecular weight of 70,000 and tetrafluoroethylene terpolymer that has a minimum number-average molecular weight of 100,000. Chlorosulfonated polyethylene is also permitted in certain food-contact or drinking water applications; specifications require that the chlorine content and the sulfur content not exceed 25 and 1.15% by weight, respectively, and that the molecular weight is in the range of 95,000 to 125,000. Permissible direct additive applications include the use of natural rubber, styrene-butadiene, and butyl rubber as masticatory substances in chewing gum base.

Reviews of analytical methods useful in assessing health and safety aspects of rubber processing and handling have been published biennially (18–21). These methods focus on many modern analytic techniques.

Toxicological Potential

Dry solid polymers usually contain less residual monomer (or solvent) than latex materials. The processing necessary to produce the dry product drives the residual monomer or solvent out of the resin, usually by heat.

Several reports address worker health problems in the rubber fabrication industry. For example, one study (22) suggests an association between the mortality risk of lung cancer and employment in operations involving reclaim, chemicals, and special products. Another study (23) showed that processing workers had increased mortality from leukemia, emphysema, and cancers of the stomach, large intestine, biliary passages, and liver. Other findings (24) demonstrated that men who were employed for at least 10 years experienced small increases in deaths from cancers of the large intestine, pancreas, and lung. Studies of cancer mortality in the British rubber industry found (25) an absence of any excess mortality from bladder cancer among men who entered the industry after January 1, 1951, possibly the result of removing putative bladder carcinogens from production processes in July 1949.

Industrial dermatitis from finished rubber products due to the various chemicals added during polymerization, curing, and processing is not uncommon (26–30). Mercaptobenzothiazole,

tetramethylthiuram disulfide, *N*-isopropyl-*N*'-*p*-phenylenediamine (IPPD), and related compounds are the most common offenders.

Elastomers degraded at high temperatures around 800°C can yield more toxic products than elastomers degraded at smoldering temperatures or gradually rising temperatures. This is to be especially so with nitrile-butadiene.

Workplace Practice and Standards

At ambient temperatures, the main concern with vulcanized polymer is possible effects from inhalation of dust generated in grinding operations and dermatitis in "rubber-sensitive" individuals. Operations that may generate dust should, as a minimum, be controlled within recommended limits for nuisance dusts (31). Dermatitis can usually be controlled only by avoiding either the specific materials that provoked the reaction or "rubber" in general. In some cases, avoiding occluded contact with the skin may eliminate dermatitis (32).

Depending on the particular polymer and type, unvulcanized rubber may require special handling because of the residual monomer or solvent content. Uncured chlorosulfonated polyethylene or other elastomers similarly prepared by dissolving an existing polymer generally contain residual solvent. Monitoring carbon tetrachloride from chlorosulfonated polyethylene, is desirable if bulk polymer is stored in warehouses with limited ventilation or if ventilation in the processing area is questionable. Ventilation adequate to protect against diffusion of the residual carbon tetrachloride should be adequate for any other vapors that may develop during normal curing operations.

Ammonia is added to NR (polyisoprene) latex to preserve it (33), and it may be released during processing. Handling of latex requires consideration of the toxic potential of the monomer(s), cosolvents, other ingredients, and also of the particular operation(s) involved to determine if monitoring the working environment is indicated. Standard operating procedures should include provisions for appropriate personal protective equipment and monitoring to ensure that exposures are well controlled where gross exposure is unavoidable, as in tank entry.

Synthetic Polymers—Olefin, Diene Elastomers, and Vinyl Halides

Bailus Walker, Jr., Ph.D., MPH, Laureen Burton, MPH

A. Olefin and Diene Elastomers

Table 89.2. Summary of Toxicity Tests of Selected Polymers

Chemical Name	CAS	Species	Exposure Route	Approximate Dose g/kg	Treatment Regimen	Observed Effects	Refer
Polyethylene	[*9002-88-4*]	Rat	ig	7.95	Single dose	No effect	
Polypropylene	[*9003-07-0*]	Mice	ig	8.0	Single dose	No effect	
Chlorosulfonated polyethylene	[*68037-39-8*]	Rat	ig	20.0	Single dose/5 days	No effect	
Polyvinyl chloride	[*9002-86-2*]	Dog	ig	25.0	Daily dose	No effect	
Polyvinylidene chloride	[*9002-85-1*]						
		Rats/mice	ig	25.0	Single oral	Tissue	

					dose	damage
Polyvinyl acetate	[*9003-20-7*]	Rats/mice	ig	2.5	Daily dose 12-months	Tissue damage
Polyvinyl alcohol	[*9002-89-5*]	Rats	ig	50g/kg	30 single doses	Minimal changes in liver and myocardial cells
Polyacrylonitrile	[*25014-41-9*]	Rat	ig	0.25 to 0.5	Daily doses for 6 months	Reversible changes in liver, kidney and thyroid
		Rats	ig	4.0		
Polyacrylamide	[*9003-05-8*]	Rats/dogs	ig	MTD[a]	Repeated oral administration for 2 years	No effect

[a] MTD = Maximum tolerated dose.

Synthetic Polymers—Olefin, Diene Elastomers, and Vinyl Halides
Bailus Walker, Jr., Ph.D., MPH, Laureen Burton, MPH

B. Vinyl Halides

The commercial polymers in this group contain chlorine atoms, fluorine atoms, or both in a few cases. In very diverse ways these halogens can be used to produce vinyl polymers that have such characteristics as increased resistance to water, oils, and solvents, plus other distinctive properties. The prototypes are polyvinyl chloride and polyvinylidene chloride. Polyvinyl chloride and its copolymers rank first in production/consumption volume among polymers in the United States and abroad. Their key attribute is low-cost versatility. Polyvinylidene chloride resins have an extremely regular, closely packed molecular structure that results in outstanding impermeability to water, oils, and gases (87, 88).

Synthetic Polymers—Olefin, Diene Elastomers, and Vinyl Halides

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Polyvinyl Acetate, Alcohol, and Derivatives, Polystyrene, and Acrylics

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A. A Polyvinyl Acetate, Alcohol and Derivative Polymers

Polyvinyl acetate, the most widely used vinyl ester, is noted for its adhesion to substrates and high cold flow. Polyvinyl acetate serves as the precursor for polyvinyl alcohol and, directly or indirectly, the polyvinyl acetals. Both polyvinyl acetate and polyvinyl alcohol are insoluble in many organic solvents but water sensitive. Polyvinyl acetate absorbs from 1 to 3% water, up to 8% on prolonged immersion (1). Polyvinyl alcohol absorbs 6–9% water when humidity conditioned and can usually be dissolved completely in water above 90°C, but it can also be insolubilized by chemical treatment. Table 90.1 gives data on properties for typical polymers.

Table 90.1. Physical Properties of Selected Polymers

Compound	CAS	Molecular Formula	Molecular Weight	Boiling Point (°C)	Specific Gravity	Melting Point (°C)
Polyvinyl acetate	[*9003-20-7*]	$(C_4H_6O_2)_n$	86,090	—	1.18	35
Polyvinyl acetate-butyl acrylate	[*25067-01-0*]	—	—	—	—	—
Polyvinyl acetate-1-ethylhexyl acrylate	[*25067-02-1*]	—	—	—	—	—
Polyvinyl acetate-ethylene	[*24937-78-8*] —	—	—	—	—	—
Polyvinyl alcohol	[*9002-89-5*]	$(C_2H_3OH)_n$	37,000–185053	—	1.3	228
Polystyrene	[*9003-53-6*]	$(C_8H_8)_n$	104.15	—	1.05	240
Polyacrylo-nitrile	[*25014-41-9*]	$(C_2H_3CN)_n$	100,000–150,000	—	1.07–1.53	317–340
Styrene-Acrylonitrile	[*9003-54-7*]	$(C_8H_8–C_3H_5N)_n$	100,000–400,000	—	1.06–1.08	—
Acrylonitrile	[*9003-56-9*]	—	60,000–200,000	—	1.02–1.07	—

Butadiene Styrene						
Polymethyl methacrylate	[*9011-14-7*]	$(C_5H_8O_2)_n$	100.13	—	1.188	160–>200
Polyacryl amide	[*9003-05-8*]	$(C_3H_5NO)_n$	91.009	—	1.302	—
Polyacrylic acid	[*9003-01-4*]	$(C_3H_4O_2)_n$	72.063	—	1.09	106
Poly (2-hydroxy-ethyl methacrylate) hydrogel	—	—	—	—	—	—
Methyl-methacrylate	[*80-62-6*]	$(C_5H_8O_2)$	100.1	100	0.943	–48
Ethyl-acrylate polymer	[*9003-32-1*]	$(C_5H_8O_2)_n$	—	—	—	—

Production and Processing

U.S. manufacturers currently sell polyvinyl acetate in emulsion form and polyvinyl alcohol as granules. Polyvinyl alcohol is processed into films and formulated with other materials into emulsion intermediates. Both polymers are typically used in aqueous systems.

Both polyvinyl acetate and polyvinyl alcohol meeting certain specifications are permitted in stated food contact applications such as packaging, coatings, and adhesives. Ethylene–vinyl acetate copolymers and ethylene–vinyl acetate–vinyl alcohol terpolymers [CAS # [*26221-27-2*] are similarly permitted in certain food contact applications. Polyvinyl acetate with a minimum molecular weight of 2000 is permitted as a synthetic masticatory substance in chewing gum base (2).

Toxicologic Potential

Monomer residue has not been considered a problem in end-use products. Latexes or solutions of polyvinyl acetate that are essentially intermediates may contain residual vinyl acetate, essential emulsifiers, or initiators (3). No detailed information is available on the amount of unreacted monomer in either polyvinyl acetate or polyvinyl alcohol resins (3).

Local sarcomas have been produced in rats with polyvinyl alcohol sponges, but implants of both polyvinyl alcohol and polyvinyl acetate in powder form did not produce tumors. IARC considered that additional studies would be required prior to evaluation of carcinogenic potential (3).

Inhalation and combustion toxicity have not been considered problems. This may be attributed to polymer structure and degradation characteristics as well as the nature of ordinary intermediate and end-use products.

Work Practices

With products formulated as solutions or emulsions, the potential for inhalation toxicity or skin reactions from residual monomer or additives may in some cases require evaluation. Recommended industrial hygiene procedures for dealing with nuisance dusts should provide adequate control for any dust hazards from solid forms of polymer. Spillage of these polymers can produce slipping hazards; spills should be cleaned up immediately to prevent falls.

Polyvinyl Acetate, Alcohol, and Derivatives, Polystyrene, and Acrylics
Bailus Walker, Jr., Ph.D., MPH, , and Laureen Burton, MPH

B. Polystyrene and Acrylics Polymers

Since the 1700s when Newman first isolated styrene by stream distillation from liquid ambar, a solid resin obtained directly from a family of trees native to the Far East and California, a substantial industry has developed for styrene-based products. Today, "styrene-based" plastics most commonly are polystyrene, successfully commercialized in 1938, plus the derivatives containing butadiene, acrylonitrile, or both. The derivatives containing acrylonitrile are also called "acrylonitrile polymers" or "nitrile polymers." Polystyrene is made in three different forms: crystal, impact, and expandable. Producers generally refer to the polystyrene market as including only crystal and impact grade. Expandable polystyrene—a foam product, with primary markets in construction and packaging—is a separate specialty product.

Structurally the acrylic polymers include those containing repeating units of acrylonitrile, acrylic acid, acrylates, methacrylates, and all the various derivatives. "Acrylic plastics" may imply only polymers of acrylic or methacrylic acid ester (29), among which the prototype is polymethyl methacrylate. The demand for sheet polymethyl methacrylate dates from World War II, when it was used for aircraft glazing (5).

Polyacrylonitrile is used primarily as fibers, commonly called "acrylic,"that have been formulated with varying amounts of comonomer. Processing may involve blending with other fibers. Dyeing may be done with either the yarn or woven fabric. "Polymeric acrylontrile" is a powder that can be hydrolyzed to form water-soluble polyacrylamides or cast as plastic or film from solvent.

The main copolymer types derived from both styrene and acrylonitrile are (*1*) styrene–acrylonitrile (SAN) copolymer resin and (*2*) acrylonitrile–butadiene–styrene (ABS), in which discrete butandiene particles are dispersed in a SAN copolymer matrix and then sold as pellets or powder. Temperatures described for ABS processing are in the 190–275°C range (30).

Acrylate and methacrylate esters are generally available from the manufacturer in granules or powder. Dyes, pigments, plasticizers, or ultraviolet absorbers may be added during processing. Commercial processing of polymethyl methacrylate per se uses three intermediate types of approach: the melt state for injection molding and extrusion; sheets, rods, and tubes that are mechined or welded; and monomer–polymer dough, primarily for dentures (5).

13.0 Ethyl Acrylate Polymer

13.0.1 CAS Number: [*900-32-1*]

The limited information in the literature focuses primarily on properties of the monomer, ethyl acrylate, described as a colorless liquid widely used in the production of polymers and copolymers. These polymers are for manufacturing textiles, latex paints, paper coatings, and specialty plastics. The monomer is an irritant of the skin, eyes, respiratory tract, and mucus membrane, and it is carcinogenic in experimental animals. The 2000 ACGIH threshold limit value (TLV) is 5 ppm, with a short-term exposure limit of 15 ppm (86).

Polyvinyl Acetate, Alcohol, and Derivatives, Polystyrene, and Acrylics

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Synthetic Polymers—Cellulosics, Other Polysaccharides, Polyamides, and Polyimides

Finis L. Cavender, Ph.D., DABT, CIH

Introduction

Natural polymers are biological macromolecules and are as old as life itself. The natural polymers include such diverse materials as proteins, polypeptides, polysaccharides, DNA, wood, wool, and silk. The word *polymer* is derived from the Greek words *poly*, or many, and *meros*, or parts. This chapter will focus on cellulose and it derivatives, polyamides such as nylon, and polyimides.

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A. Cellulosics

"Cellulose plastics are produced by the chemical modification of cellulose. Raw cellulose is not a thermoplastic: it does not melt. Cellulose is a substance that forms the cell walls of many trees and plants. Raw cellulose can be made into a fiber or film, but it must be chemically modified to produce a thermoplastic" (1).

1.0 Cellulose

1.0.1 CAS Number: [*9004-34-6*]

1.0.2 Synonyms: Regenerated cellulose, rayon, cellophane, and cellulose, microcrystalline

1.1 Chemical and Physical Properties

1.1.1 General Cellulose is a white substance that is practically insoluble in water and other solvents. It can be dissolved in zinc chloride, ammoniacal copper hydroxide, or caustic alkali with carbon disulfide (2). The specific properties of the many types of rayon vary widely (3). Rayon is readily blended with other fibers. Rayon can contribute pleasing texture and touch quality, moisture absorbency, or strength. Cellophane is noted for clarity, crisp hand, and dimensional stability. Coatings of nitrocellulose or saran reduce moisture and oxygen permeability; polyethylene or ionomer coatings reduce heat loss. Both rayon and cellophane can be highly flammable (4). See Tables 91.1–91.3.

Table 91.1. Limiting Oxygen Indices and Ignition Temperatures for Various Polymers[a]

		Ignition Temperature (°C)	
Polymer	**Range of Limiting Oxygen Indices[b]**	**Flash Ignition**	**Self-Ignition**
Wood	22.4–25.4	228–264 (white pine shavings)	260
Cotton	18.6–27.3	230–266	254
Cayon	18.7–19.7		
Cellulose acetate	16.8–27	305	475
Cellulose nitrate		141	141
Wool	23.8–25.0		
Nylon 66 fabric	20–21.5		
Nylon 6 fabric	20–21.5		
Polyethylene terephthalate fabric	20–21		

[a] Summarized from Ref. 4. Additional ignition temperatures are summarized in Table 91.2.

[b] The limiting oxygen index can also be expressed in terms of the volume of oxygen in the atmosphere, where *n* is a decimal.

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B. Polyamides and Polyimides

The synthetic polyamides and polyimides are all step-growth or condensation polymers. As a group, they are considered performance polymers, whereas the chain growth or addition polymers include the typical commodity polymers of polyethylene, polyvinyl chloride, and polystyrene as well as the high-performance fluoropolymers. Polyamides are linked with the word nylon, the first major synthetic polyamide. Nylon was developed as a fiber in the 1930s and as a plastic in the 1940s. Polyamide polymers also include protein fibers such as wool and silk that have been commercially important for several millenia (4). These natural protein fibers are not discussed in this section.

Nylon is a generic term for a synthetic aliphatic polyamide of well-defined structure and certain typical properties either as a fiber (62) or as a plastic (63) The name system reflects the chemical structure and preparation. Nylons 66, 610, and 612 are all prepared from a six-carbon diamine and a 6-, 10-, or 12-carbon dibasic acid, respectively. [The names can also be written in the style nylon 6/6, nylon 6.6, or nylon 6,6 to reflect the two-monomer origin; the simpler style of nylon 66—always "six six," or "six ten" for nylon 610—is usually preferred (28).] Nylons 6, 11, and 12 are prepared from an amino acid or derivative thereof with 6, 11, or 12 carbons, respectively. Nylon 66 was developed in the United States and nylon 6 was developed abroad (37), but both are now found worldwide. As a group, the nylons are tough, strong, abrasion resistant, and resistant to alkalies, hydrocarbons, ketones, and esters (63, 64).

Aromatic polyamides such as Nomex were formerly called nylon (65), but aramid is now the official generic classification of the U.S. Federal Trade Commission and the International Standards Organization. Aramid denotes a long-chain synthetic polyamide fiber in which at least 85% of the amide linkages are attached directly to two aromatic rings, whereas nylon now indicates that less than 85% of the amide linkages are so attached (66). Aromatic polyamide fibers typically have many desirable properties of nylon fibers plus improved heat resistance and strength (67).

Polyimides are a completely synthetic class of polymers developed as a variation on polyamides to provide increased resistance to high temperature (68). Aromatic polyimides have exceptional heat resistance. Conventional tensile strength has been measured up to 500°C (69). Thermoplastic varieties, or those that become rubbery rather than melt at the glass-transition temperature of approximately 310°C (70), retain high strength at almost 300°C. Table 91.5 summarizes some typical physical properties. Figure 91.1 compares the performance of selected aramid and nylon fibers with other types in a standardized test.

Synthetic Polymers—Cellulosics, Other Polysaccharides, Polyamides, and Polyimides

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Synthetic Polymers, Polyesters, Polyethers, and Related Polymers
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1 Overview

Commercial use of polyester resins dates from the early twentieth century, when alkyd resins were first used in surface coatings (1). The polyesters are found today as fibers, films, laminating resins, molding resins, and engineering plastics. The high-molecular-weight polyethers are known primarily as engineering plastics (an exception is high-molecular-weight polyoxyethylene, a water-soluble packaging polymer), as are the polysulfides and the polysulfones. Table 92.1 gives some basic properties.

Table 92.1. Selected Properties of Some Polyesters, Polyethers, and Related Polymers[a]

A. Polyesters			
Property	**Polyethylene Terephthalate**	**Polybutylene Terephthalate**	**Polycarbonate of Bisphenol A**

Melting temperature (°C)	254–284; 256 (commercial PET); 271 (highly crystalline PET)	221–232	215–230
Glass-transition temperature (°C)	69. 67, amorphous; 81, crystalline; 125, crystalline and oriented	17–80; 22–43; unfilled, 50	145–149
Service temperature (° C)	–60 to +150	Can be used for prolonged periods of time at 120–140°C. Embrittlement by hydrolysis on long-term aging at 60–85° C under humid conditions	135 maximum
Density	1.33 (amorphous) 1.45 (crystalline)	1.31–1.32	1.20
Refractive index, n_D	Film: amorphous, 1.5760; crystalline and biaxially oriented, 1.64		1.585
Moisture absorption 0.8%, immersion	0.55%, 24-h immersion of commercial films; 0.8%, immersion in water at 25°C for 1 wk	0.08%, 24-h immersion at 23°C	0.2% in air at 60% relative humidity
Moisture regain (fiber)	0.4%, commercial value and normal conditions		
Solvents	Crystalline: choralhydrate, phenol, phenol tetrachloroethane, (1:1 vol.), nitrobenzene, DMSO (hot)	“Complex phenols” such as *o*-chlorophenol	Methylene chloride and chloroform; less soluble in tetrachloroethane, trichloroethylene, dichloroethane, tetrahydrofuran, dioxane, cyclohexanone, dimethylformamide. Swells in benzene, chlorobenzene, acetone, ethyl acetate, carbon tetrachloride
Nonsolvents/relatively unaffected by	Crystalline: hydrocarbons, chlorinated hydrocarbons, aliphatic alcohols,	Very resistant to most chemicals	Hydrocarbons, styrene, carbon tetrachloride, acetone, lower esters.

	ketones, carboxylic esters, ethers.		
Decomposes	Strong acids and bases, particularly when hot. Hydrolyzes slowly in water at elevated temperature (fibers with ~20% loss in strength after 1 week at 100°C, without measurable loss in strength after several weeks at 70°C		Hot alcoholic alkalies, amines, and other organic bases; surface attack by aqueous alkali. Hydrolyzes in water >600°C (can withstand relatively short exposures)

B. Polyethers

Property	**Polyoxymethylene**	**Polyoxyethylene**	**Polyphenylene Oxide**
Melting point (°C)	175–200		298 (as poly-*p*-phenylene oxide); 261–272 [as poly (2,6-dimethyl-*p*-phenylene oxide]
Glass-transition temperature			105–120 (phenylene oxide-based resin)
Density	1.40–1.42 for molded parts, range to 1.56 for special grades of resin		1.314 (as poly-2,6-dimethyl-*p*-phenylene oxide); 1.408 (as poly-*p*-phenylene oxide)
Refractive index, n_D	1.489–1.553	1.51–1.54	
Water absorption, 24 h (%)	0.02–0.3		0.006
Solvents	At elevated, temperature; benzyl alcohol, phenol, chlorophenols, aniline, formamide, DMF, *y*-butyrolactone, bromobenzene, diphenylether	Benzene, chloroform, carbon tetrachloride, alcohols, cyclohexanone esters, DMF, water (cold), aqueous, K_2SO_4 (0.45 *M* above 35°C); (swells in dioxane).	Poly(oxy-2,6-dimethyl-1,4-phenylene)[b] amorphous, a-pinine (hot); crystalline, benzene, toluene, chloroform chlorobenzene poly(oxy-1,3-phenylene)[c] benzene, biphenyl, 3-pentanol, phenyl ether, pyridine, benzophenone, nitrobenzene,

			DMF, DMSO
Nonsolvents/relatively unaffected by	Aliphatic hydrocarbons, lower alcohols, diethyl ether, lower esters	Aliphatic hydrocarbons, ethers, water (hot)	poly(oxy-2,6-dimethyl-1,4-phenylene).[d] Amorphous, a-pinene (cold), methanol, ethanol; crystalline, a-pinene (hot), methanol, ethanol, nitromethane poly (oxy-1,3-phenylene).[b] methanol
Decomposes	Alkalies with pH > 9; acids with pH < 1 (extended contact)		

C. Polyphenylene Sulfide and Polysulfones

Property	**Polyphenylene Sulfide**	**Polysulfone of Bisphenol A**	**Polyethersulfone 200P**
Melting point (°C)	~285–295		
Glass-transition temperature (°C)	97	~190	230 (other polysulfones ranging to 315)
Density	1.440; 1.34, unfilled; 1.64, 40% glass	1.24	
Refractive index, n_D		1.633	
Water absorption	0.02, unfilled; 0.01, 40% glass		
Solvents	Biphenyl, dimethyl-*p*-terphenyl, chloronaphthalene, some other solvents at elevated temperature	Chlorinated hydrocarbons, dimethylformamide, *N*-methylpyrrolidone; swells in dimethyl sulfoxide	
Nonsolvents/relatively unaffected by	At reflux temperature:toluene, pyridine, phenyl oxide, phenyl sulfide	Inorganic acids, alkalies, aliphatic alcohols	
Decomposes		Concentrated sulfuric acid (dissolves with degradation)	

[a] From Ref. 2a

[b] "Phenylene-oxide based resin" may soften or dissolve in certain halogenated or aromatic

hydrocarbons. If an application requires such exposure, stressed samples should be tested under operating conditions (10).

1.1 Production and Processing

Production data for the general categories are listed in Table 92.2. Processing techniques vary widely and are discussed in the appropriate subsection.

Table 92.2. Production of Certain Synthetic and Natural Polymers

	Dry Weight Basis	
Polymer	**1000 lb**	**1000 kg**
A. U.S. Production of Plastics, Resins, and Elastomers (1990)		
Thermoplastic resins[a]		
Low-density polyethylene	7,254,891	3,291,693
Linear low-density polyethylene	3,893,252	1,766,448
High-density polyethylene	8,339,360	3,783,739
Polypropylene	8,310,409	3,770,603
Acrylonitrile–butadiene–styrene (ABS)	1,161,855	527,157
Styrene–acrylonitrile (SAN)	135,173	61,331
Polystyrene	5,021,090	2,278,172
All other styrene-based resin	1,189,204	539,566
Nylon	558,307	253,315
Polyvinyl chloride	9,095,534	4,126,830
Polyvinyl acetate	987,190	447,908
Other vinyl/vinylidene resins[c]	211,560	95,989
Thermoplastic polyester[d]	1,878,629	852,373
Engineering resins[e]	1,382,806	627,407
Acrylic[b]	1,507,031	683,771
Other thermoplastic resins	781,856	354,744
Total thermoplastic resins	51,708,147	23,461,046
Thermosetting resins[a]		
Epoxy	499,321	226,552
Polyester (unsaturated)	1,221,160	554,065
Urea–formaldehyde	1,495,531	678,553
Melamine–formaldehyde	201,986	91,645
Phenolic and other tar acid resins[f]	2,946,276	1,336,786
Polyurethane[g]	2,951,818	1,339,300
Alkyd[b]	769,238	349,019
Furfuryl type resins[b]	14,035	6,368
All other thermosetting resins[b]	152,488	69,187
Total thermosetting resins	10,251,853	4,651,475

Synthetic elastomers[h] (include latex)	Metric tons
Styrene–butadiene	852,851
Polybutadiene	403,388
Nitrile	562,261
Ethylene–propylene	255,537
Other synthetic elastomers (includes polychloroprene, polyisoprene, and butyl rubber but excludes polyurethane rubber)	
Total	2,620,535

B. World Production of Certain Textile Fibers (1990)[i]

	1000 Metric tons
Natural fibers	
Raw cotton	18,714
Raw wool	1,964
Raw silk	66
Total	20,744
Percent of world total = 54	
Man-made fibers except olefin and textile glass	
Rayon and acetate	2,846
Acrylic and modacrylic	2,326
Nylon and aramid	3,765
Polyester	8,621
Certain other noncellulosic fibers	157
Total	17,715
Percent of world total = 46	

[a] Adapted from data in Society of the Plastics Industry, "Monthly Statistical Report—Resins, Full Year 1990, Production and Sales & Captive Use of Thermosetting & Thermoplastic Resins" issued by the SPI Committee on Resin Statistics as compiled by Ernst & Young; other data reported in SPI *Facts and Figures of the U.S. Plastics Industry*, 1991 Edition; and data in *Synthetic Organic Chemicals*, USITC Publ. 2470, U.S. International Trade Commission, Washington, DC, 1991. SPI data are used where available. Data reported to the USITC do not necessarily coincide with those reported to the SPI because of differences in both the reporting instructions and the coverage of certain resins.

[c] Includes only polyvinyl butyral, polyvinyl formal, and polyvinylidene.

[d] Does not include polyester for film and tape.

[e] Engineering resins include acetal, granular fluoropolymers, polyamide-imide, polycarbonate, modified polyphenylene oxide, polyphenylene sulfide, polysulfone, polyether imide, and liquid crystal polymers, (ABS and nylon resins are listed separately.)

[b] As reported in *Synthetic Organic Chemicals*, USITC Publication 2470, December 1991.

[f] Material is reported on a "gross weight" or "as sold" basis including the weight of water and other liquid diluents.

[g] Polyurethanes are derived from starting materials isocyanates (TDI/MDI) and polyols (polyether polyester). Raw materials reported to the SPI sold in the United States for conversion into polyurethanes provide the basis for these data.

[h] The term *elastomers* may be defined as substances in bale, crumb, powder, latex, and other crude forms that can be vulcanized or similarly processed into materials that can be stretched at 68°F to at least twice their original length and, after having been stretched and the stress removed, return with force to approximately their original length (*Synthetic Organic Chemicals*, USITC Publ. 2470, U.S. International Trade Commission, Washington, DC, 1991).

Production figures are based on the *RMA Industry Rubber Report*, December 1990, and are reprinted by permission of the Rubber Manufacturers Association, Washington, DC.

[i] As listed in *Fiber Organon*, 62(6), June 1991. Data are reprinted by permission of the Fiber Economics Bureau, Inc., Roseland, NJ. "The silk and man-made fiber data are on a calendar-year basis, while the figures for cotton and wool are on a seasonal basis."

1.2 Specifications and Test Methods

Clearance for certain food contact applications with many of these materials has been obtained under Title 21 of the Code of Federal Regulations (2). Those specifically listed include polyethylene terephthalate, polybutylene terephthalate, polycarbonate, polyoxymethylene, polyoxyethylene derivatives, polyphenylene sulfide, and polysulfone. Specifications concerning mechanical and other types of performance depend on end use.

1.3 Toxicologic Potential

Industrial hygiene concerns with these polymers depend on the type of resin in use. Chemicals released in significant quantities may include (*1*) styrene during the fabrication of unsaturated polyester resins and in any subsequent release of styrene, (*2*) other volatile products generated at elevated temperatures or in fires, and (*3*) dust or particulate generated in the manufacturing and processing of polyester fibers. The use of styrene in polyester resins that are fabricated into glass-reinforced plastics can provide the greatest intensity of exposure to styrene in workplace situations (3–5). Toxic vapors can also be released by solvent systems, particularly at elevated temperatures, and during fabrication of engineering resins. For example, the processing of polyoxymethylene (acetals) in a poorly ventilated space may release biologically significant amounts of formaldehyde into the adjacent atmosphere.

Sulfur-containing engineering resins typically have a high resistance to thermal deterioration but may yield hydrogen sulfide or sulfur dioxide if heated to decomposition temperatures.

Inhalation tests in rats indicate no particular hazard to humans from particles of commercial polyester fiber but suggest that sufficient inhalation of cyclic ethylene terephthalate trimer dust may produce a granulomatous tissue response. Both types of particles produced a nonspecific inflammatory tissue response when first introduced into the lungs (6). This initial response was transitory and was not followed by collagen formation or any development of fibrosis. However, small particles of crystalline cyclic ethylene terephthalate trimer dust produced more prominent foreign body giant cell reactions than small polyester fiber particles. The latter, formed during high-speed processing by abrasive fracture of the surface of commercial fiber, produced a modest response consisting mostly of macrophages; the large nonrespirable particles produced artifactual foreign body granulomas.

1.4 Synthetic Fibers and Human Responses

Prior to 1950, "textile dust" was essentially the dust of cotton and other natural fibers. Harmful health effects were particularly identified with the inhalation of the dusts of raw cotton, flax, and hemp in the workplace. Today, the production and use of synthetic fibers is comparable to that of natural fibers (Table 92.2). No conclusive evidence links the manufacturing or processing of synthetic fibers with any serious health effects.

Except for cotton and other byssinogenic dusts, relatively few epidemiologic studies that involve exposure to organic fibers have been conducted. Three studies that consider exposure to polyacrylonitrile fiber, rayon, or an unidentified synthetic fiber, respectively, do so in the context of a comparison to cotton. Valic and Zuskin (7) report a mild reduction of ventilatory capacity in 1975 Yugoslav textile workers exposed to polyacrylonitrile fibers, including 30 with previous exposure to cotton and 77 with previous exposure to hemp; however, this response did not appear to be dose related. Tiller and Schilling (8) found an insignificant change in ventilatory capacity (less than 1%) among 26 English rayon workers, 13 of whom had been previously exposed to cotton. Another British report (9) describes a decreased prevalence of bronchitis among workers in two spinning mills using "man-made" fiber compared to workers in 14 cotton mills.

Several clinical reports record the symptoms or test results of affected textile workers but do little to

clarify the origin of these observations. The significance of these reports outside the immediate environment is difficult to determine and quite likely limited. Pimentel et al. (10) describe seven patients in Portugal with a history of exposure to various textiles during the manufacturing process. The seven patients were variously affected with asthma, extrinsic allergic alveolitis, chronic bronchitis with bronchiectasis, spontaneous pneumothorax, or pneumonia. All had worked with one or more synthetic fibers; five had also worked with wool and/or cotton. The terminal patient identified as Case 3 had been exposed to the dust of "wool, cotton, synthetic fibers" over approximately a quarter-century and had apparently continued work with fibers for some 3 years after a hospital admission for progressive breathlessness upon exertion 8 years earlier. Many fibers were found in fibrotic tissue and some were identified as polyester. However, the mere presence of particles in the respiratory tract cannot be considered pathological. Each day, the average person inhales some 20,000 L of air laden with particles, many of which are deposited on the alveolar surface (11).

Bouhuys (12) points out that this report of case histories (13) suffers from lack of control biopsy samples, specific exposure data, and information on the nature and size of the populations at risk. A later report by Pimentel et al. (14) describes two patients with unusual "sarcoid-like granulomas" of the skin that the authors attributed to acrylic or nylon fibers, respectively; one of the patients also had respiratory tract lesions that were considered similar to those described in the first report. Unfortunately, this second report does not remedy the deficiencies of the first report.

Two Finnish investigators (13) cite the first Pimentel et al. study and also fail to give exposure data when reporting the results of several inhalation challenge tests in textile workers. Neither group provides specific evidence to support its implication of an immunogenic phenomenon.

These clinical reports pay little or no attention to the dimensional characteristics of the inhaled fibers as distinct from the chemical nature of the polymer in question. Both size and shape are important factors in biologic responses to durable fibers—particularly carcinogenicity (see Section 1.4). Work with fibrous glass indicates that short fibers (<8 mm long) have negligible carcinogenic potential, but fine-diameter fibers (<1.5 mm) that are long (>8 mm) appear to increase in carcinogenic potential as their length increases (15) The synthetic organic fibers used in textiles are generally larger in diameter than this apparently critical 1.5-mm diameter (16).

1.5 Workplace Practices and Standards

No specific standards are known that pertain to ordinary industrial use of the finished polymeric products. Fabrication of the raw polymers or use of the prepolymers may release volatile materials and require appropriate industrial hygiene measures. Possible fire hazards should be considered when large amounts of these polymers are present in a given area, particularly with prepolymers of unsaturated polyester that contain appreciable amounts of flammable solvent or styrene.

In general, exposure to particles of polymeric fibers should be minimized by appropriate industrial hygiene measures for the control of exposure to insoluble organic dust. Particles of fiber dust should not be considered harmless but rather as particles that can—like particles of any dust—have biologically significant consequences if inhaled in gross concentrations. The presence of oligomers or other impurities may require evaluation in specific workplace situations.

The Textile Research Institute has provided a current review (16) on methods for collecting and measuring the particle sizes of respirable dust with special emphasis on dusts of importance to the fiber and textile industries.

1.6 Fire and Toxicity of Smoke

These polymers generally are not used in materials of construction, interior finish, or furnishings. They have had little or no study with respect to their smoke toxicity upon burning.

Synthetic Polymers, Polyesters, Polyethers, and Related Polymers
Steven T. Cragg, Ph.D., DABT

2 Linear Terephthalate Polyesters
All high-molecular-weight polyester polymers of commercial significance as fibers or films are derived from dimethyl terephthalate (or terephthalic acid). The basic structure is polyethylene terephthalate or its copolymers. Poly-1,4-cyclohexylenedimethylene terephthalate has also been used, but to a much more limited extent.

Polybutylene terephthalate is known as an engineering resin. The two fiber-forming terephthalates can also be adapted for this purpose as homopolymers or copolymers (1).
2.0 Polyethylene Terephthalate and Polyester Fibers
2.0.1 CAS Number: [*25038-59-9*]

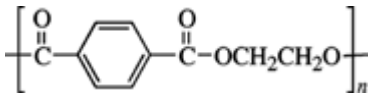
2.0.2 Synonyms: NA

2.0.3 Trade Names: NA

2.0.4 Molecular Weight The molecular weight of commercial polymers has been given as 15,000–20,000 M_n and 20,000–30,000 M_w (24). Farrow and Hill (25) describe M_n in the range of 10,000–50,000, the latter figure representing fibers used particularly for industrial applications.

2.0.5 Molecular Formula: NA

2.0.6 Molecular Structure:



2.2 Production and Use
2.2.1 Structure, Synthesis, and Processing of Polyester Fiber As noted above, the basic structure in most polyester fiber is polyethylene terephthalate.

The structure of the end groups has been described as mainly hydroxyethyl ester with a small number of carboxyl end groups (17). The Federal Trade Commission defines a polyester fiber as “a manufactured fiber in which the fiber-forming substance is any long chain synthetic polymer composed of at least 85 percent by weight of an ester of a dihydric alcohol and terephthalic acid” (18).

Most polyester fiber is composed primarily of a polyethylene terephthalate. Other fibers are derived from polycyclohexylenedimethylene terephthalate (17). Other variations include terephthalate-substituted isophthalate copolymers that provide enhanced dyeability (19, 20).

Polymerization has two basic steps (1, 17, 19): (*1*) reaction of ethylene glycol with terephthalic acid (esterification) or dimethyl terephthalate (alcoholysis) to produce oligomeric hydroxyethyl terephthalate, ranging from dimer to pentamer; (*2*) polycondensation of this oligomeric mixture to the desired molecular weight and removal of the excess glycol and by-products.

Commercial polyester fibers are prepared by melt spinning. The extruded melt is forced into filamentary streams that are formed into spun filaments and then drawn to fibers, either in a separate drawing step or in combination with spinning (19).

Two impurities are “normally” present in polyester fibers (17). Ethylene glycol used in the synthesis

may be converted to diethylene glycol, and the corresponding ether group may be present to a slight degree (1–3 mol%) in the polyester. Cyclic trimer is present to the extent of <1.5% in the polymer or in the fiber derived from it. Part of this trimer may be removed during dyeing or reprecipitate on the fiber.

"Snow" deposits that can develop on the surfaces of high-speed friction twist texturing machines (21) are aggregates of irregular polymeric particles ("skin" particles that describe the outermost layer of the individual fibers) rather loosely held together by finish oils. Analyses of these deposits average approximately half polymer, half finish. Generally the polymeric particles have the melting point and molecular weight characteristics of polyethylene terephthalate and should not be confused with cyclic trimer. "Snow" appears to be the result of local yarn heating caused by friction. Optimal control of yarn and process variables can reduce the level of snow generation.

2.2.2 Structure and Processing of Film The basic structure in most of these films is again polyethylene terephthalate. Polycyclohexylenedimethylene terephthalate can also be used (22, 23). These films can be prepared by quenching (solidifying) extruded polymer to the amorphous state and then reheating and stretching the sheet approximately threefold in each direction at 80–100°C. Orienting the film and then annealing it under restraint at 180–210°C can raise the crystallinity to 40–42% (1).

2.2.3 Properties and Applications Fabrics made of polyester fibers are noted for their strength, wrinkle resistance, and resistance to moisture at ordinary temperatures. Weathering resistance is good and superior to that of the polyamides (24); resistance to sunlight is inferior to that of the acrylics. Polyester fibers blend well with cotton or wool, and blends with cotton for clothing are easily the largest single end use (25). Industrial uses of polyester fibers include rubber reinforcing material, filter cloths, sieve cloths, and marine applications such as fishing nets or tarpaulins.

Polyethylene terephthalate film in its oriented crystalline state ranks among the strongest of the thermoplastics. Properties vary widely among the different types and subtypes, but its basic advantages are its toughness, durability, excellent flex life, resistance to most organic solvents and mineral acids, very low moisture retention, and general absence of plasticizers (26). Applications include magnetic tape, X-ray and other photographic film, electrical insulation (metallized for capacitors), food packaging, and boil-in-bag food pouches. Polyethylene terephthalate can also be blow-molded to prepare bottles (1). Additional properties are listed in Table 92.1.

2.4 Toxic Effects

2.4.1 Oral Toxicity Several 90-d feeding tests have been conducted. In a series of tests with films intended for food packaging, polyethylene terephthalate (27) and heat-treated polyethylene terephthalate (28) were fed to rats and dogs. The dietary level was 10% in all cases. No clinical, nutritional, hematologic, urinary, biochemical, or pathological evidence of toxicity was observed. Chloroform extracts of powdered resin produced no adverse effects when administered to rats in oral doses as high as 10 g/kg in an acute test and 400 mg/kg in a 90-d test (29).

2.4.2 Skin Contact As with acrylic and nylon fabrics, clinical experience over the past several decades indicates that the basic polyethylene terephthalate fiber is essentially innocuous when applied to the skin. Tests conducted by the Schwartz–Peck procedure with a 2-wk rest period (30, 31) showed no sensitization but occasional irritation reactions consistent with occlusion. Fabric made from textured yarn (false twist) has also caused some slight reactions that appeared to be related to mechanical irritation from the rough edges formed during draw texturing and to increasing denier per filament (32). Several recent tests conducted by a modified Shelanski repeated insult patch test procedure (33, 34) or a modified Draize repeated insult patch test procedure (35) were entirely negative. These procedures are described in Ref. 36.

Like acrylic fiber, 100% polyester knit fabric is low in free formaldehyde content; 15 samples of American clothing contained ≤30 ppm free formaldehyde (37), formaldehyde not attributable to the intrinsic fiber. Samples of polyester/cotton fabrics showed in some cases a relatively high level of

free formaldehyde.

2.4.3 Inhalation Toxicity, Thermal Degradation, and Related Data Insufflation tests have been conducted with the cyclic ethylene terephthalate trimer dust (38) and also with the polyester "skin" particles (39) released from some types of filament yarns during high-speed processing (see preceding). Under examination by a light microscope, the particles of trimer dust were refractile and varied in size from 1 to 7 mm; many particles were 1 to 3 mm. The dust was brilliantly birefringent under polarized light. Forty rats were given intratracheal injections of 0.25 mL of a 1% trimer dust suspension in 0.9% saline; three other groups of rats received injections of the same volume of a 10% suspension of quartz dust in saline, a 1% suspension of quartz dust in saline, or the saline diluent alone. Rats were killed serially in groups of five at 2, 7, 28, 91, 183, and 371 d after dosing. The remaining 10 rats of each group (or less if some died) were killed at 2 yr after treatment.

The injected trimer dust was found to be scattered in the alveoli adjacent to the respiratory bronchioles. Rats that were killed 2 d after exposure showed extensive acute peribronchiolar pneumonia from the dust accumulation. This reaction was much more intense than that observed after a 2-wk series of 10 4-h exposures to 0.4 mg/L trimer dust (mass median diameter = 5.9 ± 1.1 mm, histologically visible particles mostly <2 mm). The lungs of rats so inhaling trimer dust showed a nuisance dust cell reaction after the tenth exposure with significant reduction of dust-laden macrophage cells 2 wk later (6).

At 1 wk after exposure the inflammatory exudate had disappeared and a small number of minute dust-laden granulomas developed. The granulomas were readily detected under polarized microscopic examination. Dust particles a few micrometers or less in diameter were directly surrounded by foreign body giant cells and lymphocytes. Some dust particles had been transported from the lung to the tracheal lymph nodes. The number of granulomas appeared to be somewhat less at 1 yr and was further diminished at 2 yr, although a few active foreign body granulomas were still evident at this time. No fibrogenic activity was evident in the granulomas or in the dust-laden macrophages of the tracheobronchial lymph nodes.

The pulmonary reactions from the quartz-treated groups were quite different. Two years after treatment at the 2.5-mg dose level, the dust was almost entirely eliminated from the lungs and normal architecture was observed. At the 25-mg dose level, quartz lesions were characterized by silicotic nodule formation with progressive collagenization.

The polyester fiber "skin" particles appeared irregularly constricted and sausagelike when examined under a light microscope and were brilliantly birefringent in polarized light (39). Size varied from 1 to 1000 mm in length and 1 to 40 mm in width.

Forty rats given an intratracheal injection of 0.25 mL of a 1% suspension of these particles were maintained on the sacrifice schedule described for the trimer dust. The long nonrespirable particles were found in the small bronchi and terminal bronchioles, whereas shorter fibers were trapped in the respiratory bronchioles and adjoining alveoli. On the second day after exposure, the inflammatory reaction consisted of bronchitis, bronchiolitis, and peribronchial pneumonia. At 1 wk, the inflammatory reaction had disappeared; the test material was retained in the foreign body giant cells or macrophages, but no significant tissue reaction was observed. The intensity of the reaction progressively decreased at 1-mo, 6-mo, 1-yr, and 2-yr observations. At 2 years, large nonrespirable particles were retained in the terminal air passages while small respirable particles had been mostly removed by the lung clearing mechanism. No evidence of collagen formation, fibrosis, or significant alteration of the lung stromal architecture was observed.

Combustion toxicity tests (Table 92.1) show no unusual hazard from the products evolved from polyester compared to those from other fabrics similarly tested. Thermal degradation at approximately 300°C yields primarily acetaldehyde, whereas somewhat higher temperatures yield carbon monoxide (40–51).

2.4.4 Carcinogenic Potential/Cytotoxicity/Implant Studies Many studies have been conducted with implants of polyethylene terephthalate, mostly in a form described as mesh or velour but also as sutures or powder. Polyethylene terephthalates have often been favored on the basis of minimal toxicologic response, durability, and mechanical properties (52; see also 53–55). Sutures of this fiber have been preferred by some investigators (20) but not others (59). Athough relatively inert, polyethylene terephthalate fiber is subject to slow degradation in body fluids (58, 59).

Particulate polyethylene terephthalate showed little cytotoxicity when tested in rats (60, 61). Two instances have been reported in which a prosthetic graft made from this polymer was associated with tumor development in humans (62, 63); pore size between the polymeric strands was identified as a determining factor in the second case. Vascular prostheses should be knitted with the largest possible pores to promote connective tissue organization and blood supply within the knitted structure of the prosthesis (59). A Russian report states that subcutaneous implants of polyethylene terephthalate "fibers" were resorbed in humans after an average interval of 30 yr (64).

Polyethylene terephthalate has been fabricated into sutures in filamentary form (e.g., for corneal surgery) and into supporting ligature in sheet form (e.g., for hernias) in biomedical implants. Several studies have examined the types and rates of complications resulting from use of polyethylene terephthalate as opposed to other prosthetic materials (65–69). The polyesters made from polyethylene terephthalate polyesters had higher rates of infection, fistula formation, and hernia failure than materials made from polypropylene mesh (68). Biomedical implants made from polyethylene terephthalate also may cause an inflammatory response due to increased adhesion of fibrinogen to the material; this may be related to the type of weave used in the material as well as any intrinstic property of the polyester (69). Tissue compatibility may be improved to reduce the likelihood of thrombosis and inflammation by impregnating the polyester with agents that reduce fibrinogen or lymphocyte adhesion (70). The continuing use of polyethylene terephthalate as permanent prosthetic implants points to the low toxicity of these materials.

2.4.5 Biodegradation Human data as cited indicate that polyethylene terephthalate is slowly biodegradable.

3.0 Polybutylene Terephthalate

3.0.1 CAS Number: [*24968-12-5*], [*26062-94-2*], [*30965-26-5*]

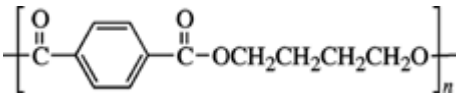
3.0.2 Synonyms: Polytetramethylene terephthalate and PBT

3.0.3 Trade Names: NA

3.0.4 Molecular Weight The low-molecular-weight polymers generally have M_n of 23,000–30,000 and M_w of 36,000–50,000. High-molecular-weight polybutylene terephthalate resins, which have preferable mechanical properties, have M_n of 36,000–50,000 and M_w of 60,000–90,000 (71).

3.0.5 Molecular Formula: NA

3.0.6 Molecular Structure:



3.1 Synthesis, Properties, and Applications

Polybutylene terephthalate can be made by the catalyzed condensation of 1,4-butanediol with either terephthalic acid or more frequently dimethyl terephthalate (71, 72).

Polybutylene terephthalate has a relatively low glass-transition temperature (see Table 92.1) and crystallizes at a rapid rate; molding cycles are very short. These resins are noted for their low coefficients of friction and are resistant to abrasion. They can be readily glass reinforced. Typical applications include exterior parts in the automotive and related fields and connectors and fuse cases in the electrical and electronic industries. Polybutylene terephthalate materials are also used in appliances, pump housings, and impellers (71). Polybutylene terephthalate has been approved for use by the FDA as a material that may contact food (21CFR 177.1655) and it is used in biomedical implants.

3.4 Toxic Effects

3.4.1 Oral Toxicity Polytetramethylene terephthalate (i.e., polybutyleneterephthalate) with a M_w of 45,000–85,000 has been fed at dietary levels up to 5%, to rats for 148 d, and to dogs for 90 d (73). At the 5% level both male and female dogs showed a somewhat enhanced food intake, but otherwise no untoward effects were observed. Analysis of urine from rats and dogs fed the 5% dietary level revealed no evidence of free or combined terephthalic acid at the detection limit of 1 mg/mL; it was therefore concluded that <0.003% of the daily intake of polytetramethylene terephthalate was absorbed from the gastrointestinal tract and then eliminated via the urine. The investigators reasoned that if the 2.5% level of polymer intake was considered an acceptable no-effect level, and the likely maximum was 1.8 mg extractable material from the polymer migrating into the total food intake, the safety factor would be in excess of 10,000.

3.4.2 Inhalation Toxicity and Thermal Degradation Data Cartier et al. (74) report a case of asthma in a 39-year-old male who developed cough, dyspnea, sweating, and tremors 2–3 wk after starting a job where he was exposed to a variety of chemicals. Challenge with heated polyester fiber would initiate an asthmatic episode.

Reported data indicate no unusual inhalation toxicity of the pyrolysis/combustion products of polybutylene terephthalate per se (75–78). Flame-retarded samples may exhibit additional toxic properties; rats inhaling vapors from some but not all brominated samples heated to simulate processing temperatures developed slightly enlarged livers.

3.4.3 Implant Studies Polybutylene terephthatate is used in a variety of biomedical implants similar to polyethylene terephthalate. It seems to have fewer coagulation, inflammatory, or rejection complications than the latter polyester. The plasma coagulation system, as measured by thrombin activation markers such as fragment 1 + 2 and fibrinopeptide A, was activated when polybutylene terephthalate was incubated *in vitro* with the coagulation system but not as great as polyethylene terephthalate (79). When used as an artificial ligament in Wistar rats, polybutylene terephthalate was less rejected than polyethylene terephthalate (Teflon was most inert) (80). As a copolymer with poly (ethylene oxide hydantoin), polybutylene terephthalate, used as an alloplastic tympanic membrane substitute, was assessed in rats for periods up to 1 yr (81). This copolymer was better accepted than a similar implant fabricated from Estane 5712 F1 polyether urethane, routinely used for this procedure, and much better than an implant made of polypropylene oxide. Minimal macrophages and foreign-body giant cells were present, but fibrous tissue and bone growth into the implant were acceptable. The continued use of polybutylene terephthalate in biomedical implants highlights the low toxicity of this polymer.

3.5 Elastomeric Polyester

This term has been used to describe a random copolymer of polybutylene terephthalate and polybutylene ether glycol. These polyester elastomers have strength comparable to many thermoplastics plus a rubberlike extensibility (82). A variety of polymers have been used in biomedical implants, indicating low toxicity, including biodegradable nerve guidance channels (83), replacement arteries (84), and biodegradable artificial skin (85).

Synthetic Polymers, Polyesters, Polyethers, and Related Polymers
Steven T. Cragg, Ph.D., DABT

4 Unsaturated Polyester Resins
Polyester resins comprise a large group of polymers and may include both these resins and the alkyds discussed in Section 4.
4.1 Properties
4.1.1 Molecular Weight, Properties, and Applications The molecular weight for uncured resins has been given as 7,000–40,000 (24). When used in polyester–glass laminates, the cured resins are noted for their good strength and rigidity, low density, toughness, and translucency. They can be formulated to be fire retardant and generally have superior heat resistance compared to most rigid thermoplastics available in sheet form.

Propylene and diethylene glycol are often used to influence the rigidity or flexibility of the resin. With phthalate–fumarate resins, increasing propylene glycol content increases hardness but may cause a reduction in tensile and flexural strength. Diethylene glycol can make the polyester more flexible and also more susceptible to water absorption. Dibromoneopentyl glycol, tetrabromophthalic anhydride, and chlorendic acid (anhydride) are used for fire retardancy. Chlorendic acid (anhydride) and propoxylated bisphenol A are used for chemical resistance.

Generally, unsaturated polyester resins are classified as either general purpose or specialty polyester resins (88). General-purpose resins are widely used in the so-called “open mold” processes (hand lay-up/spray-up) to produce a wide range of products including boats, truck components, furniture, and applications that do not require the premium performance of higher-cost grades of polyester resin. Specialty polyesters are chemically tailored to meet the requirements of a wide range of applications including flexibilized polyesters, electrical-grade polyesters, heat-resistant polyesters, low flame/low smoke, translucent polyesters, and low shrink/low profile.
4.2 Production and Use
4.2.1 Structure, Synthesis, and Processing Thermosetting, unsaturated polyester resins are made in several steps (1, 24, 86). A saturated dihydric alcohol is generally condensed with both a saturated and an unsaturated dicarboxylic acid. The alcohol used in the prepolymer is almost always a glycol such as ethylene, propylene, butylene, diethylene, or neopentyl or dipropylene glycol. The use of ethylene glycol is limited because unsaturated polyester resins made from it have poor solubility in styrene. Polyhydric alcohols are sometimes used to provide strength and chemical resistance. Maleic acid (anhydride) and fumaric acid are the usual unsaturated acids, although itaconic or mesaconic acid may be used to give flexibility. Phthalic anhydride is the most widely used saturated acid component; however, isophthalic and adipic acids have common use.

The prepolymer (or first-stage resin) is dissolved in a vinyl monomer, usually styrene, with appropriate inhibitors; the product may be supplied as a syrup containing 20–50% monomer (vinyl toluene, methyl methacrylate, diallyl phthalate, or other monomers can be used) (87). To add strength to the cured resin, glass fiber can be added as reinforcement (other fibers such as aramid, boron, carbon, nylon, polyester, polyethylene can also be used) (88). Curing is by free-radical polymerization of styrene monomer with the unsaturated acid residues of the resin. An organic peroxide is used as an initiator. Benzoyl peroxide is frequently used for elevated temperature curing; methyl ethyl ketone peroxide or cyclohexane peroxide can be used with a cobalt accelerator at room temperature.

Products of high quality often require a relatively high percentage of unsaturation in the polymeric chain. This can result in resins that during the curing process produce high temperatures that must be controlled to prevent explosions. Styrene-containing unsaturated polyesters polymerize with time at ambient temperatures.

Maximum mechanical strength may not be attained until more than a week after curing. Unsaturated polyester may remain undercured, soft, and, in some cases, tacky, if freely exposed to air during this

period.

4.4 Toxic Effects

4.4.1 Skin Reactions The finished, completely polymerized products are not considered dermatologic hazards (89), although there has been one case report of an 8-month-old child who developed contact sensitivity to cured unsaturated polyester resin in a limb prosthesis (90). Exposure to the uncured unsaturated polyester resin systems used in manufacturing have been associated with outbreaks of dermatitis during the 1960s (91, 92), but this was less common during the 1970s (89, 93). However, dermatitis can readily become a major problem in plants with poor industrial hygiene practices (94). The incompletely hardened macromolecular resin was considered the main causative agent in 17 dermatitis cases cited in a 1962 Czech report (95).

The dermatitis is reported as caused mostly by primary irritation but occasionally by sensitizing agents (92, 96–98; see also Ref. 89). Reactions are eczematous and more frequent on the backs of the hands, wrists, and forearms. The suggested patch test concentration for the unsaturated polyester resin is 10% in acetone. Malten (99) discusses several earlier studies (including Ref. 94), rates the sensitizing capacity of the polyester resin system low, and calls attention in this connection to a test with volunteers exposed to benzoyl peroxide that induced a 40% incidence of sensitization.

Kanerva et al. (100), reported two cases of hand and face contact sensitization in two car repair workers using an unsaturated polyester resin filler putty. The sensitizing agent was determined to be diethylene glycol maleate. Tarvainen et al. (101) found that some workers may react to the hardened glue of unsaturated polyester resins after becoming sensitized. These researchers also identified diethylene glycol maleate as the putative agent responsible for sensitization with this unsaturated polyester system. Irritant dermatosis of the hands in workers using unsaturated polyester resins may also be of a nonallergic origin (102).

4.4.2 Inhalation and Thermal Degradation As indicated earlier, styrene is frequently used as a cross-linking monomer in the preparation of unsaturated polyester products. Potential exposure to styrene during processing is generally considered to present the most serious inhalation hazard associated with polyester resin. Styrene invariably evaporates when the resin surface is exposed to the atmosphere during molding operations, and without proper control, operators may be exposed to unacceptable levels of vapors (103). When products are manufactured in open molds typical of boat manufacturing, as much as 10% of the styrene can volatilize into the workplace air (104). Overall exposure to styrene monomer in seven representative U.S. plants in the fiberglass plastic boat industry ranged from 2 to 183 ppm; mean exposures for the primary job categories ranged from 44 to 78 ppm (3); see also Refs. 4, 105, 106, and 107. A Scandinavian report indicates that workers can be exposed “to a styrene concentration typically ranging from 20 to 300 ppm” (5). A French study (108) conducted under model laboratory conditions indicates that a standard-type resin released the equivalent of 4.3 mg styrene/cm^2 surface in 4 h, whereas a resin with reduced potential for evaporation of styrene yielded 0.7 mg/cm^2.

Other studies of boat manufacturing facilities report average exposures during work shifts typically did not exceed the then current OSHA PEL of 100 ppm (99, 109); however, those exposures did exceed the current PEL of 50 ppm. Studies of other hand lay-up and spray-up operations also report typical exposure levels below the then-current 100 ppm PEL (110–112). In 1989, OSHA reduced the 8-h TWA PEL for styrene from 100 to 50 ppm. In the rule making, OSHA noted that, with the exception of hand lay-up and spray-up operations in the boat building industry, the 50 ppm PEL could be achieved with engineering and work practice controls. OSHA found, for these boat-building and similar large scale lay-up operations, that employers must use respiratory protection in combination with engineering controls and work practices to achieve these limits (113). The PEL for styrene has since been increased to 100 ppm.

Fiberglass particles released during processing may be coated with a mixture of resins and finishes. Lim et al. (94) report finding minute amounts of trivalent and hexavalent chromium on fiberglass

samples collected during walk through plant surveys.

When exposed to fire, both conventional and fire-retarded formulations of unsaturated polyester resins typically yield copious amounts of smoke because the major decomposition product is usually styrene, which burns with a very smoky flame (86). Resins based on alkyl and particularly acrylate monomers may produce less smoke (114). Tests conducted by German investigators indicate that products evolved from pyrolysis in the 330–400°C range or above may be lethal to rats. Carbon monoxide can be released in biologically significant amounts but is not necessarily the cause of death. Additional details can be found in Refs. 114–117.

4.4.3 Cyto-/Genotoxicity Furniture workers exposed to unsaturated polyester resins showed increased frequencies of sister chromatid exchanges in their circulating lymphocytes compared to controls (118). Frequencies were higher than for nonexposed smokers. The specific agent responsible for the increase was not identified.

Synthetic Polymers, Polyesters, Polyethers, and Related Polymers
Steven T. Cragg, Ph.D., DABT

5 Alkyd Resins
Commercial production of alkyd resins was begun in the 1920s, and by the 1940s they had become the backbone of the coatings industry, widely used in paints, varnishes, lacquers, baking enamels, and other surface coatings. In 1973, consumption of alkyd resins peaked—they constituted about one-third of all synthetic resins used in coatings. Now they comprise about one-fourth (119).

Because of environmental concerns for the solvents typically associated with these resins and the better performance of latex paints aimed at the consumer architectural coatings market, their use has declined and will continue to do so. However, they are one of the more versatile binders with potential for modification for use in high-solids coatings, an attribute that will make them important for some time to come.
5.1 Production and Chemical Characteristics
Alkyd resins are condensation polymers formed from esterification reactions. However, they differ from other polyesters that are unsaturated and thermosetting in that they are modified with a triglyceride oil or the fatty acids of that oil. They are the reaction products of a polybasic acid, a polyhydric alcohol, and a monobasic fatty acid or oil. The name alkyd is derived from a combination of alcohol and acid (120).

The most commonly used polybasic acids are the anhydrides of dicarboxylic acids, with phthalic anhydride being by far the most important. Pentaerythritol is the most commonly used polyhydric alcohol; others used frequently include glycerol, trimethylol-propane, and trimethylolethane. When oils are used as starting materials, alcoholysis from a polyol, glycerol being very common, must first be carried out to form the monobasic fatty acid. This reaction is often catalyzed by a very small quantity of basic compounds such as lithium hydroxide. Currently, most alkyd resins are manufactured using the solvent process that refluxes the solvent and the reactants until the completion of the reaction. The final product is usually let down or thinned with a solvent or diluent to a 50% or more solids content in solution.

The fatty acid moiety determines whether the alkyd is drying or nondrying. Unsaturated fatty acids in the alkyd undergo oxidation in air and cross-link or “dry.” The cross-linking is catalyzed by “driers,” usually metallic soaps added during the paint formulation stage. Alkyds without these unsaturated groups are nondrying and are usually used as plasticizers with other resins. Sometimes monobasic acids other than fatty acids are used as starting materials to make “oil-free” alkyds (e.g.,

rosin acids) or to terminate an alkyd chain [e.g., *p*(*tert*-butyl)benzoic acid].

Alkyds may be modified chemically by combining them with other molecules. Vinyl modification is common and occurs by grafting such molecules as styrene, vinyltoluene, and acrylic esters to the unsaturated groups in the resin chain via free-radical initiation. Alkyd resins may also be modified by alkoxypolysiloxanes, phenolics, polyamides, and diisocyanates. Alkyd resins may also be mixed with other resins to obtain the desired properties. They are commonly added to nitrocellulose lacquers.

By varying the starting materials, the modifiers, and/or the polymers with which they are blended, they may be "designed" for a wide variety of uses. Vapor emissions and hazards from solvents may also be minimized by making an alkyd resin water reducible. This is accomplished by creating an emulsion or introducing groups into the resin to make it water soluble.

Exposure to the ingredient dicarboxyic acid precursors, phthalic, trimellitic, and maleic anhydrides, was evaluated in a retrospective cohort study of alkyd resin workers (121). This study found that exposures in alkyd resin production facilities were generally low in recent years at levels below the TLVs for these anhydrides capable of causing occupational asthma. Another similar study in a cushioned flooring manufacturing plant showed similar low exposures (122).

5.4 Toxic Effects

Little information exists on the toxicity of the alkyd resins themselves. It is quite common to perform no toxicity tests at all on new alkyd resins for two reasons. First, they are almost always encountered as part of formulations that contain other chemicals assumed to present greater hazards. Thus exposure is controlled by limiting the exposure to the other chemicals. Second, the precursors to alkyd resins and any residual monomers are considered to be far more toxic than these large molecules, most of which exceed 1000 molecular weight.

Aside from the solvents, the dibasic acids used as starting materials for the basic alkyd resins present the greatest hazards during the manufacturing process. Phthalic anhydride, along with other low-molecular-weight anhydrides, is a known irritant and has been identified as a sensitizer, with a potential for respiratory sensitization. The EPA has identified carboxylic acid anhydrides as a category of concern for potential pulmonary sensitization and may require testing for new chemicals containing this group during the premanufacture notification review process (123). (These groups are not present in the resin owing to esterification.) Yokota et al. (124) recently have reviewed prevention of occupational allergy due to these anhydrides. The chain terminator, *p*-(*tert*-butyl) benzoic acid, has been identified as a potential reproductive toxin. The toxicity of such ingredient monomers, stabilizers, plasticizers, catalysts, and other performance enhancing chemicals that may be present as precursors or residuals, is dealt with in other chapters of this treatise.

Chemical modifiers such as styrene, acrylic esters, and diisocyanates present health hazards, including irritation and sensitization potential, unique to these chemicals during the manufacturing process (125). The hazards associated with the solvents used to manufacture the resin are also associated with the processing and use of the resin and the coatings formed from it. Small amounts of residual monomers (usually well below 1% by weight) remain in the resin and may present a potential for exposure during their use. Release of monomers (e.g., phthalic anhydride) may be of concern during heat-accelerated curing processes such as baking.

Toxic combustion products usually are not a problem. Most of these resins contain only carbon, hydrogen, and oxygen, and they are contained, owing to their customary use, in thin films, making less of a contribution to the combustion products than the substrates and other materials in the environs. Protective measures aimed at solvents and other attendant chemicals encountered during the manufacturing, processing, and use of alkyd resins should protect against any hazards from the resins themselves, residual monomers, or low-molecular-weight species. Additional protection may be required when handling raw materials such as acid anhydrides, styrene, and acrylic esters, for the manufacturing operation.

5.5 Additives
Other substances may be used as modifiers or additional ingredients, including phenolic resins, epoxy resins, styrene, cobalt naphthenate, lead soaps, and fire retardants. Additives are used to resist mildew and ultraviolet light. Curing or cross-linking is accomplished by air oxidation of the unsaturated groups (24, 86).

Synthetic Polymers, Polyesters, Polyethers, and Related Polymers
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6 Allyl Polymers
The term *allyl resin* typically refers to unsaturated polyester cross-linked with an allyl-type monomer, such as allyl alcohol, rather than styrene. Such resins are notable for their retention of electrical properties under conditions of high temperature and high humidity. "Allyl molding compounds" may refer to "nonpolymeric" substances used in the preparation of thermoset moldings. Those in widest commercial use are the monomers and prepolymers of diallyl phthalate and diallyl isophthalate (126). Another self-polymerizing monomer, CR-39 (CAS # [*142-22-3*]; a.k.a., diethylene glycol *bis*(allyl carbonate) or diallyl diglycol carbonate), is used for lenses and optical devices because of its light weight and resistance to impact, scratch, and abrasion.

CR-39 monomer is a colorless, slightly volatile liquid (molecular weight 274) prepared from diethylene glycol chloroformate and allyl alcohol (127). A peroxide catalyst (typically, benzoyl peroxide, isopropyl percarbonate, cyclohexyl percarbonate) is dissolved at about 3% by weight in the diallyl glycol carbonate and then the liquid is polymerized first to a gel and then to a fusible solid.

The monomer is known to be an irritant. Skin contact during the polymerization process may result in a rapidly developing, irritant dermatitis with an incidence as high as 70%. Dermatitis frequently appears to result from direct contact with the liquid monomer. Some cases would appear to be traceable to residual monomer or other ingredient(s) in partially polymerized polymer because "adherence of the polymer to the molds is often associated by the workers with the irritant nature of the resin" (127). The National Fire Protection Association ranks the health hazard for this monomer as a 1 (slightly toxic) (128).

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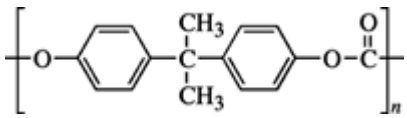
7 Polycarbonate Resins
7.1 Chemical and Physical Properties
Polycarbonate resins are characterized by water-white clarity and high impact resistance. They are extremely tough and rigid and have good electrical insulation characteristics (1, 86).

7.1.1 Structure Thousands of polycarbonates have been prepared since polycarbonate was first introduced in the late 1950s. Approximately 99% of the polycarbonate sold is the polycarbonate of bisphenol A with the basic structure



7.1.2 Properties The properties of polycarbonates are dramatically affected by the comonomers, molecular weight, end groups and branching agents. BPA polycarbonate homopolymer has a T_g of 145–150°C. Polycarbonate is typically amorphous. The polymer has a polymer decomposition temperature as measured by thermal gravimetric analysis in nitrogen of ~510°C. The polymer is soluble in solvents such as chloroform, methylene chloride, and tetrachloroethane. Other nonchlorinated solvents include pyridine, *m*-cresol, and phenol. Polycarbonates are insoluble in water, alcohol, organic acids, and hydrocarbons (130). The resin swells in various aromatic solvents, ketones, and esters.

7.2 Production and Use

7.2.1 Preparation Aromatic polycarbonates are prepared by the condensation of a bisphenol with a carbonic acid derivative. Commercially, the bisphenol is typically 4,4'-hydroxyphenylpropane (BPA), and the carbonic acid derivative is normally phosgene. Other comonomers can be added to tailor the properties of the resin to specific applications. In addition, various monofunctional compounds are added to control the molecular weight of the resin.

The interfacial polymerization process is the most widely used method in the manufacture of polycarbonates and polycarbonate copolymers. Two variations of the process have been described in the literature (129).

In the standard interfacial process, the bisphenol, chain terminator, catalyst, organic solvent, water, and caustic are charged into a stirred reactor followed by the addition of phosgene. The sodium salt of BPA is generated in the aqueous phase and allowed to react with phosgene in the organic phase in the presence of a catalyst. The catalyst is typically a tertiary amine. In this process, the phosgene reacts with the sodium salt of BPA to form BPA chloroformates. Concurrently, the catalyst facilitates the reaction of phenoxide with the chloroformates to form high polymer. The molecular weight of the resin is controlled by chain terminators, typically monofunctional phenols, carboxylic acids, or acid chlorides.

In the second process the tertiary amine catalyst, and in some cases the terminator, are not added in the first step. Without the catalyst present, the reaction of phenoxide with the chloroformate end group is suppressed resulting in the formation of BPA chloroformates and chloroformate oligomers. After the chloroformates are formed, the terminator and the tertiary amine are added. The amine catalyzes the condensation of the phenoxides with the chloroformates affording high polymer. This process has been claimed to produce resin with less carbonate functionality.

In both processes, after the reaction is complete, the organic phase is separated from the aqueous phase and washed free of catalysts and salts. Isolation of the polymer can be accomplished by antisolvent precipitation, spray drying, and devolatization using an extruder (129).

7.2.2 Additives A variety of additives are added to polycarbonate to enhance its properties, its retention of properties, and/or its processability. These include the following:

- UV stabilizers (typically benzotriazoles)
- Thermal stabilizers [such as phosphonites, phosphites, and organosilicon compounds (131–133)]
- Epoxides for increased hydrolytic stability (134)
- Release agents [typically, long-chain carboxylic acids and esters (135, 136)]

Other commercially significant additives and fillers include the following:

- Fire-retardant agents such as brominated polycarbonate copolymers (137) organic sulfonates (138–141), and finely dispersed fluoropolymer

- Glass fiber
- Blowing agents, such as 5-phenyltetrazole (142) or henyldihydrooxadiazinone (143), for use in foamed polycarbonate

7.2.3 Processing 7.2.3.1 Injection Molding Although polycarbonate has been processed in most common injection molding machines, in-line reciprocating screw machines are preferred. Melt temperatures of 280–350°C and mold temperatures of 80–120°C are typically recommended for general-purpose grades.

7.2.3.2 Extrusion Film, sheet, multilayer sheet, profiles, tubes, and rod stock can be manufactured using high-viscosity polycarbonate resin in extrusion processes. Melt temperatures of 230–260°C are typically recommended.

7.2.3.3 Thermoforms Polycarbonate sheet can be thermoformed. The sheet must be dried at 80–110° C prior to forming. Typical forming temperatures are 175–205°C.

7.2.3.4 Blow Molding Blow molding of branched polycarbonate has been extensively used to manufacture a wide variety of items from baby bottles to 5-gal water bottles. Typically, the non-Newtonian rheological properties obtained with branched resin are needed for blow-molding applications.

7.2.3.5 Applications Applications include medical equipment, beer pitchers, automotive lenses and trim extrusions, drapery fixtures, door and window components, furniture, and plumbing. Foamed polycarbonate is used in major automotive components such as a one-piece bus seat frame. Sheet glazing products that conform to specifications for safety glazing and burglar resistance may be used in schools, off-highway installations, and security facilities. Coated thin-gauge sheet has been used for protective eyewear and business machines (144). Registration of fast-neutron-induced recoil and (*n, a*) tracks in polycarbonate foils provides a sensitive means of dosimetry (145). Polycarbonate resins are approved for use with foods by the FDA (21 CFR 177.1580).

7.4 Toxic Effects

7.4.1 Toxicologic Information Polycarbonates in general are not considered primary eye irritants. When polycarbonate products, in finely divided form, were placed into the eyes of rabbits, slight transient redness or discharge occurred, consistent with the expected slightly abrasive nature of the resin particles (146).

Polycarbonates are not considered primary skin irritants. The Draize skin primary irritation score (rabbit) for polycarbonate resins, in finely divided form, for a 24-h exposure is 0. These resins are not expected to be skin sensitizers based on results of modified Buehler guinea pig sensitization. The dermal LD_{50} (rabbit) is estimated to be greater than 2 g/kg (146).

The estimated acute oral LD_{50}(rat) is greater than 5 g/kg (147). Bisphenol-A polycarbonate has been found to be physiologically inert when fed to rats at a level of 6% in food (148).

In acute inhalation tests, laboratory rats were exposed to processing fumes at concentrations exaggerating those that would likely occur in workplace situations. No deaths or signs of toxicity, except transient irritancy in some cases, were noted during the 6-h fume exposure tests. There were no distinct or consistent treatment-related tissue or organ changes noted in gross necropsies (149).

Recently, bisphenol A has been implicated as an environmental “endocrine disruptor” or chemical that interferes with normal endocrine metabolism by mimicking estrogen. Brotons et al. (150) reports finding the “xenoestrogen” bisphenol A in foods from cans lined with a polycarbonate resin. However, other studies that have evaluated the migration potential of bisphenol A from polycarbonate indicate that degradation of polycarbonate and consequent migration of bisphenol A is minimal. Specifically, a study using FDA worst-case extraction procedures found no

migration/extraction of bisphenol A from several polycarbonate formulations (151). Bisphenol A was found not to migrate from 24 different brands of polycarbonate baby bottles following sterilization by steam, alkaline hypochlorite, or washing in an automatic diswasher at 65°C with detergent (152).

Toxicologic aspects of plastic combustion products are very complex. This is due mainly to the fact that it is very difficult to simulate real-world environments under controlled conditions. Depending upon a variety of factors, the qualitative and quantitative nature of chemicals present in the combustion product mixtures will vary. Factors contributing to toxicity of real-life fires include increase of carbon monoxide and carbon dioxide, decrease of oxygen, and the presence of irritant gases. The primary effects from fires are asphyxia due to oxygen deficiency, poisoning from carbon monoxide, heat damage to tissues, and irritation of the respiratory tract by combustion gases (see Section 1.5). A study using rats as models found that combustion products from polycarbonate resins induce rapid sensory irritation of the upper respiratory tract. Rapid recovery also occurred following termination of exposure (153). Another study on toxicity of plastic products using eight different plastic resins found that combustion products from polycarbonate were among the least toxic relative to the other resins (154). Polycarbonates manufactured with the flame retardant tetrabromobisphenol A should not present an additional toxicological hazard during manufacturing since this compound has low acute or chronic toxicity (155). Its combustion toxicity has not been assessed. When polycarbonate products were manufactured with a flame-retardant metallic covering film, combustion toxicity products were no worse than for noncoated polycarbonate (156).

7.4.2 Plastic Processing Fumes The chemical composition of processing fumes of polycarbonates, like any other plastic materials, depends greatly on product formulation. In general, processing fumes from polycarbonates processed at recommended processing conditions may include trace levels of phenol, alkylphenols, and diarylcarbonates. Polycarbonate treated with brominated fire retardants may also evolve small traces of hydrogen bromide. Products formulated with polyfluorocarbon additives may evolve hydrogen fluoride and fluorocarbon compounds in the resulting processing fumes. Thermal emissions from impact-modified polycarbonate resins may also include styrene and acrylates, depending on the impact modifier used in its formulation.

In some instances, additives containing certain heavy metal compounds may be present. These ingredients are essentially bound in the plastic matrix and are unlikely to contribute to workplace exposure under recommended processing conditions.

Processing fumes may cause irritation to the eyes, skin, and respiratory tract, and in cases of severe overexposure, nausea and headaches. Fumes from plastic thermal processes may condense on processing equipment, ventilation systems, and other surfaces. These greaselike processing fume condensates can cause irritation and injury to skin. Use of proper personal protection while cleaning or handling these condensates should be observed.

When polycarbonate was machined using either hot-gas welding or laser cutting techniques, significant particulate was formed compared to polymethyl methacrylate polymer or polyethylene terephthalate (157, 158).

7.4.3 Exposure Controls and Personal Protection A continuous supply of fresh air to the workplace sufficient to replace that used to remove processing fumes through local exhaust systems is necessary for proper operation of these systems. Processing fume condensate may be a fire hazard and toxic; it must be removed periodically from exhaust hoods, duct work, and other surfaces. Persons performing such tasks must be provided appropriate personal protection including face protection and respirators. Ventilation requirements must be locally determined to limit exposure to materials at their point of use.

8 Polyethers
8.0 Acetal Resins—Polyoxymethylene
8.0.4 Molecular Weight Most manufacturers supply a number of different molecular-weight resins. The Mw of some commercial polyoxymethylenes has been reported in the range from 20,000 to 110,000 (1). In general, increasing molecular weight leads to increased toughness, and increased melt viscosity. Table 92.3 provides an example of the effect of molecular weight on properties. Coupled with low density (as compared to metal) and ease of fabrication, acetals are used as replacements for metal in many applications (1).

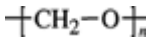
Table 92.3. Effect of Molecular Weight on Impact Properties of Acetal Homopolymer*

Approximate M_n	Notched Izod (ft-lb/in)[a]	Tensile Impact (ft-lb/in^2)[b]
65,000	2.4	170
40,000	1.4	100
30,000	1.3	70

* *Source*: Ref. 2a
[a] Method: ASTM D256.
[b] Method: ASTM D1822.

8.0.6 Molecular Structure Acetal resins [*9002-81-7*] are also known as polyformaldehyde and polyoxymethylene. Polyoxymethylene heart valve biopolymeric materials may be found in the biomedical literature with the name Delrin [*9085-38-5*]. Although paraformaldehyde [*30525-89-4*] also is a polymer of formaldehyde, this material has repeating units of 8–100 according to Hawley's Condensed Chemical Dictionary (159) and should not be considered the same as the larger polyformaldehyde resins discussed here. Unlike the larger, more refined polyoxymethylene polymers, paraformaldehyde may be highly irritating and an allergic sensitizer, perhaps due to large amounts of residual free formaldehyde (160, 161). High-molecular-weight acetal resins are highly crystalline, resulting in excellent retention of properties and dimensions and predictable behavior. Because of these notable features of metal-like stiffness, resistance to fatigue, and resistance to organic solvents, they are referred to as engineering resins.

The dominant structural repeat unit of acetal resins is



or formaldehyde. Acetal homopolymers consist entirely of these repeating units, with acetate and caps to provide stability. In acetal copolymers, the structural regularity of—OCH_{2-n} is interrupted after approximately 65 units (n = 65) by a comonomer unit derived from ethylene glycol, 1,4-butylene glycol, or diethylene glycol. The purpose of including comonomer units is to provide depolymerization stoppers. The inclusion of the comonomer units also reduces the inherent crystallinity, affecting the strength and rigidity of the resin. Reduction of properties is generally

compensated to some extent by addition of nucleating agents.

8.1 Properties

Typical properties of the intermediate molecular weight, probably the most widely sold grades of acetal resins, are listed in Table 92.4. Again, owing to the highly crystalline nature, acetals have excellent solvent resistance. However, all acetals are attacked by strong acids; copolymer resins in general are resistant to strong bases.

Table 92.4. Properties of Typical Acetal Resins at 23°C

Property	Method	Acetal[a]
Tensile strength	ASTM D638	8,800–10,000 psi
Elongation at break	ASTM D638	40–50%
Flexural modulus	ASTM D790	375,000–400,000 psi
Melting point		165–175°C
Specific gravity	ASTM D792	1.41–1.42 g/ml

[a] Range accounts for both homopolymer and copolymer values.

Acetals in contact with steel generally produce less friction than acetals with other metals, and acetals used with nylon are usually preferable to either alone (1). Most manufacturers also sell resins modified with various additives, including fluoropolymer fibers for reduced friction and wear, glass fiber for increased modulus and strength, and toughener to increase impact resistance.

8.2 Production and Use

Acetal resins are manufactured from monomeric formaldehyde or from its cyclic trimer, trioxane. Homopolymers are manufactured from highly purified anhydrous formaldehyde (1, 162). One process for making these resins starts with aqueous formaldehyde. The manufacture of polymers with useful molecular weights (typical M_w are 25,000–80,000 with M_w/M_n~2) requires very high-purity monomer. Thus the concentration of chain transfer agents such as water and methanol must be reduced to very low levels. All acetal homopolymers are believed to be manufactured by anionic polymerization. To ensure good thermal stability, the homopolymers are end capped with acetate end groups. Esterification with acetic anhydride or other anhydrides can be conducted at 130–200°C with sodium acetate as a catalyst.

Most copolymers are manufactured from trioxane by cationic polymerization. Like the formaldehyde used for making homopolymers, the trioxane must also be highly purified to be able to produce copolymer resins of useful molecular weights. (M_n of 15,000–40,000, with M_w/M_n~3–80). Because the "as-polymerized" copolymer resins contain unstable ends, the polymer is typically stabilized by thermal or hydrolytic degradation back to depolymerization-stopping comonomer units.

Acetal resins may be readily processed on conventional injection molding, blow molding, and extrusion equipment, provided that overheating is avoided. Overheating can lead to the production of formaldehyde gas and a serious or even dangerous buildup of pressure. Gas pressure created by decomposition can rapidly become extremely high when processing machines are not properly vented. A shotgun-like reaction (blow-back) from a pellet hopper was reported to develop within a few minutes after failure of one of three heating zone circuits (163). Recommended control measures (164, 165) include (*1*) the use of vented feed screw and proper design of injection nozzle, (*2*) preventive maintenance and replacement of worn gaskets and valves, (*3*) automatic heat regulation and monitoring of excess temperature conditions by an audible alarm or warning device in direct view of the operator, (*4*) a standby water cooling device not dependent on the main electrical system, and (*5*) personnel instruction.

8.4 Toxic Effects

8.4.1 Oral Toxicity and Skin Contact Ninety-day feeding tests have been conducted with two different types of polyoxymethylene (96+ and 99% active ingredient, respectively, both with M_w of 25,000–30,000). Rats in groups of 40 and dogs in groups of 4 were fed a 10% dietary level of each test polymer with Alphacel® cellulose as a control (28). One or two rats died in each of the two test groups; one death was also observed in the corresponding control group. No deaths occurred among any of the dogs. No changes attributable to the test polymer were evident in behavior and appearance, body weight, food consumption, ophthalmoscopy, and hematologic, biochemical, or urinalysis studies. No gross or microscopic lesions or variation in organ weight attributable to treatment were observed in any of the animals.

Skin irritation and sensitization tests with 1-in disks of polyoxymethylene extruded sheeting were conducted by the Schwartz–Peck procedure (36). In another study with a 10-d rest period, on a panel of 212 volunteers (166), some mild or moderate erythema consistent with occlusion was observed at the 6-d reading, but otherwise no reactions were observed. The panel included one subject known to be sensitive to urea–formaldehyde who showed no reaction through 4 d after removal of the test polymer.

8.4.2 Inhalation Toxicity and Thermal Degradation Data A massive single 6-h dust inhalation exposure (47 mg/L nominal concentration) caused emphysema and atelectasis in rats. Fumes evolved at temperatures as low as 150°C, in sufficient quantity, can be lethal to animals that are exposed for 4 h. Both formaldehyde and carbon monoxide have been identified in the effluent evolved at elevated temperatures. More details can be found in Refs. 168–171.

8.4.3 Cytotoxicity/Implant Studies Many studies have evaluated the long-term efficacy and biocompatability of heart valves manufactured from Delrin, a highly refined polyoxyethylene, in humans (172–180). Other than mechanical wear, sometimes manifesting as distortions in the shape of the valve as a result of cavitation and other hemodynamic stresses, no toxicity and little evidence of rejection have been reported in heart-valve patients for periods as long as 20 yr. Delrin, used as a bone substitute in a rabbit model, was less inert than titanium inducing foreign body reactions (181). Polyoxyethylene (Delrin) was more cytotoxic than polyvinyl chloride, inhibiting cell growth in the continuous cell line, L-929, as measured by cell density, total protein, total per cell, protein fraction of cells in mitosis and other parameters (182).

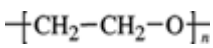
8.4.4 Injection Studies Rats receiving intraperitoneal injections of an unstated concentration of dust suspension showed granulomas with some scarring when examined 90 d later (183). In another study 40 mg/kg was administered to male guinea pigs. One animal died due to pneumonia and infection. The other four animals survived the 32-d observation period. At sacrifice, peritoneal nodules consisting of the polymer surrounded by grant cells were found in all animals. The nodules showed no inflammation and were typical of the reaction caused by an inert, insoluble material (184).

9.0 Polyoxyethylene

Polyoxyethylene is available as high- or low-molecular-weight polymer.

9.0.4 Molecular Weight One group of low-molecular-weight polyoxyethylenes range from liquids to waxy solids, with a molecular weight up to 10,000. High-molecular-weight resins have a molecular weight described as ≥100,000 (16) and ranging up to 4,000,000 (185).

9.0.6 Molecular Structure: The generic structure is



9.1 Properties and Applications

Even the high-molecular-weight resins are water-soluble thermoplastic polymers that can be extruded as films. They can be used in packaging for food, as textile sizes, and for the reduction of

hydrodynamic friction.

9.4 Toxic Effects

9.4.1 Acute Toxicity Polyoxyethylene polymers (a.k.a, polyethylene glycols or PEGs) with molecular weights below 10,000 have very low acute oral toxicity with LD_{50}s generally above 5,000 mg/kg and often above 10,000 or even 20,000 mg/kg (160). Even intraperitoneal and intravenous LD_{50}s often are above 5,000 mg/kg (160). In an older report (185), solutions of 0.1% commercial material killed rats when first administered intravenously at a dosage of 3 mg/kg (0.3 mL). This may have been due to clumping of cells and death from embolism. Subsequent injection of this concentration after shearing the polymer in an Osterizer did not kill rats receiving 40 mg/kg (4 mL). Few dermal LD_{50}s were found for polyethylene glycols of any molecular weight. Those found generally were greater than 5,000 mg/kg with no deaths reported at the highest dose tested (160).

Primary irritation testing of a variety of low-molecular-weight PEGs in rabbits reveals minimal irritation of eyes or skin (160, 161). PEG 400 (molecular weight = 400) has been used to wash human eyes as a 50% aqueous solution (160). Low-molecular-weight polyoxyethylenes were found to be nonsensitizing in patch tests. Low-molecular-weight PEGs have parasympathomimetic properties (160).

9.4.2 Repeat-Dose Toxicity Polyoxyethylene (PEG 400) was administered to Fischer 344 rats by daily gavage 5 d/wk for 13 wk at doses of 0, 1, 2.5, or 5 mL/kg/d (186). No changes were noted in mortality, clinical chemistries, or hematology. High-dose animals showed a slight decrease in body weights. Mid- and high-dose groups exhibited loose stools. All treatment groups consumed water in excess of controls in a dose-related manner. Kidney weights were slightly increased, but histopatholgy revealed no lesions. A functional difference was seen in kidney function evidenced by increased urinary *N*-acetyl-b-D-glucosaminidase, vascular cell findings, and bilirubin levels. Animals allowed to recover for 6 wk showed no kidney changes.

Rats were exposed to aerosols of polyoxyethylene (PEG 3350) at concentrations of 0, 109, 567 or 1008 mg/m^3, 6 h/d, 5 d/wk for 2 wk (187). No effect was noted on clinical signs, ophthalmology, clinical chemistries, urinalyses, or gross pathology. Body weight gains in males of both groups were statistically decreased but with no associated dose–response effect. Lung weights of both sexes were increased, and histopathology revealed some macrophage-filled alveoli. No histological lesions were found in other tissues.

Polyoxyethylene with a mean molecular weight of 4,000,000 was fed to rats for 90 d at dietary levels averaging 8.0 and 18.4 g/kg/d (188). These rats showed changes, rated minor, in the liver and kidney. Two-year tests with rats fed at dietary levels averaging up to 2.76 g/kg/d and dogs fed at dietary levels in the range of 0.6 g/kg/d showed no detectable effect. Testing with a ^{14}C sample revealed no significant absorption of the polymers *per se* from the gastrointestinal tract of the rat or dog. The content of glycols and polyglycols in the tagged sample was considered sufficient to account for all the radioactivity found in the urine (0.72 and 1.1% of the dose administered to 20 rats and 1 dog, respectively).

9.4.5 Reproductive Toxicity Facial malformations have been reported in the offspring of mice but not rats where pregnant mice were dosed orally with 0.5 and 0.7 mL/kg/d on days 6–17 of gestation, and rats were dosed orally with 1.5–5 mL/kg/d on days 6–14 or 11–16 (188). Maternal toxicity was evident in rats but not mice. Offspring of mice exhibited marked facial and thoracic skeletal defects. In the rabbit, PEG 300 and 400 caused maternal toxicity at daily oral doses of 2 mL/kg during organogenesis but no adverse effects on the fetus (189). Gupta et al. (190) reported no malformations in soft or skeletal tissue in either rats or rabbits (10 dams/group) treated daily during organogenesis with oral doses of 1 mL/kg (rats) or 2 mL/kg (rabbits).

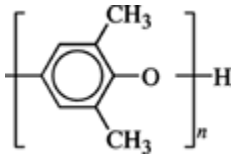
9.4.6 Human Clinical Use Review of the biomedical literature reveals many studies where polyoxyethylene polymers have been evaluated for efficacy and adverse effects when used as vehicles for medications and as oral or rectal colonic cleansers prior to colonoscopies. The continued use of polyoxyethylene polymers of diverse molecular weights points toward the low toxicity of this family of polymers.

10.0 Polyphenylene Oxide-Based Resin

Polyphenylene oxide can be blended with crystal polystyrene (PS) in all proportions, forming an alloy with a single glass-transition temperature. The higher the PS content, the lower the heat distortion temperature of the material and the easier the alloy to process. These alloys can be brittle and must be further modified to improve toughness by the addition of rubber impact modifiers. In practice, polyphenylene oxide–PS resin blends are also compounded with many additives, including stabilizers and fire retardants. The resulting resins are cream colored and have excellent melt flow. Alloys of polyphenylene oxide can be modified with glass or carbon fibers and a variety of mineral fillers to improve rigidity, tensile strength, and static dissipative properties. This resin family can be filled to high levels with combinations of fiber and mineral fillers to provide high-modulus, controlled shrinkage resins.

10.0.1 CAS Numbers: [*9041-80-9*], [*25134-01-4*]

10.0.6 Molecular Structure:



10.1 Physical and Chemical Properties

Polyphenylene oxide is a thermoplastic resin made from phenolic monomers. Commercially available resins are based on 2,6-dimethylphenol (a.k.a., 2,6-xylenol) and are produced by oxidative polymerization in the presence of an amine catalyst.

Polyphenylene oxide homopolymers have a relatively high T_g (above 212°C) and are very difficult to process (191). At normal processing conditions (300–350°C), melt flow is very stiff, and special precautions must be taken to minimize oxidation.

The blendability of polyphenylene oxide and PS in all proportions provides the capability of producing materials with a wide variety of physical properties and heat resistance. Products are available over the 75–175°C heat distortion range (192). Because both polyphenylene oxide and polystyrene are hydrophobic in nature, the resulting alloys are characterized by low moisture absorption; this, in turn, results in very good electrical properties over a wide range of temperature and humidity.

These resin blends have relatively low coefficients of thermal expansion. In fact, glass-reinforced resins have nearly the same coefficient of thermal expansion as that of metals, such as aluminum.

Alloys of polyphenylene oxide and PS are amorphous materials and can be chemically attacked by a number of organic solvents. These resins will soften or dissolve in many halogenated and aromatic hydrocarbons. Several alloys, however, have been developed to provide improved chemical resistance. These blends are based on polyphenylene oxide and crystalline polymers, such as nylon. Polyphenylene oxide provides excellent heat resistance and toughness, and the crystalline resin provides chemical resistance. These types of blends have utility in the automotive industry, where chemical resistance to compounds such as oils and gasoline is needed in addition to good heat resistance at relatively high temperatures.

10.2 Production And Use

Polyphenylene oxide–PS resins can be processed by standard injection molding, extrusion, blow molding, and structural foam molding. Processing temperatures vary, depending on resin grade, from 230 to 320°C. These resins are easily foamed either by chemical heat-activated blowing agents or by physical injection of inert volatile gases.

Major applications of polyphenylene oxide–PS blends include automotive interiors, such as instrument panels and seat backs; automotive exteriors, such as wheel covers, mirror housings, and rear spoilers; and electrical applications such as fuse boxes and connectors. Other applications include telecommunications and business machines. For telecommunications and computer and business equipment applications, these resins are available with varying levels of flame retardants to meet a wide range of applications: computer housings, card frames, keyboard bases, printer housings, and so on. High-modulus grade resins also find applications in chassis for copiers and laser printers. Examples of home appliance applications include power tools, hair dryers, pump housings, and portable mixers (193). These resins also find extensive use in food contact applications in cookware and food packaging. In food contact applications, these resins offer great improvements over polystyrene in heat resistance for microwave food packaging.

10.4 Toxic Effects

Polyphenylene oxide is not considered a primary eye irritant. In a primary eye irritation study, polyphenylene oxide produced mild and transient irritation in albino rabbits (194). Within 1 h of instillation, redness of the conjunctivae and chemosis was observed, but had resolved by 48 h.

Polyphenylene oxide is not considered a primary skin irritant or a skin sensitizer. Polyphenylene oxide was nonirritating when applied dermally (500 mg/site) to rabbits for 4 h and examined for 3 d following removal (194). Polyphenylene oxide did not cause delayed contact hypersensitivity in guinea pigs given three weekly 6-h epicutaneous applications of a 100% concentration of polyphenylene oxide and challenged 2 wk later with a final application to a naive site (195).

Estimated acute oral exposure LD_{50} (rat) is greater than 5 g/kg. No mortality or signs of toxicity were reported in a group of five male and five female Sprague–Dawley rats given polyphenylene oxide acutely at 5000 mg/kg (146). In two other acute oral toxicity studies in rats, up to 15 g/kg produced no mortality or signs of toxicity (196, 197).

A no observed adverse effect level (NOAEL) for repeated inhalation of polyphenylene oxide powder is estimated to be 7 mg/m^3. In a 13-wk repeated inhalation study, a group of Fischer 344 rats (10 of each sex/group) receiving 1, 7, or 50 mg/m^3 of polyphenylene oxide dust for 6 h/d, 5 d/wk for 2 wk had no treatment-related mortality, clinical signs of toxicity, significant body weight or food consumption differences, or changes in hematology and clinical chemistry parameters (198). Gross and microscopic examination in the 50-mg/m^3 group revealed an exposure-related localized toxicity in the lungs and regional lymph nodes, consisting of a significant increase in lung weights and lung to body weight ratio and a mild, acute/chronic pulmonary inflammation and thymic/peribronchial lymph node histiocytosis. These symptoms were still apparent in the high-exposure group following a 13-wk recovery period.

Groups of 30 male and 30 female rats fed 1.0, 5.0, and 10% of polyphenylene oxide in the diet for 22 mo had no treatment-related mortality, clinical signs of toxicity, body weight differences, changes in clinical chemistry parameters, or apparent gross or microscopic alterations (12). Beagle dogs fed 1.0, 5.0, and 10.0% of polyphenylene oxide in the diet for 2 yr developed no treatment-related changes in mortality or physical parameters, and there were no alterations noted upon gross or histopathological examination (199).

Polyphenylene oxide is not a mutagen by the Ames assay. Several samples of polyphenylene oxide were negative in the *in vitro* Ames *Salmonella*/microsome plate test with and without activation at concentrations up to 2500 mg/plate (200, 201).

10.4.1 Exposure to Processing Fumes In acute inhalation tests, laboratory rats were exposed to processing fumes at concentrations exaggerating those that would likely occur in workplace situations. During the exposure periods (6-h duration) signs of eye and nasal irritation were observed. These signs of irritation disappeared shortly after the animals were removed from the exposure chamber. No deaths or signs of toxicity were noted during the fume exposure period. There were no distinct or consistent treatment-related tissue or organ changes noted in gross necropsies (202).

10.4.2 Exposure to Combustion Products The toxicologic aspects of plastic combustion products are very complex. This is mainly because it is very difficult to simulate real-world environments under controlled conditions. Depending on a variety of factors, the qualitative and quantitative nature of chemicals present in the combustion product mixtures will vary. Factors contributing to toxicity of real-life fires include increase of carbon monoxide and carbon dioxide, decrease of oxygen, and the presence of irritant gases. The primary effects from fires are asphyxia due to oxygen deficiency, poisoning from carbon monoxide, heat damage to tissues, and irritation of the respiratory tract by combustion gases.

Some older studies have attempted to elucidate the pyrolysis products of polyphenylene oxide and compare the toxicity of combustion products from this polymer and natural fibers. Under varying fire generation conditions, carbon monoxide, carbon dioxide, and particulates were major combustion products of polyphenylene oxide (203, 204). Bucci et al. attempted to characterize the lung histopathology of mice exposed to the pyrolysis products of several synthetic polymers, including polyphenylene oxide (205). Except for the lungs, no histopathology was evident in major organs from survivors 2 wk after exposure. In the lungs, extensive damage was found 2 wk post-exposure, but damage was too extensive to distinguish differences among polymers. Hilado et al. found that a modified polyphenylene oxide were less toxic than cellulosic materials, based on time of death (206). Based on time to incapacitation, however, synthetic polymers were more toxic. A fire-retarded polyphenylene oxide produced carbon monoxide less rapidly than non-fire-retarded synthetic polymers or natural materials (207). The authors of this study concluded that qualitatively identifying chemicals produced from pyrolysis should be the goal of such studies rather than ranking the toxicity of various polymers or natural materials. These results should be interpreted with caution since, as stated previously, the conditions of fire generation may profoundly influence the formation rates of toxic combustion species.

10.4.3 Plastic Processing Fumes Processing fumes from polyphenylene oxide and its blends, like any other plastic materials, depend highly on product formulation. In general, processing fumes from polyphenylene oxide processed under recommended conditions may include trace levels of alkylphenols, aliphatic amines and aldehydes, dimethylcyclohexanone, and toluene. Polyphenylene oxide/polystyrene blends may evolve styrene, styrene dimers, toluene, aliphatic amines, aldehydes and alcohols, ethylbenzene, and 4-vinylcyclohexene. Polyphenylene oxide/polystyrene blends flame retarded with triarylphosphate esters also evolve triarylphosphate esters and phenol. Products formulated with polyfluorocarbon additives may evolve hydrogen fluoride and fluorocarbon compounds in the resulting processing fumes. In some instances, additives containing certain heavy metal compounds may be present. These ingredients are essentially bound in the plastic matrix and are unlikely to contribute to workplace exposure under recommended processing conditions.

Processing fumes may cause irritation to the eyes, skin, and respiratory tract, and in cases of severe overexposure, nausea and headaches. Fumes from plastic thermal processes may condense on processing equipment, ventilation systems, and other surfaces. These grease-like processing fume condensates can cause irritation and injury to skin. Use of proper personal protection while cleaning or handling these condensates should be observed.

10.4.4 Exposure Controls and Personal Protection A continuous supply of fresh air to the workplace together with removal of processing fumes through exhaust systems is recommended. Processing

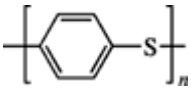
fume condensates may be a fire hazard and toxic; it should be removed periodically from exhaust hoods, duct work, and other surfaces using appropriate personal protection. Ventilation requirements must be locally determined to limit exposure to materials at their point of use.

Synthetic Polymers, Polyesters, Polyethers, and Related Polymers
Steven T. Cragg, Ph.D., DABT

11 Sulfur Polymers
The main commercial polymers are polyphenylene sulfide and the polysulfones.
11.0a Poly(p-phenylene sulfide)
11.0.1a CAS Number: [*53027-72-8*], [*9016-75-5*]

11.0.2a Synonyms: Poly(thio-1,4-phenylene)

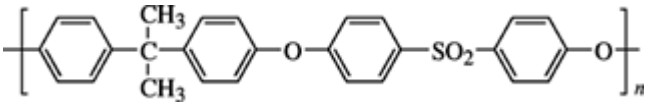
11.0.6a Molecular Structure:



11.0.b Polysulfone of Bisphenol A

11.0.1b CAS Number: [*25135-51-7*]

11.0.6b Molecular Structure:



Other polysulfones, such as polyether sulfone and polyaryl sulfone, that exist as powders differ in the types of linkage between aromatic rings and vary in their properties accordingly.
11.1a Synthesis, Properties, and Applications of Polyphenylene Sulfide
This polymer has been manufactured commercially by reacting *p*-dichlorobenzene and sodium sulfide, apparently in *N*-methylpyrrolidone (as cited in Ref. 208). Heating under oxygen cures the product to form a fine white powder, apparently linear. The white, lightly crystalline polymer discolors on heating in air to form a brown product, presumably cross-linked. Polyphenylene sulfide is known for thermal and chemical resistance, toughness, and flexibility. Additional properties are summarized in Table 92.1 (209).

Polyphenylene sulfide molded parts can be used in submersible and centrifugal pumps, computer housings, and telecommunications. Coatings of this polymer often utilized for chemical resistance in industrial process operations (210).
11.1b Synthesis, Properties, and Applications of Polysulfone
For commercial products an aryl ether can be treated with sulfonyl chloride in the presence of catalysts to give sulfone groups (polysulfonylation) or sulfones can be treated with phenolates to give ether groups (polyetherification). The structures made by one route are usually not made by the other, although some can be made by either process. All polysulfones have excellent creep resistance. They are stable to oxygen and thermal degradation and are flame resistant. Their toughness is affected by the inclusion of bulky side groups in the polymer structure or deviations

from the all-*para* orientation of groups linking the aromatic rings (208, 211). See Table 92.1 for additional data.

11.4 Toxic Effects

Several experimental tests indicate that products evolved at elevated temperatures can be rapidly toxic to mice. Thermal degradation of polyphenylene sulfide may yield hydrogen sulfide; the sulfur of polysulfone is typically evolved as sulfur dioxide. See Table 92.1. Additional details may be found in Refs. 40 and 212–216.

Ground fiberglass-reinforced polyphenylene sulfide (CAS# [*9016-75-5*]) was fed to rats in their diets at concentrations of 0, 0.5, 2.75, or 5% for 6 mo. A small number of high-dose rats exhibited yellow staining of the anogenital region. Red or black staining was noted in some rats around the eyes and masses on the neck. No changes were noted in behavior or hematology, and clinical chemistries revealed a transient elevation in blood urea nitrogen and a decrease in SGOT in the two highest-dose groups. No gross lesions were evident at necropsy, and organ weights were normal (217).

Highly refined polysulfone has been used as membranes in kidney dialysis machines and other biomedical applications with little toxicity.

Synthetic Polymers, Polyesters, Polyethers, and Related Polymers

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Overview

The toxicity of the polymers discussed in this chapter may be generally attributed to the residual monomers, catalysts, and other additives present rather than the polymer *per se*. The cured polymer itself may be of high molecular weight and, consequently, more or less toxicologically inert.

Carefully manufactured, highly refined polymers contain few residual toxic chemicals. However, some of the polymers discussed in this chapter, at least in some applications, go through an intermediate stage consisting of "prepolymers" (sometimes referred to as "resins") that react further to achieve their final, cured form. An example is a polyurethane system for making foam cushions. To manufacture polyurethane foam for cushions, workers combine diisocyanate molecules with a polyol prepolymer. Such "systems" inherently have more potential for exposure of workers if not the general public to toxic monomers or other reactive chemicals. The exposure potential of glues, paints, and coatings may extend more broadly to the consumer. Thus, examination of the toxicity of the polymers discussed in this chapter focuses on monomers and prepolymers. This is not always so. Some of polymers in this chapter are used in biomedical devices or in a way that puts them in intimate contact with humans. Here, the issue of biodegradation becomes important because of potential toxicity from breakdown products of the polymer, or rejection may ensue if the polymer is incompatible with the surrounding tissues.

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A. Polyurethanes

Polyurethanes are an extremely complex class of polymers (1) that are essentially ester-amide derivatives of carbonic acids (2). They were first developed commercially about 1937–1941 as nylon-like fibers (3, 4). Today they exist as foams, elastomers, coatings, adhesives, and elastomeric fibers. A major concern of the polyurethanes, polymers and silicones is the toxic health effects not only during manufacture, but also during installation, use and combustion of these materials. The exposed populations, the chemicals and types of exposure may vary considerably. This information is provided when it is available.

Polyurethanes, also called polyurethans, urethanes (these compounds should not be confused with urethane gas, a chemical used as an anesthetic), and polycarbamates, are polymers that have a urethane linkage in the polymer backbone, which is derived from the condensation of an isocyanate group and an alcohol group. A typical polyurethane may contain aliphatic and aromatic hydrocarbon moieties, linked as esters, ethers, or amides (5). Polyurethanes can be prepared by reacting bischloroformates with diamines or by other techniques, but are most commonly made by reacting isocyanates with polyhydroxy compounds. These reactions characteristically involve polycondensation by the addition of hydrogen across the carbon–nitrogen double bond of the isocyanate group (6). The term "polyurethane" now generally includes all of the complex polymers formed from diisocyanates and polyols (3).

1.0 Polyurethane

1.0.1 CAS Number: [*9009-54-5*]

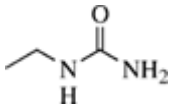
1.0.2 Synonyms: Polyurethane; polyurethane foam

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 88.109

1.0.5 Molecular Formula: $[C_3H_8N_2O]_n$

1.0.6 Molecular Structure:



1.2 Production and Use
Polyurethane compounds are formed by reacting polyisocyanates with polyalcohols (or “polyols”).

The use of polyurethane is expanding worldwide and exceeded 11 billion lb in 1990. The United States accounted for about 29% of world use (11–13). In 1991, 51% of the U.S. market was in flexible foam, 26% in rigid foam, and 23% in elastomerics and other types. Production data for polyether and polyester polyols are given in Table 93.1. Toluene diisocyanate (TDI) and 4,4'-methylenebisphenyl diisocyanate (MDI) are the principal commercial aromatic diisocyanates. Commercial aliphatic diisocyanates include isophorone diisocyanate (IPDI), hexamethylene diisocyanate (HDI), methylene cyclohexyl diisocyanate, and naphthalene diisocyanate (NDI)

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B. Miscellaneous Organic Polymers
Miscellaneous organic polymers discussed in this section include phenolics, aminoplastics including urea formaldehyde and melamine-formaldehyde; furan polymers and resins; polyvinylpyrrolidone and polybenzimiadiazole.
Phenolics
The phenolics were the first completely synthetic class of resins developed commercially and are still a major product line (Tables 93.1 and 93.4). The term phenolic describes a resinous material produced by reacting a phenol or a mixture of phenols with an aldehyde. Phenol itself, or sometimes cresols, are usually combined with formaldehyde and occasionally with other aldehydes such as furfural (3). The resin has sometimes been associated with dermatitis that is traceable to the phenolic monomer component, the resin itself, or less frequently formaldehyde. Inhalant effects from dust or fumes during processing have also been reported. No toxicologically significant emission of volatile substances is has been connected with the cured resin. Phenol-formaldehyde is highly resistant to biological decay (124). Other common resins of this class include (*1*) *p-tert*-butylphenol-formaldehyde [*25085-50-1*], (*2*) bisphenol A/epichlorohydrin/formaldehyde [*28906-96-9*], and (*3*) aniline/phenol/formaldehyde [*24937-74-4*] copolymers.

Table 93.4. Some Commercial Polymers and Approximate Year of Introduction[a]

Date	Material	Typical Application
1868	Cellulose nitrate	Eyeglass frames, table tennis balls
1900	Viscose rayon	Lining in clothing, curtains, tablecloths
1909	Phenol–formaldehyde	Telephone handset, electrical insulators
1919	Casein	Knitting needles
1926	Alkyd	Exterior paint, electrical insulators,

	distributor caps
1927 Cellulose acetate	Toothbrushes, packaging film, lacquers
1927 Polyvinyl chloride	Wall coverings, pipe, siding, flooring
1929 Urea–formaldehyde	1,1,0,3.1631,0,0,0,0,0,0,5 Lighting fixtures, wood adhesives, electrical fixtures and parts
1931 Polychloroprene	Industrial hoses, wire and cable, footwear
1935 Ethyl cellulose	Flashlight cases, coatings
1936 Acrylic	Display signs, brush backs
1936 Polyvinyl acetate	Flashbulb lining, adhesives
1937 Styrene–butadiene copolymers	Tires, footwear, molded items
1938 Cellulose acetate butyrate	Packaging, tubing, lacquers
1938 Polystyrene	Kitchenware, toys
1939 Nylon	Fibers, films, gears
1939 Polyvinylidene chloride	Packaging film, paper coating
1939 Melamine–formaldehyde	Tableware
1942 Unsaturated polyester	Boat hulls
1942 Low-density polyethylene	Packaging film, squeeze bottles
1943 Silicone	Rubber goods, motor insulation
1943 Fluoropolymers	Industrial gaskets, coatings
1943 Polyurethane	Foam cushions, insulation, adhesives
1943 Butyl rubber	Tubeless tire liner, inner tubes
1945 Cellulose propionate	Pens and pencils
1947 Epoxy	Coatings, industrial equipment
1948 1,1,0,3.1631,0,0,0,0,0,0,5 Acrylonitrile–butadiene–styrene (ABS)	Pipe and fittings, luggage, appliances
1950 Polyacrylonitrile	Sweaters, knitwear, blankets
1950 Chlorosulfonated polyethylene	Automotive hoses, wire and cable
1952 1,1,0,3.1631,0,0,0,0,0,0,5 Polyethylene terephthalate (fiber grade)	Clothing, fiberfill, sailcloth
1954	Housewares, automotive trim
1956 Styrene–acrylonitrile (SAN)	Auto parts
1956 Acetal	High-temperature seals and gaskets
1957 Fluoroelastomers	Milk bottles
1957 High-density polyethylene	Safety helmets, carpet fiber, battery cases
1957 Polypropylene	Appliance parts
1958 Polycarbonate	Wire insulation, film
1959 Fluorinated ethylene propylene	Valves and fittings
1961 Chlorinated polyether	Tires, footwear, medical items
1962 Polyisoprene (high cis)	Tires, general-purpose rubber
1962 Ethylene propylene rubber	Bottles

1964 Phenoxy	Skin packaging moldings
1964 Ionomer	High-temperature moldings
1964 Polyphenylene oxide	High-temperature films, wire coatings
1964 Polyimide	Adhesives and coatings
1965 Ethylene–vinyl acetate	Electrical/electronic parts
1965 Polysulfone	Clear moldings
1965 Poly (4-methylpentene-1)	Electrical/electronic parts
1970 Thermoplastic polyester	Piping, film
1973 Polybutylene	Telecommunications
1974 Polyphenylene sulfide	Printed circuit boards
1974 Polyethersulfone	1,1,0,3.1631,0,0,0,0,0,0,5 Clothing, reinforcement/on tires and plastic composites
1975 Aromatic polyamides	Non-food packaging
1978 Nitrile barries resins	Extruded film
1982 Linear low-density polyethylene	Electrical/electronic parts
1983 Polyetherimide	Wire and cable
1984 Polyetheretherketone	Electrical/electronic parts
1985 Aromatic copolyester	Electrical/electronic parts
1988 Liquid crystal polymers	High temperature transparent
1988 Polymethylpentene	Packaging, electrical electronic, medical products

[a] Adapted with permission from a complilation by H. G. Mark and S. Atlas, "Introduction to Polymer Science," in H. S. Kaufman and J. J. Falcetta, Eds., *Introduction to Polymer Science and Technology*, Copyright © 1977 by John Wiley and Sons, Inc., New York, and from *Facts and Figures of the U.S. Plastics Industry*, (1991 Edition) prepared annually by The Society of the Plastics Industry, Inc., Washington, D.C.

C. Silicones

Silicones or silicon hydrides of increasing chain length up to about Si_6H_{14} are known. Above this length however, the Si–Si chain becomes thermally unstable. Commercial silicone polymers contain the siloxane link Si–O–Si.

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Organic Sulfur Compounds
Howard G. Shertzer, Ph.D.

A. Mercaptans

The toxicological mechanisms for organic mercaptans (RSH, also known as thiols or sulfhydryls) are based on their chemical and biochemical properties. They are best known for their strong odors, most notably in *Allium* vegetables (garlic, onion, leek, shallot), rotting foodstuff (cabbage, eggs) and as the characteristic odorant for natural gas.

Mercaptans are the essential functional chemical moiety for synthesizing other organosulfur

compounds. They are more acidic than the corresponding alcohols and readily form the reactive soft-nucleophilic thiolate anion (RS^-). The most significant difference between the chemistry of alcohols and mercaptans is the relative ease of mercaptan oxidation that produces (in order of oxidant strength) disulfides (RSSR'), sulfoxides (RSOR'), and sulfones (RSO_2R'). Thus, mercaptan oxidation tends to occur at the sulfur atom itself, whereas the oxidation of an alcohol usually increases the oxidation state of an adjacent carbon (as in the oxidation of organic alcohols to produce aldehydes or acids). Mercaptans are extremely important in fundamental biological processes. The thiol-containing amino acid cysteine is important in maintaining proper protein structure via disulfide bonds between two cysteine residues. Cysteine is also important in regulating genetic events in cells, including DNA replication, gene transcription, and protein translation. In addition, cysteine forms the reactive moiety of the intracellular antioxidant glutathione that helps maintain the highly reduced state of cells and protects cells from potentially toxic electrophiles and radicals that may originate from metabolism or from foreign sources (xenobiotics).

Mercaptans, it has long been known, react with several heavy metals, including mercury. The formation of insoluble mercury complexes is characteristic of this class of compounds and is the source of the name *mercaptan* (*mercurium captans*, capturing mercury). Although not in current use, the dithiol 2,3-dimercapto-1-propanol (BAL, dimercaprol, British anti-Lewisite CAS Number [*59-52-9*]) was developed to protect against arsenical war gases (including Lewisite) and has been used as an antidote for exposure to arsenic, mercury, and other heavy metals. Interestingly, mercaptans such as the intracellular antioxidant glutathione activate the environmentally and occupationally important heavy metal Cr^{6+} and also the economically important solvent methylene chloride to genotoxic products.

1.0 Methyl Mercaptan

1.0.1 CAS Number: [*74-93-1*]

1.0.2 Synonyms: Mercaptomethane; methanethiol; methylthioalcohol; methyl sulfhydrate; thiomethanol

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 48.10

1.0.5 Molecular Formula: CH_4S

1.0.6 Molecular Structure:

Organic Sulfur Compounds
Howard G. Shertzer, Ph.D.

B. Sulfides

Sulfides (RSR', also known as thioethers) are weak Lewis bases and are highly nucleophilic due to the lone pairs of electrons on sulfur. Sulfides are readily oxidized to sulfoxides (RSOR') and then to

sulfones (RSO_2R'). Sulfides tend to form insoluble complexes with heavy metal salts, such as mercuric chloride. Sulfides also react with alkyl halides to form the corresponding sulfonium halide salts ($R_3S^+X^-$). Sulfides readily form disulfides (RSSR') under mild oxidizing conditions, such as in the presence of iodine. The amino acid cysteine forms intramolecular and intermolecular protein disulfide bonds to maintain proper conformation essential for activity, such as enzyme-mediated catalysis. Protein cysteinyl residues also form mixed disulfides with glutathione (protein-cysteine-*SS*-cysteine-glutathione) during episodes of cellular oxidative stress and for gene regulation. A number of cellular enzymes (thiol isomerases and reductases) are involved in regulating the oxidation state of protein disulfides.

Organic Sulfur Compounds
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C. Sulfones, Sulfoxides, Sulfonium chlorides, Sulfonates
The formation of sulfoxides, sulfones, and sulfonium chlorides from sulfides was discussed previously. Because sulfoxides contain sulfur in an intermediate oxidation state, they are readily oxidized to sulfones or reduced to the corresponding sulfides by mercaptans, hydroiodic acid, or tertiary phosphorus (R_3P^{3+}) compounds. Sulfones are not very reactive but can be reduced to sulfides by lithium aluminum hydride or sodium borohydride. Because of electron withdrawal by the sulfone substituent group, most reactions involving sulfones occur at the electropositive a-carbon.

Sulfonic acids (RSO_3H) are stronger acids than the corresponding sulfuric acids ($ROSO_3H$), but are weaker oxidizing agents. Therefore, these compounds are used industrially as acid catalysts. Aromatic sulfonic acids are typically produced by *p*-sulfonation of the corresponding hydrocarbon (e.g., toluene + $H_2SO_4 \rightarrow$ *p*-toluenesulfonic acid). Aliphatic sulfonic acids and their salts (sulfonates) can be produced by a variety of methods, including oxidation of the corresponding mercaptan (RSH), nucleophilic displacement of the corresponding alkyl halide (RX), or a radical-mediated addition to an alkene ($RCHCH_2$). An important industrial synthesis of phenols involves reacting benzenesulfonyl chloride or other aryl sulfonates with molten sodium hydroxide.

Combustion or contact with strong oxidizing materials (including high oxygen concentrations) may yield hazardous decomposition or oxidation products.

Organic Sulfur Compounds
Howard G. Shertzer, Ph.D.

D. Benzothiazole Derivatives
When heated to decomposition, compounds containing the benzothiazole moiety emit very toxic fumes of nitrogen and sulfur oxides, as well as cyanide gas.
1.0 Benzothiazole
1.0.1 CAS Number: [*95-16-9*]

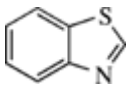
1.0.2 Synonyms: Benzosulfonazole; 1-thia-3-azaindene

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 135.2

1.0.5 Molecular Formula: C_7H_5NS

1.0.6 Molecular Structure:



1.1 Chemical and Physical Properties

Melting point (°C)	2
Boiling point	231
Specific gravity	1.238

1.2 Production and Use

Benzothiazole is an isolated intermediate used in synthesizing mercaptobenzothiazoles and substituted benzothiazole sulfenamides.

1.4 Toxic Effects

1.4.1 Experimental Studies 1.4.1.1 Acute Toxicity Following acute single doses benzothiazole is slightly to moderately toxic by both oral and dermal routes of administration. Oral LD_{50} values in the rat are 380 to 492 mg/kg. An oral LD_{50} for mice of 900 mg/kg has also been reported (82). Two dermal LD_{50} values in the rabbit have been reported: between 630 and 1000 mg/kg and between 126 and 200 mg/kg. Exposure of rats to a saturated vapor for 6 h did not cause toxicity or mortality. It is slightly irritating to rabbit skin and eye (Monsanto, Younger Laboratories, 1964 and 1976).

1.4.1.6 Genetic and Related Cellular Effects Studies No mutagenic activity was observed with or without metabolic activation in the Ames *S. typhimurium* or *S. cerevisiae* assays (Monsanto, Bionetics, 1976). A conflicting positive with *S. typhimurium* strain TA 1537 was reported with metabolic activation (117).

2.0 2-Mercaptobenzothiazole

2.0.1 CAS Number: [*149-30-4*]

2.0.2 Synonyms: 2(3H)-Benzothiazolethione; 2-benzothiazolyl mercaptan; benzothiazole-2-thione; MBT

2.2 Production and Use

2-Mercaptobenzothiazole is a cream to light yellow solid used as an accelerator in rubber vulcanization. It does not measurably hydrolyze over a 7-day period (Monsanto, ABC Laboratories, 1984).

2.4 Toxic Effects

2.4.1 Experimental Studies 2.4.1.1 Acute Toxicity The acute oral and dermal toxicities are low; LD_{50} values are >3800 mg/kg (rat) and >7940 mg/kg (rabbit), respectively (Monsanto, Younger Laboratories, 1975). An oral LD_{50} was also determined in rabbits and was in the range 7500 to 8750 mg/kg (Monsanto, Scientific Associates, 1974).

It was practically nonirritating in rabbit eye and skin irritation studies (Monsanto, Younger Laboratories, 1975). In a delayed contact sensitization assay in guinea pigs (modified Buehler), challenges from 0.5% and 2% petrolatum formulations elicited positive responses (118). A strong positive response was also reported in a Magnusson–Kligman guinea pig sensitization assay (119).

Dietary administration for 4 weeks to rats at levels of up to 2500 ppm reduced body weight increments in males at levels above 1500 ppm and in females at 2000 ppm and above. Increased liver weights were observed in all treated groups. 2-Mercaptobenzothiazole was administered by gavage (diluted in corn oil) to rats and mice of both sexes for 13 weeks at dosages up to 3000 mg/kg in rats and 1500 mg/kg in mice. Mortality was noted in rats at 3000 mg/kg and in mice at dosages of 750 mg/kg and above. Reduced body weight gains were noted in rats and mice at 750 mg/kg and above. Necrosis of the renal distal convoluted tubular epithelium was seen in rats at 3000 mg/kg (Monsanto, Monsanto Environmental Health Laboratory, 1988).

2.4.1.4 Reproductive and Developmental In a rat teratology study 2-mercaptobenzothiazole was administered to pregnant rats on days 6 to 15 of gestation at dosages of 300, 1200, and 1800 mg/kg. Signs of maternal toxicity were seen at 1200 mg/kg and above. There were some equivocal intergroup differences in postimplantation loss, but these are unlikely to be of toxicological significance. 2-Mercaptobenzothiazole was also administered to pregnant rabbits on days 6 to 18 of gestation at dosages of 50, 150, and 300 mg/kg. Signs of maternal toxicity were seen at 300 mg/kg. There were no indications of fetal or developmental toxicity at any dosage (Monsanto, Springborn Laboratories, 1991). In a two-generation reproduction study in rats, parental animals received diets that contained 2500, 8750, or 15,000 ppm from the premating period through gestation and weaning. Body weights of F1 pups were reduced at 8750 ppm and higher; similar effects were noted in all groups from day 14 of lactation in all treatment groups in the F2 generation. Reproductive indexes were unaffected by treatment at any level. Renal changes (pigmentation of proximal convoluted tubules and kidney weight increases) were seen at 8750 ppm and above in both the F0 and F1 animals. Hepatocyte hypertrophy in both sexes was seen at 8750 ppm and above in the F1 generation, which was accompanied by hepatomegaly at 8750 ppm and higher in males and at 15,000 ppm in females (Monsanto, Springborn Laboratories, 1981).

2.4.1.5 Carcinogenesis Some evidence of carcinogenicity was reported in male (increased incidences of preputial and adrenal tumors) and female F344 rats (increased pituitary and adrenal tumors). No increased tumor incidences were seen in either male or female B6C3F1 mice (Monsanto, 1993).

2.4.1.6 Genetic and Related Cellular Effects Studies 2-Mercaptobenzothiazole was not mutagenic in Ames *S. typhimurium*, *S. cerevisiae*, L5178Y mouse lymphoma, CHO/HPRT, mouse micronucleus, or dominant lethal assays (Monsanto, Bionetics, 1976; Monsanto, Pharmakon Research International, 1986; Monsanto, Litton Bionetics, 1986; Monsanto, Springborn Laboratories, 1991).

2.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization In an acute neurotoxicity evaluation in rats at dosages of 500, 1250, and 2750 mg/kg, responses to treatment were confined to nonspecific effects such as decreased motor activity, salivation, and decreased vocalization. Motor activity testing and a functional observation battery indicated that the responses were likely to be related to nonspecific effects (Monsanto, Bio-Research Laboratories, 1991).

2.4.2 Human Experience There was no evidence of primary skin irritation or delayed-contact skin sensitization following a repeated insult patch test in 50 human volunteers (Monsanto, Product Investigations, 1976). Skin sensitization reactions have been reported in humans repeatedly exposed to rubber articles containing 2-mercaptobenzothiazole (120). Positive reactions to 2-mercaptobenzothiazole or 2-mercaptobenzothiazole mixtures containing other sulfur rubber accelerators have also been reported (121, 122). Individuals that responded to 2-mercaptobenzothiazole often responded to other rubber additives, although similar cross-reactions were not seen by other investigators (123, 124).
3.0 **N**-Isopropyl-2-benzothiazolesulfenamide
3.0.1 CAS Number: [*10220-34-5*]

3.0.2 Synonyms: *N*-(1-methylethyl)-2-benzothiazolesulfenamide; *N*-isopropylbenzothiazol-2-sulfenamide
3.2 Production and Use

N-Isopropyl-2-benzothiazolesulfenamide is a solid material used as an accelerator in rubber vulcanization.
3.4 Toxic Effects
3.4.1 Experimental Studies 3.4.1.1 Acute Toxicity The acute oral and dermal toxicity is low; LD_{50} values are >7940 mg/kg (rat) and >7940 mg/kg (rabbit), respectively. Exposure of a group of six rats for 1 h to a nominal concentration of 200 mg/L did not cause any mortality (Monsanto, Younger Laboratories, 1975).

Slight eye irritation but no skin irritation were noted in rabbit irritation studies (Monsanto, Younger Laboratories, 1975).

Oral administration for 3 months to rats of both sexes at 0, 10, 50, 125, or 500 mg/kg/day reduced body weight gains in males at 500 mg/kg and increased liver weights in females at the same level. There was no other evidence of systemic toxicity, and microscopic examination of the livers from female animals did not provide any corroborative evidence for an adverse effect on the liver of females at the high dosage (Monsanto, Monsanto Environmental Health Laboratory, 1988).

3.4.1.6 Genetic and Related Cellular Effects Studies No evidence of genotoxicity was found in an Ames *S. typhimurium* assay with and without metabolic activation, an *in vitro* cytogenetics assay in Chinese hamster ovary cells with or without metabolic activation, or in an *in vitro* unscheduled hepatocyte DNA synthesis (UDS) assay (Monsanto, Stanford, Research Institute, 1986).

3.4.2 Human Experience Patch testing of a panel of 54 human volunteers using a 1% preparation demonstrated the material was not a primary skin irritant but one individual demonstrated a positive response for delayed contact sensitization. The material is considered to possess weak sensitization potential at this concentration (Monsanto, Product Investigations, 1986).
4.0 **N**,**N**-Diisopropyl-2-benzothiazolesulfenamide
4.0.1 CAS Number: [*95-29-4*]

4.0.2 Synonyms: *N*,*N*-Bis(1-methylethyl)-2-benzothiazolesulfenamide
4.1 Chemical and Physical Properties
It is completely hydrolyzed to mercaptobenzothiazole and isopropylamine during an 8-day period at pH 8.0; hydrolysis occurs more readily at lower pH values (Monsanto, ABC Laboratories, 1984).
4.2 Production and Use
It is a solid material used as an accelerator in rubber vulcanization.
4.4 Toxic Effects
4.4.1 Experimental Studies 4.4.1.1 Acute Toxicity The acute oral and dermal toxicity is low; LD_{50} values are 5700 mg/kg (rat) and >2000 mg/kg (rabbit), respectively. An oral LD_{50} value in mice was 3892 mg/kg (Monsanto, Bio/dynamics Inc., 1982).

Slight eye (mild, transient irritation of the conjunctiva) and slight skin (slight erythema and edema) irritation were observed in rabbit irritation studies (Monsanto, Bio/dynamics Inc., 1982).

Oral administration to rats of both sexes for 3 months at 0, 250, 500, or 100 mg/kg/day reduced body weight increments in males at 500 mg/kg and higher. Increased absolute and relative liver weights in both sexes at all dosages were related to hepatocellular hypertrophy. There was an accumulation of hyaline droplets in the renal tubular epithelium in males at all dosages. This finding was not present in females, but a brown pigment was present in the same cells in females at dosages of 500 mg/kg and above (Monsanto, Monsanto Environmental Health Laboratory, 1987).

4.4.1.6 Genetic and Related Cellular Effects Studies No evidence of mutagenicity was found in an Ames *S. typhimurium* assay or in *S. cerevisiae* (Monsanto, Bionetics, 1976). It was also negative in an *in vitro* unscheduled heptocyte DNA synthesis assay. An *in vitro* chromosomal aberration assay in Chinese hamster ovary cells was positive without metabolic activity but not when a source of

metabolic activation was included (Monsanto, SRI International, 1986). This positive result is not considered indicative of a clastogenic hazard when compared to a negative *in vivo* rat bone marrow cytogenetics assay following oral administration of 2850 mg/kg and bone marrow cell harvests at 6, 18, and 30 h after administration (Monsanto, Pharmakon Research International, 1987).

4.4.2 Human Experience Patch testing of a panel of 54 human volunteers using a 1% preparation in petrolatum indicated that the material was neither a primary skin irritant nor a delayed contact sensitizer (Monsanto, Product Investigations, 1986). Patch testing of humans previously demonstrated as sensitized to 2-mercaptobenzothiazole gave positive results, although the likely presence of impurities and inadequate documentation of sample quality and source render the validity of this result questionable (123).
5.0 **N-tert**-Butyl-2-benzothiazolesulfenamide
5.0.1 CAS Number: [*95-31-8*]

5.0.2 Synonyms: *N*-(1,1'-dimethylethyl)-2-benzothiazolesulfenamide
5.1 Chemical and Physical Properties
It is completely hydrolyzed to 2-mercaptobenzothiazole and *tert*-butylamine within a 25-h period at pH 7.0; the hydrolysis rate is slower at pH 9.0 (Monsanto, ABC Laboratories, 1984).
5.2 Production and Use
It is a solid material used as an accelerator in rubber vulcanization.
5.4 Toxic Effects
5.4.1 Experimental Studies 5.4.1.1 Acute Toxicity The acute oral and dermal toxicities are low; LD_{50} values are >6310 mg/kg (rat) and >7940 mg/kg (rabbit), respectively. Slight eye irritation and minimal skin irritation were defined in rabbit irritation studies (Monsanto, Younger Laboratories, 1973). A 25% solution in ethanol did not induce any delayed-contact sensitization reactions in a guinea pig sensitization (Buehler) assay (Monsanto, Pharmakon Research International, 1982).

Oral administration for 3 months to rats of both sexes at 0, 100, 300, or 1000 mg/kg/day reduced body weight increments in males at dosages of 300 mg/kg and higher. Liver and kidney weights were also increased in females at 1000 mg/kg, but there was no microscopic evidence of morphological change in these organs and the findings were not considered of toxicological significance (Monsanto, Monsanto Environmental Health Laboratory, 1982). A dust inhalation study of rats (6 h/day, 5 days/week) for 4 weeks at 0, 2.4, 29, and 84mg/m^3 elicited morphological effects on the liver and lymph nodes at 84mg/m^3 that were detected during microscopic examination (Monsanto, International Research and Development Corporation, 1978). Repeated daily dermal applications of 0, 125, 500, or 2000 mg/kg/day caused slight dermal irritation but no evidence of systemic toxicity (Monsanto, International Research and Development Corporation, 1979).

5.4.1.4 Reproductive and Developmental No maternal toxicity, fetal toxicity, or developmental toxicity were seen in rats following oral administration of 0, 50, 150, or 500 mg/kg/day to pregnant female rats on days 6 to 15 of gestation (Monsanto, International Research and Development Corporation, 1978).

5.4.1.6 Genetic and Related Cellular Effects Studies No evidence of mutagenicity was found in Ames *S. typhimurium*, *E. coli*, *S. cerevisiae*, or Chinese hamster ovary HPRT assays (125; Monsanto, Bionetics, 1978). Positive results were obtained in mouse lymphoma assays of L5178Y cells with metabolic activation (Monsanto, Bionetics, 1978). Cell transformation was noted at the highest concentration tested in BALB/3T3 cells, but significant cytotoxicity may confound the relevance of this finding (Monsanto, Monsanto Environmental Health Laboratory, 1993).

5.4.2 Human Experience Patch testing of a panel of 54 human volunteers using a 60% preparation in petrolatum indicated the material was not a primary skin irritant, but a strong delayed contact sensitization response occurred (Monsanto, Product Investigations, 1982). Patch testing of humans previously demonstrated to be sensitized to 2-mercaptobenzothiazole gave positive results, although

the likely presence of impurities and inadequate documentation of sample quality and source render the validity of this result questionable (123).
6.0 **N**-Cyclohexyl-2-benzothiazolesulfenamide
6.0.1 CAS Number: [*95-33-0*]
6.1 Chemical and Physical Properties
It is a pale, buff-colored powder or granule completely hydrolyzed within 25 h at pH 7.0 (Monsanto, ABC Laboratories, 1984).
6.2 Production and Use
N-Cyclohexyl-2-benzothiazolesulfenamide is used as an accelerator in rubber vulcanization.
6.4 Toxic Effects
6.4.1.1 Acute Toxicity The acute oral and dermal toxicities are low; LD_{50} values are 5300 mg/kg (rabbit) and >7940 mg/kg (rat), respectively (Monsanto, Younger Laboratories, 1973). It is slightly irritating to the rabbit eye (Monsanto, Younger Laboratories, 1973) and practically nonirritating to rabbit skin (Monsanto, Pharmakon Research International, 1982).

In a guinea pig delayed-contact skin sensitization assay (Buehler) using a 25% preparation in ethanol, no evidence of sensitization was found after challenge with the 25% solution. No evidence of comedogenicity was detected in rabbits when solutions in chloroform up to 10% were applied to the inner surface of the ears for 4 weeks (Monsanto, Pharmakon Research International, 1982).

Dermal application of up to 2000 mg/kg/day to intact and abraded skin of rabbits for 21 days did not elicit any evidence of toxicity (Monsanto, International Research and Development Corporation, 1979). Inhalation exposure of rats for 4 weeks (5 days/week) to dust concentrations of 4.3, 14.4, and 48.0 mg/m^3 caused microscopic lesions of the conjunctivas, lymph nodes, and spleen at 48 mg/m^3. Elevated aspartate aminotransferase activities at 14.4 mg/m^3 and above were not associated with any morphological abnormalities (Monsanto, International Research and Development Corporation, 1978). Administration to rats of diets that contained levels approximating 100, 250, 500, 1000, or 3000 mg/kg for 4 weeks reduced food intake and body weight gain at 500 mg/kg and higher; there was no other evidence of systemic toxicity (Monsanto, International Research and Development Corporation, 1979). Administration to rats by gavage for 5 weeks (5 days/week) of dosages up to 1.25 mg/kg/day reduced body weight gain and increased thyroid weights relative to body weight. There was no evidence of pathological change, so the thyroid weight finding may reflect reduced body weight gain (Monsanto, 1993).

superscript Excretion After a single oral dosage of 250 mg/kg of ^{14}C-labeled material 65 and 24% of the dose was excreted with in 3 days in the urine and feces, respectively. Biliary excretion over this period accounted for approximately 5% of the dose. There was no evidence of selective accumulation or concentration in any organs. The urinary metabolites were identified as cyclohexylamine and 2-mercaptobenzothiazole (129).

6.4.1.4 Reproductive and Developmental Oral administration to pregnant rats of dosages of up to 500 mg/kg on days 6 to 15 of gestation caused maternal toxicity at 500 mg/kg and concomitant reduction in fetal body weight; there were no teratological responses at this dosage. No maternal or fetal effects were noted at 300 mg/kg (Monsanto, International Research and Development Corporation, 1978). In a separate study, oral administration, of dosages of 50, 150 and 450 mg/kg to pregnant rats during organogenesis, produced maternal toxicity at the highest dosage and dose-dependent fetal toxicity (fetuses/litter and hydrocephalus) (126). These investigators found that the dosage of 450 mg/kg produced embryotoxicity, shown by increases in late resorptions and post implantation losses, decreased fetal body weight and length, and subcutaneous hemorrhage (127). In another study, dietary administration at dietary levels approximating dosages of 0.7, 7.1, 69.6, and 288.8 mg/kg to pregnant female rats on days 0 to 20 of gestation caused reduced maternal food intake and body weight gains at 288.8 mg/kg and a concomitant reduction of fetal body weight. Maternal body weight gain was also reduced at 69.6 mg/kg, although there were no effects on fetal body weight. No effects on pre- or postimplantation loss, litter size, or the incidence of

malformations or visceral or skeletal variations were reported (128).

6.4.1.6 Genetic and Related Cellular Effects Studies No evidence of mutagenicity either with or without metabolic activation was found in the Ames *S. typhimurium, E. coli*, or Chinese hamster ovary HPRT assays (Monsanto, Bionetics, 1976; Monsanto, 1993), the *S. cerevisiae* assay (Monsanto, Bionetics, 1976), or the L5178 mouse lymphoma assay (Monsanto, Bionetics, 1978).

6.4.2 Human Experience Occupational exposure reportedly causes irritation of the eyes, skin and upper respiratory tract. Patch testing of a panel of 51 human volunteers using a 70% preparation in petrolatum did not cause primary or cumulative irritation, but sensitization responses occurred in 5 of the 51 subjects (Monsanto, Product Investigations, 1982). The literature contains many reports of skin sensitization, but in most cases the patients were also sensitized to other components of the "mercapto mix" used for skin testing. Industrial experience indicates that this material is a weak sensitizer.
7.0 **N,N**-Dicyclohexylbenzothiazolesulfenamide
7.0.1 CAS Number: [*4979-32-2*]

7.0.2 Synonyms: *N,N*-dicyclohexyl-1-benzothiazolesulfenamide.
7.2 Production and Use
It is an off-white solid, a powder or pellet, that is used as an accelerator in rubber vulcanizing.
7.4 Toxic Effects
7.4.1 Experimental Studies 7.4.1.1 Acute Toxicity The material has low acute oral and dermal toxicities; LD_{50} values are >5000 mg/kg (rat) and >2000 mg/kg (rabbit), respectively. It was practically nonirritating in rabbit skin and eye assays (130); (Monsanto, Bio/Dynamics Inc., 1984). Using the Magnusson–Kligman maximization assay for delayed-contact cutaneous sensitization, it was concluded that it is not a skin sensitizer (Monsanto, International Research and Developmental Corporation, 1984).

7.4.1.2 Chronic and Subchronic Toxicity Administration to rats in the diet for 4 weeks at 2000 to 10,000 ppm caused a dose-related decrease in food consumption and body weight increments at all dietary concentrations. There was no evidence of any systemic toxicity based on evaluations of the cellular and chemical constituents of blood, organ weight analysis, or macroscopic pathology examinations (130); (Monsanto, Bio/Dynamics Inc., 1987). Administration to rats in the diet for 13 weeks at 2500 or 5000 ppm decreased food intake and reduced body weight increments at both dietary concentrations. There was no evidence of any systemic toxicity or microscopic pathology changes at either dietary concentration. The no-effect level on subchronic administration in the diet was 500 mg/kg diet (130; Monsanto, Monsanto Environmental Health Laboratory, 1988).

7.4.1.5 Carcinogenesis An increased incidence of sarcomas occurred at the site of subcutaneous administration of 20 g/kg body weight, administered as 1 g/kg body weight at irregular intervals during 413 days (130). However, there was no evidence for mutagenic or clastogenic effects in the Ames *S. typhimurium* assay, the Chinese hamster ovary HPRT assay, and an *in vitro* hepatocyte DNA repair (UDS) assay, or in an *in vivo* rat bone marrow chromosomal aberration assay after oral administration of a single 1000-mg/kg dose (130); (Monsanto, Pharmakon International, 1984; Monsanto, Hazelton Laboratories, 1984; Monsanto, 1993; Monsanto, SRI International, 1984).
General
Internet site references with chemical and safety information:

http://ecdin.etomep.net Environmental Chemicals Data Infor-mation Network
http://ecphin.etomep.net European Community Pharmaceutical Information Network
http://www.jrc.org.isis Institute for Systems Information and Safety
http://www.msdsonline.com MSDS Information
http://www.safety.utoledo.edu/safety/msds.htm MSDS links

http://www.chem.uky.edu/resources/msds.html One of the better MSDS and chem-istry information sites

http://www.aitl.uc.edu Academic Information Technology and Libraries at the University of Cincinnati

http://www.vmi.edu/~chem/ind-home.html Chemical Industries Homepages

http://www.chemweb.com Chemistry information site

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Organophosphorus Compounds
Jan E. Storm, Ph.D

1.0 Introduction
Organophosphate pesticides are a highly diverse group of chemicals to which workers may be exposed during manufacture and formulation and during or after application for their intended uses (1, 2). They are all characterized by their ability to inhibit the enzyme acetylcholinesterase (AChE) that deactivates the neurotransmitter acetylcholine (ACh).

Compounds in this class are numerous and have been categorized in many ways according to the nature of the substituents. Gallo and Lawryk, for example, categorized them into four main categories (Groups I-IV) based on the characteristics of the leaving group (X) (1). Group I compounds, phosphorylcholines, have a leaving group that contains a quaternary nitrogen and are among the most potent organophosphates (e.g., Shradan). Group II compounds, fluorophosphates, have a fluoride leaving group and are also generally highly toxic (e.g., diisopropyl fluorophosphate). Group III compounds have leaving groups that contain cyanide or a halogen other than fluoride and are generally less potent than Groups I or II (e.g., Parathion). Group IV contains most of the organophosphates used as insecticides today. These compounds have alkoxy, alkylthio, aryloxy, arylthio or heterocyclic leaving groups and a wide variety of other substituents.

Another classification scheme is based on the nature of the atoms that immediately surround the central phosphorus atom and results in 14 different categories (2). According to this scheme, phosphates are the prototype for the entire class and are those compounds where all four atoms that surround the phosphorus atom are oxygen (e.g., dichlorvos, mevinphos). Sulfur-containing organophosphate compounds (phosphorothioates; phosphorothiolates; phosphorodithioates; phosphorodithiolates) are far more numerous than phosphates and include well recognized organophosphate insecticides such as parathion, diazinon, chlorpyrifos, etc. Other groups contain nitrogen (phosphoramides and phosphorodiamides), nitrogen and sulfur (phosphoramidothionates and phosphoramidothiolates), carbon (phosphonates and phosphinates), or carbon and sulfur (phosphonothionates, phosphonothionothiolates and phosphinothionates).

All aspects of organophosphate chemistry, toxicity, analysis, and exposure potential have been previously reviewed (1–9). Additionally information regarding the toxicity of this class of compounds has expanded greatly in recent years as a result of toxicity data supplied by registrants to the U.S. EPA's Office of Pesticides to support reregistration. These data are being made publically available by the U.S. EPA on their internet web site (9a). The following discussion draws heavily from recent reviews but also includes summaries of relevant toxicity data submitted to the U.S. EPA available when this chapter was completed. Due to space limitations detailed data reviews are

included here for only 30 organophosphate pesticides. Information on other pesticides registered or undergoing reregistration in the United States can be readily obtained from the previously mentioned website.

1.1 Production and Use

Organophosphates are the most widely used insecticides today; more than 40 are currently registered for use in the United States (3). They were the number one cause of symptomatic illnesses reported in 1996, according to the American Association of Poison Control Centers (3). The earliest organophosphates (e.g., schradan) were initially developed as war gases, and they have also been used as therapeutic agents, gasoline additives, hydraulic fluids, cotton defoliants, fire retardants, plastic components, growth regulators, and industrial intermediates (363). Their use as insecticides far exceed these uses.

Organophosphorus Compounds
Jan E. Storm, Ph.D

2.0 Azinphos-Methyl

2.0.1 CAS Number:

[*86-50-0*]

2.0.2 Synonyms:

Phosphorodithioic acid *O*,*O*-dimethyl-*S*-((4-oxo-1,2,3,-benzotirazin-3 (4*H*)-yl)methyl)ester; metiltriazotion guthion; Guthion, Gusation; S-(3,4-dihydro-4-oxobenzo[d][1,2,3]triazin-3-ylmethyl) *O*,*O*-dimethyl phosphorodithioate; Azinphos-Me; Gusathion; Methyl guthion; Guthion(R); Phosphorodithioic acid *O*,*O*-dimethyl *S*-[4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl] ester; phosphorodithioic acid *O*,*O*-dimethyl ester, *S*-ester with 3-mercaptomethyl-1,2,3-benzotriazin-4 (3*H*)-one; Bayer 17147; Cotnion-methyl; Gusathion M; Azimil; Bay; R 1582; Gusthion M; Gution; *O*,*O*-dimethyl *S*-(4-oxobenzotriazino-3-methyl) phosphorodithioate; *S*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-ylmethyl) *O*,*O*-dimethyl phosphorodithioate; azinophos-methyl; bay 9027; bay 17147; bayer 9027; 3-(mercaptomethyl)-1,2,3-benzotriazin-4(3*H*)-one *O*,*O*-dimethyl phosphorodithioate; carfene; cotneon; crysthion 21; crysthyon; DBD; *O*,*O*-dimethyl *S*-(benzaziminomethyl) dithiophosphaate; *O*,*O*-dimethyl *S*-(1,2,3-benzotriazinyl-4-keto)methyl phosphorodithioate; *O*,*O*-dimethyl *S*-(3,4-dihydro-4-keto-1,2,3-benzotriazinyl-3-methyl) dithiophosphate; dimethyl dithiophosphoric acid *N*-methylbenzazimidyl ester; *O*,*O*-dimethyl *S*-(4-oxo-3*H*-1,2,3-benzotriazine-3-methyl) phosphorodithioate; *O*,*O*-dimethyl *S*-(4-oxo-1,2,3-benzotriazino (3)-methyl) thiothionophosphatae; *O*,*O*-dimethyl *S*-4-oxo-1,2,3-benzotriazin-3(4*H*)-ylmethyl phosphorodithioate; gothnion; gusathion-20; gusathion 25; gusathion k; gusathion methyl; 3-(mercaptomethyl)-1,2,3-benzotriazin-4(3*H*)-one *O*,*O*-dimethyl phosphorodithioate *S*-ester; methylazinphos; *N*-methylbenzazimide, dimethyl dithiophosphoric acid ester; metiltriazotion; Beetle Buster; Ketokil No. 52; Crysthyon 2L; Dimethoxy ester of (4-oxo-1,2,3-benzotriazin-3(4*H*)-yl) methyl ester of dithiophosphoric acid; dimethyl *S*-((4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl) phosphorodithioate; dimethyl *S*-(3-(mercaptomethyl)-1,2,3-benzotriazin-4(3*H*)-one) phosphorodithioate; Methyl gusathion; Guthion (Azinphos-Methyl)

2.0.3 Trade Names:

Guthion®, Gusathion®, methyl Guthion, Azimil, Bay 9027, Bay 17147, Carfene

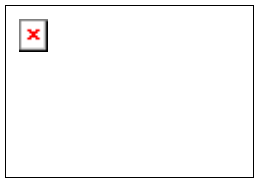
2.0.4 Molecular Weight:

317.34

2.0.5 Molecular Formula:

$C_{10}H_{12}N_3O_3PS_2$

2.0.6 Molecular Structure:



2.1 Chemical and Physical Properties

Pure azinphos-methyl is a white crystalline solid; the technical material is a brown, waxy solid.

Specific gravity	1.44 at 20°C
Melting point	pure 73–74°C; technical 65–68°C; unstable at temperatures higher than 200°C
Solubility	soluble in methanol, ethanol, propylene glycol, xylene, and other organic solvents: slightly soluble in water (33 mg/L)
Vapor pressure	$<3.8 \times 10^{-4}$ mmHg at 20°C

2.2 Production and Use

Azinphos-methyl is an insecticide used for control of pests on various fruits, melons, nuts, vegetables, field crops, ornamentals and shade trees. It is formulated as a liquid (20% active ingredient) and a wettable powder (20–50% active ingredient). Azinphos methyl is a restricted use pesticide.

2.3 Exposure Assessment

Absorption after dermal exposure constitutes the primary source of azinphos-methyl exposure (57a). Urinary alkyl phosphate metabolites of azinphos-methyl have been proposed as reliable markers of exposure regardless of the route of exposure (58–66).

2.4 Toxic Effects

2.4.1.1 Acute Toxicity Azinphos-methyl is a highly acutely toxic organophosphate that has oral LD_{50}s of 4–20 mg/kg, (242). The dermal LD_{50} for azinphos-methyl is 220 mg/kg in both males and females (64a). One-hour LC_{50} values in rats for azinphos-methyl are 310 to 396 mg/m^3. Four-hour LC_{50} values in rats are 107–155 mg/m^3 (61). An oral LD_{50} of 7 mg/kg and an LD_{01} of 4–5 mg/kg in male and female mice, respectively, demonstrated that the dose–lethality curve is very steep (62). At the LD_{50}, cholinergic signs occur within 4–6 minutes; death usually occurs within 10–30 minutes. Rats tolerated cumulative oral doses of up to five to ten times the LD_{50} given as daily doses of 0.5–2 mg/kg for 2–8 weeks demonstrating the lack of cumulative toxicity.

When 2, 6, or 12 mg/kg (males) and 1, 3, or 6 mg/kg (females) azinphos-methyl was given by gavage to rats, plasma and RBC cholinesterase inhibition occurred at the lowest dose tested (63). Brain cholinesterase inhibition and cholinergic effects occurred in males and females at 6 and 3 mg/kg, respectively. A high incidence of mortality (28% males and 83% females) was observed at the 6- and 12-mg/kg dose.

Azinphos-methyl did not cause acute delayed neurotoxicity in atropinized hens administered 0.1, 1.0, 10.0, 100.0 or 300 mg/kg in corn oil followed by a second dose at 21 days.

Azinphos methyl was judged to be a mild eye irritant, but nonirritating to the skin, and it did produce dermal sensitization in guinea pigs (242).

2.4.1.2 Chronic and Subchronic Toxicity A 90-dose LD_{50} was 10.5 mg/kg for rats fed ground chow that was contaminated with azinphos-methyl (196). Using the 90-dose LD_{50} and the single dose LD_{50} of 11.0 mg/kg (196), a “chronicity factor” (single-dose $LD_{50/90}$ dose LD_{50}) of about 1 was

calculated, indicating that azinphos-methyl did not have a cumulative effect.

When rabbits were treated dermally with 2, 4, 8 or 20 mg/kg azinphos-methyl for 6 h/day, 5 days/week, 15 times over three weeks, RBC cholinesterase activity was inhibited at 4 mg/kg/day and higher (242). Spleen and kidney weights increased in males and body weight gain decreased in females at this exposure level.

In rats fed diets that contained 15, 45, 90 (females), or 120 (males) ppm azinphos-methyl (about 0.9, 2.8, and 7.9 mg/kg/day (males) and 1.1, 3,2, and 7.0 mg/kg/day (females)) for 13 weeks, body weight gain decreased in both males and females fed 120 or 90 ppm, respectively (63). In males, 120 ppm (7.9 mg/kg/day) was associated with increased reactivity and autonomic cholinergic; no cholinergic signs were associated with 45 or 15 ppm. In females, 90 ppm (7.0 mg/kg/day) was associated with neuromuscular cholinergic signs and perianal staining; 45 ppm (3.2 mg/kg/day) was associated with increased reactivity and urine stains; no cholinergic effects were associated with the 15-ppm diet. Brain and RBC cholinesterase was inhibited at all dietary levels. In dogs given dietary levels of 0, 20, 50, 100, 200, or 400 ppm azinphos-methyl for 19 weeks, dose-related cholinesterase inhibition (whole blood) was observed at all dose levels. No information was provided on the occurrence of cholinergic effects.

In rats exposed to 0.195, 1.24, or 4.72 mg/m^3 azinphos-methyl aerosol for 6 h/day 5 days/wk, for 12 weeks, no effects occurred at the two lower exposure levels (242). Male rats exposed to 4.72 mg/m^3 showed lower body weight gain, and plasma and RBC cholinesterase inhibition (30–40%) occurred in both sexes exposed to 4.72 mg/m^3. Brain cholinesterase activity was not affected at any dose.

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Studies that showed that oral, intraperitoneal, inhalation, and intravenous LD_{50}s and LC_{50}s are equivalent on a milligram per kilogram basis indicate that azinphos-methyl is equally well absorbed following oral or inhalation exposures. Neither oral nor inhalation absorption has been quantified. However, a study in humans showed that about 70% of an intravenous dose was absorbed and excreted within 5 days (66). About 30% of the dose was excreted in the urine in the first 24 hours after exposure; 20% was excreted in the second 24 hours, and 11% was excreted in the third 24 hours. An i.v. elimination half-life of 30 hours was calculated.

Dermal absorption of azinphos-methyl can be considerable. Dermal absorption of azinphos-methyl was determined in rats exposed to 0.93, 9.3 and 93 mg azinphos-methyl/cm^2 as the wettable powder (equivalent to 0.056, 0.56, or 5.6 mg/kg) on their clipped dorsal skin (242). By 10 hours, 32%, 22%, and 24% of the applied doses respectively, remained on the skin, suggesting that absorption had been 68%, 78%, and 76% of the applied dose (uncorrected using intravenous absorption), respectively. To simulate worker exposure, the test site of rats exposed for 24, 72 and 168 hours was wiped with a moistened gauze pad after 10 hours of exposure. Maximum systemic absorption occurred 168 hours after exposure, and 42% 22% and 18% of the applied dose was recovered in urine, feces, carcass, and cage wash combined for the 0.056, 0.56 and 5.6 mg/kg doses, respectively. In humans, about 16% of an applied dermal dose (4 mg/cm^2 on ventral forearm) was absorbed within 5 days. About 5.5% of the applied dose was excreted in urine within the first 24 hours, 5% was excreted during the second 24 hours, and 3% was excreted during the third 24 hours (corrected using intravenous excretion).

By 72 hours after oral dosing of rats with azinphos-methyl, 92–109% of the dose had been excreted. Between 63–79% of the dose was eliminated in urine, and between 20–27% was eliminated in feces. The highest residual concentrations of dose occurred in the blood, kidney, live, lung, and brain.

Azinphos methyl requires metabolic activation to azinphos-methyl oxon by microsomal mixed-function oxidases to inhibit cholinesterase (67). However, hydrolytic deactivation of the active

metabolic is also very rapid (67). *In vitro* studies of azinphos-methyl metabolism indicate that metabolism of azinphos-methyl in rats proceeds largely through the actions of glutathione *S*-transferase and a mixed-function oxidase (242).

Cysteinyl methyl benzazimide sulfone (13–20% of the dose) and methyl sulfonly methyl benzazimide (14–20% of the dose) were the major urinary metabolites in rats given oral doses of azinphos-methyl (67). In feces, the methyl sulfonly methyl benzazimide, cysteinyl methyl benzazimide sulfoxide, desmethyl isoazinphos-methyl, azinphos-methyl oxygen analog, and methyl thiomethyl benzazimide were identified, but did not comprise greater than 5% of the administered dose. No azinphos-methyl or glucuronic or sulfate conjugates were found in urine or feces.

2.4.1.4 Reproductive and Developmental Azinphos-methyl did not cause developmental effects or fetotoxicity at maternally nontoxic doses when given to rats (0.5–2 mg/kg/day) or rabbits (1–6 mg/kg/day) during gestation, at maternally nontoxic doses (242).

In a two-generation reproductive study, rats were given diets that contained 5, 15, or 45 ppm azinphos-methyl (0.25, 0.75 or 2.25 mg/kg/day) (242). Increased dam mortality, decreased body weight of parental males and F1 males and females, and cholinergic signs (“poor condition”, convulsions) occurred among rats given 45 ppm. Reduced pup viability and lactation indexes (death between postnatal days 0–5 and 5–28) and decreased mean total litter weights at weaning on postnatal day 28 occurred among rats given 15 and 45 ppm. No adverse effects occurred among rats given 5 ppm. In a supplementary study, rats were given diets that contained 15 or 45 ppm azinphos-methyl (0. 43, 1.30 or 3.73 mg/kg/day (males); 0.55, 1.54, or 4.87 mg/kg/day (females)) for one year. The pup viability index (death of offspring during postnatal days 0–5) was reduced, and pup weights decreased at postnatal days 14 and 21 among the 15- and 45-ppm groups, but not the 5-ppm group. At 45 ppm, reduction in brain cholinesterase activity occurred in pups on postnatal days 5 and 28; a reduction in brain weight occurred on postnatal day 5 but not day 28.

2.4.1.5 Carcinogenesis In a 52-week study, dogs were given diets containing 5, 25, or 125 ppm azinphos-methyl (equivalent to 0.149, 0.688, or 3.844 mg/kg/day (males); 0.157, 0.775, or 4.333 (females)) (242). Mucoid diarrhea occurred in males given 25 ppm and in males and females that received 125 ppm. Both sexes given 125 ppm exhibited inhibition of plasma, RBC, and brain cholinesterase that began at week 4 of treatment and continued until week 52. In an earlier study, dogs given diets that contained 20 ppm azinphos-methyl for 36 weeks exhibited “irregular, slight” RBC cholinesterase depression, dogs given diets that contained 50 ppm for 15 months exhibited “slight to moderate” RBC cholinesterase inhibition, dogs given diets that contained 100 ppm exhibited “moderate” RBC cholinesterase inhibition; and dogs given diets that contained 150 ppm for 27 weeks followed by a diet that contained 300 ppm for 21 weeks exhibited “severe” (>75% inhibition) RBC cholinesterase inhibition (64). Cholinergic signs occurred only in dogs given 300 ppm.

When rats were given diets that contained 5, 15, and 45 ppm azinphos-methyl (equivalent to 0, 0.25, 075, and 2.33 mg/kg/day (males); 0.31, 0.96 and 3.11 mg/kg/day (females)) for up to 24 months, no cholinergic signs occurred, nor was clinical chemistry affected (242). There was, however, a marked inhibition of RBC, plasma and brain cholinesterase at 45 ppm, inhibition of RBC cholinesterase in males at 15 ppm, and, inhibition of RBC and plasma cholinesterase in females at 15 ppm. At 5 ppm, RBC cholinesterase decreased by 12% in male rats. When rats were fed a diet that had 50 ppm azinphos-methyl for 47 weeks followed by 100 ppm for 49 weeks, consistently depressed brain, plasma, and RBC cholinesterase activity occurred. When they were given a diet of 20 ppm for 97 weeks, depression of plasma and RBC cholinesterase activity occurred that decreased as the study progressed; exposure to diets of 2.5 or 5 ppm had no effect (64). Convulsions were seen in a “small number of female rats” (*sic*) (5/40) after increasing their dietary exposure from 50 to 100 ppm.

When azinphos-methyl was fed to mice at 0, 5, 20, or 40 ppm (about 0.79, 3.49, 11.33 (males); 0.98, 4.12, 14.30 (females)) for two years, no compound-related toxicity or evidence of cancer occurred

(242). However, up to 80% inhibition of plasma, RBC, and brain cholinesterase activity occurred in mice given 20 and 40 ppm. At 5 ppm, RBC cholinesterase was still slightly inhibited.

In a chronic bioassay, rats were fed diets that contained 78 or 156 ppm (males) or 62.5 or 125 pm (females) azinphos-methyl for 80 weeks, then observed for 34-35 weeks, and mice were fed diets that contained 31.3 or 62.5 ppm (males) or 62.5 or 125 ppm (females) for 80 weeks, then observed for 12–13 weeks (65). Body weight gain decreased in male rats and mice given either diet and in female rats or mice given the high dose diet. Signs of organophosphate intoxication (hyperactivity, tremors, dyspnea) occurred "in a few animals of both species" (*sic*) fed the higher dose diets. During the second year, cholinergic toxicity occurred at both dietary levels. An equivocal increase in the incidence of tumors of the pancreatic islets and follicular cells of the thyroid suggested, but did not provide sufficient evidence of, carcinogenicity in male rats. There was no increased incidence of tumors of any kind among mice.

2.4.1.6 Genetic and Related Cellular Effects Studies Azinphos-methyl with and without metabolic activation showed no evidence of mutagenicity in *Salmonella typhirium* (242). Azinphos-methyl was also negative in the reverse mutation induction assay with *Sacharomyces cerevisiae* and in the primary rat hepatocyte unscheduled DNA synthesis assay (242). In an *in vitro* cytogenetics assay using human lymphocytes, azinphos-methyl was clastogenic only with a metabolic activating system (242). However, a clastogenic effect was not observed in femoral marrow prepared from mice treated intraperitoneally with 5 mg/kg azinphos-methyl (242).

2.3.5 Biomonitoring/Biomarkers Among rats exposed dermally to 100, 200 or 400 mg azinphos-methyl on the shaved dorsal skin in the scapular region, there was a good correlation between dose and amount of dimethylthiophosphate in urine (69).

Studies of agricultural field workers exposed to azinphos-methyl have shown that they excrete dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), and dimethyl dithiophosphate (DMDTP) in urine (59, 60, 69–71). However, urinary metabolite excretion is not always well correlated with serum or RBC cholinesterase inhibition (60, 71).

2.4.2 Human Experience 2.4.2.2.1 Acute Toxicity A pilot who had spilled azinphos-methyl concentrate on his hands experienced visual disturbances, headache, tightness in the chest, abdominal cramps, nausea, vomiting, weakness and some excessive salivation (72).

2.4.2.2.2 Chronic and Subchronic Toxicity Work in orchards treated with azinphos methyl is associated with blood cholinesterase activity reductions of up to 70% (30% of pre exposure baseline) and that intake is primarily due to dermal exposures (70). It was estimated that workers who sprayed apple orchards (with solutions of 0.5 to 6 lb of 25% wettable powder per 100 gallons of water) were exposed to 0.05 to 2.55 mg/m^3 (average 0.64 mg/m^3) azinphos-methyl for periods of 15 to 45 minutes; workers responsible for filling tanks were exposed to 0.26 to 6.20 mg/m^3 (average 2.76 mg/m^3) azinphos-methyl for brief periods; and formulators were exposed to 1.07 to 9.64 mg/m^3, presumably for 8 hours/day. In all cases, dermal exposures exceeded inhalation exposure when quantified on a milligram per day basis. Serum cholinesterase activities were slightly depressed (78–91% of preexposure levels) after exposure, but no other effects were noted (73).

Orchardists who sprayed azinphos-methyl (wettable powder) were potentially exposed to an average concentration of 0.05 mg/m^3 (range 0.02–0.11 mg/m^3) based on air concentrations "measured near the spraymen during spraying operations," although inhalation exposures were probably significantly less than this because workers reportedly wore respirators. Dermal exposures were estimated at from 9 to 43 mg/kg. No evidence of serum or RBC cholinesterase inhibition was observed (57a). However, in another study of orchard workers, where exposures were primarily dermal (ranging up to 8,315 mg/hand wipe sample in thinners; up to 14,498 mg/sample on shirts of harvesters), median RBC cholinesterase activity declined by about 19% during a 6-week spraying season, and median

plasma activity fell by about 12% (60).

Workers engaged for 5 days in thinning a peach orchard after it was treated with azinphos-methyl, showed very slightly inhibited RBC cholinesterase activity (mean decrease of about 6% compared to baseline) and essentially no change in plasma cholinesterase activity. No symptoms associated with cholinesterase inhibition occurred. Daily urinary excretion of dimethyl phosphate (DMP) and dimethyl phosphorothionate (DMPT) increased in exposed workers, and daily mean DMP and DMTP excretion was highly correlated with the mean percentage decline in RBC cholinesterase activity from baseline (74).

No changes in plasma or RBC cholinesterase activities occurred in human volunteers given oral doses 4, 4.5 or 6 mg/day (0.06, 0.06 or 0.09 mg/kg/day) (75); 7, 8 or 9 mg/day (0.10, 0.11 or 0.13 mg/kg/day) (76); or, 10, 12, 14 or 16 mg/day (0.14, 0.17, 0.20 or 0.23 mg/kg/day) for 30 days (77).

2.5 Standards, Regulations, or Guidelines of Exposure

All azinphos-methyl liquids with a concentration greater than 13.5% are classified as restricted use pesticides by the U.S. EPA because of their high toxicity.

The ACGIH TLV for azinphos-methyl is 0.2 mg/m^3 and is associated with a skin notation (154). OSHA has established a PEL-TWA of 0.2 mg/m^3 with a skin notation, NIOSH has established a REL-TWA of 0.2 mg/m^3 with a skin notation, and most other countries have also established Occupational Exposure Limits of 0.2 mg/m^3 (e.g., Australia, Austria, Belgium, Denmark, Federal Republic of Germany, Netherlands, Philippines, Switzerland, Thailand, United Kingdom). Finland has established an OEL of 0.02 mg/m^3.

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Jan E. Storm, Ph.D

3.0 Chlorpyrifos

3.0.1 CAS Number:

[*2921-88-2*]

3.0.2 Synonyms:

(*O*,*O*-diethyl *O*-(3,5,6-trichloro-2-pyridinyl) phosphorothioate, Dursban; Lorsban; Dursban(R); chlorpyrifos-ethyl; Dowco 179; Pyrinex; phosphorothioic acid *O*,*O*-diethyl *O*-(3,5,6-trichloro-2-pyridinyl) ester; Brodan; Chloropyrifos; *O*,*O*-diethyl *O*-(3,5,6-trichloro-2-pyridyl) phosphorothioic acid; *O*,*O*-diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate; *O*,*O*-diethyl *O*-(3,5,6-trichloro-2-pyridinyl) phosphorothioic acid; 3,5,6-trichloro-2-pyridinol *O*-ester with *O*,*O*-diethyl phosphorothioate; chlorpyriphos-ethyl; detmol u.a.; dursban f; oms-0971; stipend; dursban 4E; chloropyriphos; killmaster; dursban 10cr; suscon; lorsban 50sl; coroban; terial 401; terial; danusban; durmet; *O*,*O*-diethyl *O*-(3,5,6-trichloro-2-pyridinyl) phosphorothioate; Dursban/Lorsban; Lorsban 4E-SG; Chlorpyrifos 4E-AG-SG; diethyl *O*-(3,5,6-trichloro-2-pyridyl) phosphorothioatae; diethyl *O*-(3,5,6-trichloro-2-pyridinyl) phosphorothioate; Dursban HF; Eradex; Pyrindol. 3,5,6-trichloro-, *O*-ester with *O*,*O*-diethyl phosphorothioate; Super I.Q.A.P.T.; Trichlorpyriphos

3.0.3 Trade Names:

Dursban®; Dowco 179®; ENT-27,311; Eradex®; Lorsban®; Pyrinex ®

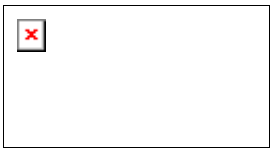
3.0.4 Molecular Weight:

350.57

3.0.5 Molecular Formula:

$C_9H_{11}Cl_3NO_3PS$

3.0.6 Molecular Structure:



3.1 Chemical and Physical properties
Pure chlorpyrifos is a white crystalline powder; technical chlopyrifos is an amber to white crystalline powder.

Specific gravity	1.398 g/cm^3 at 43.5°C
Melting point	42.5–43°C
Boiling point	decomposes at approximately 200°C
Vapor pressure	1.87×10^{-5} mmHg at 20°C
Solubility	soluble in most organic solvents; 0.00013 g/100 mL in water

3.1.2 Odor and Warning Properties Mild mercaptan odor due to diethyl disulfide in technical product.
3.2 Production and Use
Chlorpyrifos is a broad spectrum pesticide and acaracide that acts as a contact poison. Originally used to control mosquito larvae, it is no longer registered for this use. It has a wide range of applications on crops, lawns, ornamental plants, domestic animals, and a variety of building structures. Chlorpyrifos is available as 25% wettable powders, 1–10% granules, and emulsifiable concentrates of 2 and 4 lb/gal.
3.3 Exposure Assessment
Most exposures to chlorpyrifos are anticipated to be via inhalation of aerosols during its application; dermal absorption in humans is not significant (56, 199). Chlorpyrifos metabolism yields a unique urinary metabolite, 3,5,6-trichloro 2 pyridinol (TCP), which has been correlated to chorpyrifos exposure if analyzed within 48 hours of exposure (200, 201).
3.4 Toxic Effects
3.4.1.1 Acute Toxicity Chlorpyrifos is an organophosphate compound that has moderate toxicity and oral LD_{50}s of 80–250 mg/kg (64a, 202). Inhalation LD_{50}s of 78 and 94 mg/kg were calculated for female mice and rats, respectively, based on lethality observed after 60- to 180-minute exposures to aerosol concentrations of 5900 mg/m^3–7900 mg/m^3 (203). In female and male rats, 20 and 80% mortality occurred following 4-hour exposure to 5300 mg/m^3 chlorpyrifos, respectively, whereas no mortality occurred after exposure to 2500 mg/m^3 (56). A dermal LD_{50} of 202 mg/kg was reported in rats (64a). There is evidence that young animals are more sensitive than older animals; and that females are more sensitive than males to the lethal effects of chlorpyrifos (64a, 203a, 204).

Signs typically associated with organophosphate poisoning do not necessarily precede death caused by chlorpyrifos (203). “Apparent” (*sic*) tremors occasionally occurred in neonatal rats treated with a maximum tolerated dose (MTD) (45 mg/kg), but typical signs of a “cholinergic crisis” were not noted. Adult mice treated with a MTD (279 mg/kg) showed only slight to moderate signs of toxicity (e.g., diarrhea, fasciculations, lacrimation, slight tremors) (204). Cholinergic toxicity associated with sublethal exposure to chlorpyrifos was reflected only as mild diarrhea and hypoactivity evident only for the first two days following single s.c. injection of 279 mg/kg and not evident at all following repeated s.c. injections of 40 mg/kg (1×, 4 days, 16 days) (205, 206). Brain cholinesterase activity, however, was markedly depressed for at least 6 weeks following a single subcutaneous dose of 279 mg/kg and for at least 4 days following repeated subcutaneous doses of 40 mg/kg.

Prolonged cholinesterase inhibition occurred in rats given single subcutaneous injections of 0, 60, 125, or 250 mg/kg and examined up to 53 days later (207). Cholinergic toxicity was evident as a fine tremor in rats given 250 mg/kg but not 60 mg/kg (tremors in the 125 mg/kg group were not reported). Tremor intensity reached a peak in 9 days and returned to normal by 14 days after dosing. No overt signs of cholinergic toxicity occurred in rats treated with 0, 30, 60, or 125 mg/kg subcutaneously at any time from 1 to 35 days after dosing, although RBC cholinesterase activity was significantly inhibited in all groups (44). However, deficits in conditioned behavior occurred 2–16 days after dosing rats with 60, 125, or 250 mg/kg (207), and single oral doses of 12.5, 25, 37.5, or 50 mg/kg chlorpyrifos (or repeated doses of 12.5 mg/kg/day 5 days/week for eight weeks) caused significant deficits in response acquistition and performance measurements in a conditioned behavior task (208).

In rats given single oral doses of 20, 50, or 100 mg/kg chlorpyrifos by gavage, cholinergic signs peaked at 3½ hours in the 100-mg/kg group, were still present at 24 hours, and had disappeared by 72 hours after dosing (324). Only hypoactivity occurred in the 20-mg/kg group. When rats were given single oral doses of 10, 30, 60, or 100 mg/kg chlorpyrifos, no cholinergic effects occurred at 10 mg/kg, rats exhibited cholinergic signs at 30 mg/kg, tremors were also evident at 60 mg/kg, and cholinergic symptoms were present and severe at 100 mg/kg (43). The time of peak effect was always 3½ hours after dosing, and by 24 hours all symptoms had disappeared in the 30 mg/kg, but ataxia and hypoactivity were still evident in the 60- and 100-mg/kg group. Brain, plasma, and RBC cholinesterase inhibition were significantly and dose-dependently depressed at all dose including the 10 mg/kg group at both 3½ and 24 h. Thus, behavioral and biochemical effects of chlorpyrifos exposure were poorly correlated; and, behavioral signs showed recovery at 24 h whereas cholinesterase activity did not (43).

When rats were given 10, 50, or 100 mg/kg chlorpyrifos orally and observed 1, 8, and 15 hours later, cholinergic effects occurred only on day 1 in 100-mg/kg treated female rats (209). One female rat treated with 50 mg/kg had tremors, two exhibited incoordination, and one showed pronounced lacrimation. One male rat given 100 mg/kg exhibited only minimal tremor, and one male exhibited incoordination and lacrimation. Rats treated with 50 or 100 mg/kg were significantly hypoactive only on day 1. Thus, cholinergic effects were widespread at 100 mg/kg, minor at 50 mg/kg, moderated over a few days, and were more severe in females than males.

Responses of adult rats given single oral doses of 80 mg/kg were compared with those of 17-day-old rats treated with single doses of 15 mg/kg; these doses were equally effective in inhibiting cholinesterase (203a). Compared to adults, young rats showed similar behavioral changes and cholinesterase inhibition although at a fivefold lower dose. The onset of maximal effects was somewhat delayed, cholinesterase activity recovered more quickly, more extensive muscarcinic receptor down-regulation occurred, and no gender-related difference in sensitivity was noted.

Chlorpyrifos caused neurotoxicity, indicated by leg weakness. Onset was 3-18 days after dosing and lasted from 10–20 days when given subcutaneously to atropinized chickens at a dose of 200 mg/kg but not 100 mg/kg (64a).

3.4.1.2 Chronic and Subchronic Toxicity No treatment-related signs of toxicity, changes in body weight; or, in plasma, RBC, or brain cholinesterase activities occurred among rats exposed for 6 h/day, 5 days/week, 13 weeks, nose-only, to 72, 143, or 287 mg/m^3 chlorpyrifos (210). Nor was there any adverse effect at any exposure level based on urinalysis, clinical chemistry, hematology, gross pathological or histopathological evaluation.

When rats were exposed to 0.1, 1, 5, 15 mg/kg/day chlorpyrifos via the diet for 13 weeks, mild clinical effects (perineal soiling) were noted in females given 5 and 15 mg/kg/day (209). Plasma cholinesterase was significantly inhibited in males and females given 1 mg/kg or more, RBC cholinesterase was significantly inhibited in females given 1 mg/kg or more, and, brain

cholinesterase was inhibited in both males and females given 5 or 15 mg/kg. Motor activity of males and females given 15 mg/kg mildly decreased only at week 4 of exposure, and no treatment related differences were apparent subsequently, consistent with the occurrence of tolerance upon repeated exposure to chlorpyrifos.

Oral treatment of hens with 1, 5, or 10 mg/kg/day chlorpyrifos for 13 weeks did not induce neurotoxicity (1237).

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms There are no studies available that describe the pharmacokinetics of chlorpyrifos following inhalation exposure. However, absorption via inhalation was demonstrated indirectly in mice and rats who experienced lethality when exposed to 5900–7900 mg/m^3 aerosolized chlorpyrifos for 27–180 minutes (203). Indirect evidence of inhalation absorption in humans was provided in a study showing urinary excretion of diethyl phosphate chlorpyrifos metabolities by pesticide workers involved in treating structures with a spray emulsion of chlorpyrifos and vaponite (212).

Chlorpyrifos is well absorbed orally. Nearly 90% of orally administered chlorpyrifos was eliminated by rats in urine by 48–66 hours after dosing (201, 200a). The remaining 10% was eliminated in the feces. Chlorpyrifos was distributed especially to tissues involved in metabolism and excretion (liver and kidney), to tissues with considerable blood circulation (e.g., muscle, heart, lungs, spleen, testes, and bone), and to tissues high in lipids (e.g., fat and skin). It was eliminated nearly exclusively in urine (primarily as 3,5,6-trichloro-2-pyridinol phosphate). Elimination half-lives for liver, kidney, muscle, and fat were 10, 12, 16, and 62 hours, respectively, indicating considerable storage in fat.

About 72% of an oral dose of chlorpyrifos was absorbed (following a 1–2 hour delay), metabolized, and nearly completely eliminated (primarily as 3,5,6-trichloro-2-pyridinol (TCP)) in urine by male volunteers within 120 hours (199). Following either exposure route, chlorpyrifos was widely distributed and was eliminated from blood with a half-life of about 27 hours. In three individuals who ingested a concentrated solution of chlorpyrifos, its elimination was biphasic (276). An average elimination half-life for chlorpyrifos of 6 ± 2 hours in the initial elimination phase and of 80 ± 25 hours in a slower elimination phase was calculated.

Skin absorption of chlorpyrifos by humans is limited (56). In humans, less than 3% of a dermal dose of 5 mg/kg was absorbed (following a 22 hour delay) and was eliminated in urine within 180 hours (199). Considerable dermal absorption of chlorpyrifos has been reported in animals, although irritation and/or blistering from some high doses may have compromised the skin barrier. For example, 80–96% of a 22-mg/kg dermal dose was absorbed by goats by 12–16 hours after dosing and was distributed primarily to blood, liver, and fat, and lesser amounts were distributed to heart, gastrointestinal tract, and skeletal tissue (56, 57). About 60% of a dermal dose of chlorpyrifos (3–15 mM/5.6 cm^2) applied to rats was absorbed by 72 hours after dosing; young rats absorbed up to 90% of the applied dose. Eight hours after dermal treatment of mice with 1 mg/kg chlorpyrifos, about 74% of the dose was found primarily in urine and feces, carcass, blood, intestine, liver, and kidney, and an elimination half-life of 21 hours was estimated (213).

Chlorpyrifos is metabolized to chlorpyrifos oxon via cytochrome p450-dependent desulfuration (16, 215, 216). The oxon is rapidly hydrolyzed to 3,5,6-trichloro-2-pyridinol (TCP) via microsomal esterase (including paraoxonase and chlorpyrifos oxonase) (49, 217, 218) or via a nonenzymatic process (14, 215, 216). Alternatively, chlorpyrifos is dearylated to form diethyl thiophosphoric acid and TCP in a reaction also catalyzed by microsomal enzymes. TCP is a relatively unique metabolite of chlorpyrifos and it (or one of its conjugates) is almost exclusively (90%) excreted in the urine (200a, 201).

Chlorpyrifos oxon binds to and irreversibly inhibits acetylcholinesterase. However, the relative affinity of chlorpyrifos oxon for plasma and hepatic esterase exceeds that for acetylcholinesterase

(13, 14, 219). Moreover, chlorpyrifos oxon causes relatively greater and longer lasting inhibition of hepatic esterase *in vivo* compared to brain acetyklcholinesterase (13, 14, 219). Noncatalytic binding of chlorpyrifos oxon to hepatic and plasma esterase represents a significant detoxication mechanism because it prevents much hepatically generated chlorpyrifos oxon from entering the general circulation and target tissues (56). High rates of hepatic dearylation and esterase binding may represent protective factors but it should also be recognized that chlorpyrifos can be activated in extrahepatic tissues such as brain (219).

Comparative differences in the rates of hepatic esterase binding and rates of dearylation have been implicated as contributors to the greater sensitivity of female rats to chlorpyrifos toxicity compared to male rats, to the greater sensitivity of some tissues (e.g., brain) to chlorpyrifos compared to other tissues (17), to the greater sensitivity of young animals to chlorpyrifos toxicity compared to adults (18), and to the greater toxicity of parathion compared to chlorpyrifos (13, 15, 19, 221).

Although human chlorpyrifos oxonase has not been shown to exhibit clear genetic polymorphism as has been shown for paraoxonase (218, 222), a 13-fold variation in chlorpyrifos oxonase activity has been found in human serum (223–225).

3.4.1.4 Reproductive and Developmental No effects on reproduction, fertility indexes, or neonatal development were noted in two generations of rats fed diets that contained 0.1,1.0, and 5 mg/kg/day chlorpyriphos (211). Parental toxicity at the highest dose was accompained by a decrease in pup body weight and increased pup mortality in the F1 litters.

Chlorpyrifos was not fetotoxic to rats given 0, 0.1, 3.0, or 15 mg/kg/day chlorpyriphos by gavage on days 6 through 15 of gestation (211). When pregnant mice were given 0,1,10, or 25 mg/kg/day chlorpyriphos by gavage on gestation days 6 through 15, minor fetotoxic responses and skeletal variations were noted at 25 mg/kg/day, a dose that also caused severe maternal toxicity (589). Teratogenicity (exencephaly) was observed in one pup at 1 mg/kg/day, but was not noted at 10 or 25 mg/kg/day.

3.4.1.5 Carcinogenesis Neither rats maintained for 2 years nor dogs maintained for 1 or 2 years on diets that contained 0.01, 0.03, 0.1, 1, or 3 mg/kg chlorpyrifos showed signs of cholinergic toxicity or carcinogenicity at 12, 18, or 24 months (202). However, RBC cholinesterase activity was intermittently depressed among female rats given 0.1 mg/kg (at 30 and 365 days only) and was consistently depressed among male and female rats given 1 mg/kg and 3 mg/kg (202). Brain cholinesterase activity in rats was intermittently depressed in both sexes given 1 mg/kg (at 180 days and 547 days in females; at 365 and 730 days in males), and was consistently depressed in both sexes given 3 mg/kg. RBC and brain cholinesterase returned to normal levels within 7–8 weeks in a subset of exposed rats after they were switched to control diets. RBC cholinesterase activity was significantly depressed in dogs given 1 or 3 mg/kg diets from day 30 through 730. Brain cholinesterase activity in dogs exposed for 1 or 2 years was slightly depressed in the 3-mg/kg group (81–92% of control levels).

No evidence of cholinergic toxicity occurred in rhesus monkeys given 0.08, 0.40, or 2.0 mg/kg/day chlorpyrifos orally for six months, although plasma cholinesterase activity was reduced in all dose groups and RBC cholinesterase activity was reduced in the 0.40- and 2.0-mg/kg/day groups (220).

3.4.1.6 Genetic and Related Cellular Effects Studies Chlorpyrifos is genotoxic based on a recent review (56). Chlorpyrifos induced micronuclei in erythroblasts and caused cytogenetic effects in human lymphoid cells in a dose-related fashion (56). Chlorpyrifos produced significant increases in sister chromatid exchanges and caused X chromosome loss in *Drosophila melanogaster* and chromosomal aberrations and sister chromatid exchanges in spleen cells. Spindle poisoning and induction of micronuclei and polyploidy have been reported following chlorpyrifos exposure. Sex-linked recessive lethals have also been produced in *Drosophila melanogaster* by chlorpyrifos exposure, indicating that chlorpyrifos is genotoxic to both somatic and germ cells.

3.3.5 Biomonitoring/Biomarkers TCP is a unique urinary metabolite of chlorpyrifos. Variation in urinary TCP was investigated in termite control workers frequently involved in spraying chemicals in closed environments (226). Variation in the urinary TCP level corresponded to the termite control season and the length of the working period.

3.4.2 Human Experience 3.4.2.2 Clinical Cases Unconsciousness, cyanosis, wheezing, and uncontrolled urination and diarrhea occurred within 18 hours after an individual ingested an estimated dose of 300 mg/kg chlorpyrifos (227). In another suicide attempt, a 27-year-old male experienced extreme agitation, diaphoresis and excessive oral secretions, muscle weakness and fasciculations 14 hours after ingestion of an unknown amount of chlorpyrifos (228). RBC cholinesterase activity was within normal limits. He was administered atropine, pralidoxime, and ventilatory support, and symptoms resolved after 72 hours without permanent sequelae. In another case of chlorpyrifos poisoning, a woman presented with stupor, increased muscle tone, absence of superficial reflexes, and striking choreoathetotic movements of all limbs (229). Serum and RBC cholinesterase activities were markedly depressed (about 20 and 2% of normal, respectively). Atropine relieved the symptoms, and the patient was completely well one month later. A 5-year-old girl who ingested an unknown amount of Rid-A-Bug® which contains chlorpyrifos and a 3-year-old boy who experienced frothing at the mouth, coma, pinpoint pupils, nasal secretions, fasciculations of the eyelids, and twitching of the extremities after ingesting an unknown amount of Dursban®, survived through treatment with atropine and pralidoxime (230, 231). In the boy, a distal polyneuropathy developed 18 days later, but all symptoms were fully resolved by day 52.

An intermediate syndrome that required endotracheal intubation and intermittent positive pressure ventilation followed by vocal cord paralysis was reported in an individual who had recovered from a cholinergic crisis due to acute chlorpyrifos ingestion (232). Immediate and delayed toxicity was reported in eight individuals exposed to Dursban® presumably via inhalation and dermal contact as a result of its use as a commercial fumigant (233). Immediate symptoms included nausea, vomiting, and lightheadness in a worker after chlorpyrifos was inadvertently introduced into the workplace ventilating system, and headaches, nausea, and painful muscle cramps in a family of four after their house was sprayed with chlorpyrifos by an exterminator. About 4 weeks after initial exposure, the affected worker developed paresthesia in his feet, urinary frequency and pain in the suprapubic, groin, and thigh regions, and the affected family developed numbness and paresthesias especially in the legs which was accompanied by reported memory impairment. Nerve conduction studies were consistent with distal axonopathy. Delayed sensory neuropathies were also described in two women whose houses had been treated with chlorpyrifos 3–4 weeks earlier and in an exterminator who was exposed repeatedly to chlorpyrifos during a 6-month period (233). All symptoms resolved by 2 weeks–3 months after exposure stopped. No estimates of exposure or cholinesterase activity levels were provided.

A spectrum of common birth defects that involved central nervous system malformations, ventricular, eye, and palate defects, hydrocephaly, microcephaly; mental retardation; blindness; hypotonia; widely-spread nipples; and deformities of the teeth, external ears and external genitalia was described in four infants (two of whom were siblings) and attributed to maternal exposure to chlorpyrifos during the first trimester of pregnancy either in the home or at work (234, 235). However, no confirmation of exposure either through chlorpyrifos measurements or cholinesterase activities was provided nor was any estimate of dose attempted. Reports of an additional nine cases of birth defects that had the same or similar spectrum of effects associated with *in utero* chlorpyrifos exposure were provided to the EPA and reviewed by the Centers for Disease Control (CDC) (236). The EPA concluded that the cases did not support a finding of teratogenicity (236).

3.4.2.2.2 Chronic and Subchronic Toxicity The prevalence of selected illnesses and symptoms in 175 employees involved in producing chlorpyrifos for more than one day between 1 January 1977 and 31 July 1985 and in 335 individually matched controls were compared (237). Subjects were subdivided into three exposure groups (high, moderate, and low) on the basis of job title and air monitoring data.

Estimated TWA concentrations of chlorpyrifos were not provided by exposure group, but for all employees reporting ranged from 0.01 to 0.37 mg/m^3. Company medical records were examined for evidence of gastrointestinal tract and nervous symptoms. No significant differences in illness or prevalence of symptoms were observed between the exposed and unexposed groups or among the three exposure subgroups. The observation period was extended to 31 December 1994, and the study group size was increased to 496 potentially exposed employees and 911 controls in a follow-up study (238). High, moderate, low, and negligible exposures were defined as □0.2 mg/m^3 chlorpyrifos or high potential for dermal exposure, □0.03 mg/m^3 or moderate potential for dermal exposure, □0.03 mg/m^3 or low potential for dermal exposure, and □0.01 mg/m^3 or negligible dermal exposure, respectively. Employees were categorized into moderate, low or negligible exposure levels on the basis of plasma cholinesterase activities. Prevalence odds ratios for various nervous, respiratory, and digestive system symptoms were calculated by exposure as well as plasma cholinesterase inhibition, and no exposure-related effects were observed.

An increase in the frequency of blurred vision, flushing of skin, and decreased urination were reported by pet control employees who used chlorpyrifos within the previous three months (239). However, no estimates of chlorpyrifos exposure were obtained, and exposure was not confirmed with biomarkers of exposure.

Volunteers were treated with 0.014, 0.03 or 0.10 mg/kg/day chlorpyrifos by capsule for a total of 20 days at the low and mid-dose and for 9 days at the high dose (95). Treatment of the high-dose group was discontinued after 9 days due to a runny nose and blurred vision in one individual. Mean plasma cholinesterase in this group was inhibited by about 65%. No effect on RBC cholinesterase activity was apparent at any dose. No signs of toxicity were reported among human volunteers given daily oral doses of 0.014, 0.030, or 0.100 mg/kg chlorpyrifos for up to four weeks (210). Plasma cholinesterase inhibition was reported in the 0.100-mg/kg group, but RBC cholinesterase was reportedly unaffected at all exposure levels.

No signs of toxicity or depression in RBC acetylcholinesterase activity occurred among human volunteers given 0.5 mg/kg orally or 0.5 or 5 mg/kg dermally. Plasma cholinesterase activity was reduced to 15% of predose levels after the 0.5 mg/kg oral dose, but RBC cholinesterase activity was unchanged after this dose or the 5 mg/kg dermal dose (199).

3.5 Standards, Regulations, or Guidelines of Exposure

The EPA established a 24-hour reentry interval for crop areas treated with emulsifiable concentrate or wettable powder formulations of chlorpyrifos unless workers wear protective clothing. Chlorpyrifos is undergoing reregistration by the EPA (242).

The ACGIH TLV and the NIOSH REL-TWA for chlorpyrifos is 0.2 mg/m^3 with a skin notation (154). There is no OSHA TWA-PEL for chlorpyrifos. Most other countries have also established Occupational Exposure Limits of 0.2 mg/m^3 with skin notation for chlorpyrifos (e.g. Australia, Belgium, Denmark, Finland, France, Netherlands, Switzerland, and United Kingdom). NIOSH has also established a 0.6 mg/m^3 STEL for chlorpyrifos.

Organophosphorus Compounds
Jan E. Storm, Ph.D

4.0 Coumaphos

4.0.1 CAS Number:

[*56-72-4*]

4.0.2 Synonyms:

O,*O*-diethyl *O*-(3-chloro-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl) phosphorothioate; 3-chloro-7-diethoxyphosphinothioyloxy-4-methylcoumarin; Diolice; Meldane; Muscatox; Resistox; Asuntol; Bay 21/199; Bazmix; Umbethion; phosphorothioic Acid *O*-(3-chloro-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl) *O*,*O*-diethyl ester; Asantol; Baymix; Resitox; *O*,*O*-diethyl *O*-(3-chloro-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl)phosphorothioate; 3-chloro-7-hydroxy-4-methylcoumarin *O*-ester with *O*,*O*-diethyl phosphorothioate; 3-chloro-4-methylumbelliferone, *O*-ester with *O*,*O*-diethyl phosphorothioate; *O*,*O*-diethyl *O*-(3-chloro-4-methyl-7-coumarinyl) phosphorothioate; *O*,*O*-diethyl *O*-(3-chloro-4-methylumbelliferone); 3-chloro-7-hydroxy-4-methyl-coumarin *O*,*O*-diethyl phosphorothioate; 3-chloro-4-methyl-7-coumarinyl diethyl phosphorothioate; 3-chloro-4-methyl-7-hydroxycoumarin diethyl thiophosphoric acid ester; *O*,*O*-diethyl *O*-(3-chloro-4-methyl-2-oxo-2*H*-benzopyran-7-yl)phosphorothioate; asunthol; coumafos; agridip; *O*-(3-chloro-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl) *O*,*O*-diethyl phosphorothioate; Coumarin, 3-chloro-7-hydroxy-4-methyl-, *O*-ester with *O*,*O*-diethylpyrophosphorothioate; diethyl *O*-(3-chloro-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl) phosphorothioate; Umbelliferone, 3-chloro-4-methyl-, *O*,*O*-diethyl phosphorothioate

4.0.3 Trade Name:

Agridip; Asuntol®; Bay 21; Baymix®; Co-Ral®; ENT-17957; Meldane®; Muscatox®; Negashunt; Resitox®; Suntol, Umbethion

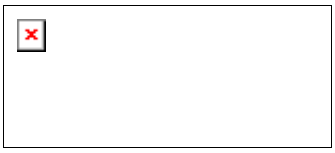
4.0.4 Molecular Weight:

362.8

4.0.5 Molecular Formula:

$C_{14}H_{16}ClO_5PS$

4.0.6 Molecular Structure:



4.1 Chemical and Physical Properties

Technical coumaphos is a colorless or white and tan powder. Coumaphos is stable under normal use conditions but hydrolyzes slowly under alkaline conditions

Specific gravity	1.47 at 20°C
Melting point	91–92°C
Boiling point	20°C at 1×10^{-7} mmHg
Vapor pressure	1×10^{-7} mmHg at 20°C
Solubility	soluble in acetone and diethyl phthalate; much less soluble in denatured alcohol and xylene; only slightly soluble in octanol, hexane and mineral spirits; insoluble in water

4.1.2 Odor and Warning Properties Slight sulfur odor.

4.2 Production and Use

Coumaphos is an organophosphate insecticide used to control anthropoid pests on beef cattle, dairy cows, goats, horses, sheep, and swine. Formulations include wettable powders, emulsifiable liquids, flowable concentrate, ready-to-use liquids, and dusts. Coumaphos is applied by aerosol can, dust bags, hand-held dusters, dip vats, high- and low-pressure hand-held sprayers, back rubber oilers, mechanical dusters, shaker can, and squeeze applicators (241). The EPA issued a Registration Standard for coumaphos in 1989 and a Reregistration Standard in 1996 (45). Currently 26

coumaphos products are registered (243).

4.4 Toxic Effects

4.4.1.1 Acute Toxicity Coumaphos is highly toxic and has an oral LD_{50} of 16–41 mg/kg in rats (64a). However, the EPA noted that the oral LD_{50} in male rats was >240 mg/kg and oral LD_{50} in female rats was 17 mg/kg (241). The dermal LD_{50} for coumaphos was previously reported as 860 mg/kg in rats (Gaines 1969) although EPA noted that the dermal LD_{50} was >2400 mg/kg in male and female rats (241). One-hour LC_{50}s of 1081 mg/m^3 and 341 mg/m^3 and 341 mg/m^3 were reported for male and female rats (241).

When male rats were given single oral doses of 250 mg/kg and female rats were given single oral doses of 17.5 mg/kg, cholinergic signs occurred and lasted for 12–13 days (242). RBC cholinesterase activity was depressed at 2 mg/kg in both sexes. When sheep were given 2 or 4 mg/kg/day coumaphos orally for 6 days, 4 mg/kg/day caused RBC cholinesterase inhibition and signs of cholinergic toxicity (*sic*); 2 mg/kg/day inhibited RBC cholinesterase but caused no apparent overt cholinergic toxicity (240). Treatment with coumaphos did not significantly alter the anticholinesterase effects of the second treatment 6 weeks later, suggesting no cumulative effect. Simultaneous treatment with coumaphos (4 mg/kg/day) and an intravenous dose of trichlorfon (insufficient to cause significant inhibition of RBC cholinesterase alone) resulted in an additive effect on RBC cholinesterase inhibition (240).

When rats were treated dermally for 2 or 5 days with 0, 2.5, 5, 10, 20, or 50 mg/kg/day coumaphos, no cholinergic toxicity was noted (241). Brain, plasma, and RBC cholinesterase activity, however, were depressed at 50 mg/kg after 2 days, and RBC and brain cholinesterase activity were depressed at 20 mg/kg/day after 5 days (241).

Coumaphos is a mild eye irritant, but is not irritating to the skin and is not a skin sensitizer; nor does it produce delayed neurotoxicity in hens (241).

4.4.1.2 Chronic and Subchronic Toxicity No signs of cholinergic toxicity were observed at any dose in rats fed diets that contained 0, 2, 5, or 10 ppm coumaphos for 13 weeks (about 0, 0.2, 0.5, or 1.0 mg/kg/day) (241). However, plasma cholinesterase was inhibited at 10 ppm (1 mg/kg/day), and RBC cholinesterase was inhibited at all dose levels. Brain cholinesterase was not inhibited at any time at any dietary level.

When rats were dermally treated with 2, 4, 20, or 100 mg/kg/day coumaphos for 21 days, cholinergic toxicity (muscle fasciculation, tremors) occurred at 20 or 100 mg/kg/day (241). RBC cholinesterase was inhibited at all doses, and brain cholinesterase was inhibited at 20 and 100 mg/kg. In another 21-day dermal study, when female rats were given 0, 0.1, 0.5, 1.1, or 2.1 mg/kg/day coumaphos, no signs of cholinergic toxicity were observed at any dose, although RBC cholinesterase was significantly inhibited at 1.1 and 2.1 mg/kg/day (242).

4.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Coumaphos is well absorbed orally. The plasma half-life for coumaphos following oral exposure ranges from 2–3 hours at 1.0 mg/kg and 3–5 hours at 15.0 mg/kg (241). Urinary excretion is rapid; and 63–87% of an administered dose was excreted within 24 hours, and 76–96% of an administered dose was excreted within 168 hours. Tissue residues were highest in fat, kidney, liver, and muscle. Seven days after rats were given single oral doses of about 1 mg/kg coumaphos, about 55% had been excreted in urine and about 24% has been excreted in feces (246). The remaining dose was distributed primarily to the liver, abdominal fat, skin, and kidney.

The fate of dermally applied coumaphos was examined in lactating goats given about 14 mg/kg coumaphos (243). During the 7 days after treatment, an average of <0.1, 4.7, and 1% of the administered dose was eliminated in milk, urine, and feces, respectively. When goats were killed

after 7 days, the highest coumaphos residues were in adipose tissue (mainly unmetabolized coumaphos) followed by the kidney and liver.

Coumaphos is extensively metabolized. The urine of rats treated orally with coumaphos contained five to eight metabolites, and the feces contained five to seven metabolites (242). The major metabolite is chlorferone (the hydroxylated leaving group). Coumaphos represented 0.1% of the urinary metabolites. Coumaphos represented 0.2% of the fecal metabolites when administered intravenously but approximately 15 to 55% of the fecal metabolites when given orally, suggesting that the process of oral absorption may slow metabolism.

4.4.1.4 Reproductive and Developmental Reproductive toxicity did not occur in rats fed diets that contained 1, 5, or 25 ppm coumaphos (0.07, 0.30, and 1.79 mg/kg/day (F_0 males) and 0, 0.08, 0.34, or 2.02 mg/kg/day (F_0 females)) during premating for two generations (241). Dose-dependent decreases in plasma and RBC cholinesterase activity occurred among rats fed 5 or 25 ppm. Brain cholinesterase was significantly inhibited in F_0 and F_1 females. In pups, plasma and RBC cholinesterase levels were inhibited at 25 ppm on lactation day 21 but not on lactation day 4.

No developmental effects occurred in offspring of rats given 1, 5, or 25 mg/kg/day coumaphos by gavage on gestation days 6 to 15 (242). Three rats in the 25-mg/kg/day group showed tremors, and two showed additional signs of cholinergic toxicity. No developmental effects occurred in rabbits given 0.25, 2.0, or 18.0 mg/kg/day coumaphos by gavage during gestation days 7 through 19 (242). Maternal toxic signs, including death and abortion, were observed in the 18-mg/kg/day group. When pregnant bovines were dermally treated with coumaphos at various stages of gestation by pouring it along the dorsal midline, there was evidence of increasing embryonic death rates or teratogenic effects (245).

4.4.1.5 Carcinogenesis There was no evidence of carcinogenicity at any dose in rats fed diets that contained 1, 5, or 25 ppm coumaphos (0.05, 0.25, or 1.22 mg/kg/day (males); 0.07, 0.36, or 1.70 mg/kg/day (females)) for two years (241). Body weight gain decreased in females given the 25-ppm diet (1.7 mg/kg/day). Plasma and RBC cholinesterase was inhibited in females given the 5- or 25-ppm diet (0.36 or 1.7 mg/kg/day) and in males given the 25-ppm diet (1.22 mg/kg/day). There was no evidence of carcinogenicity in another study when rats were given diets that contained 10 or 20 ppm coumaphos for 103 weeks (244). The only adverse effect observed was slightly decreased body weight gain in females given either the 10- or 20-ppm diet. No adverse effects of any kind were observed in mice given diets that contained 0, 10, or 20 ppm coumaphos for 103 weeks (241).

There were no treatment related effects other than cholinesterase inhibition in dogs given 1, 30, or 90 ppm coumaphos in the diet for one year (0.025, 0.775, or 2.295 mg/kg/day (males); 0.024, 0.7095, or 2.478 mg/kg/day (females)) (241). Plasma, RBC, brain, and ocular muscle cholinesterase activity levels were depressed in the 30- and 90-ppm fed dogs (0.775/0.7095 and 2.295/2/478 mg/kg/day).

4.4.1.6 Genetic and Related Cellular Effects Studies Coumaphos was not mutagenic in *S. typhimurium* with or without metabolic activation, was negative in a mouse micronucleus test, and was negative in a Pol A test on *E. coli* with and without metabolic activation (241).

4.4.2 Human Experience 4.4.2.2 Clinical Cases Six individuals suffered serious organophosphate poisoning after ingesting coumaphos mistakenly used as a food flavoring in two separate incidents (247). In the first incident, four adults developed symptoms of poisoning (nausea, vomiting, and abdominal pain) 1 hour after eating seafood flavored with coumaphos which had possibly been mistaken for monosodium glutamate. After 2 hours, obvious signs of cholinergic toxicity (sweating, urination, miosis, bronchorrhea, and hypersalivation) were apparent. One adult female died at home after about 3 hours; the remaining three adults were treated with atropine and pralidoxime and gradually recovered. In the second incident, a man and wife developed signs of organophosphate

poisoning (nausea, vomiting, diarrhea, abdominal pain, and blurred vision) after eating coumaphos-contaminated fried fish and recovered with atropine and PAM.
4.5 Standards, Regulations, or Guidelines of Exposure
The EPA classifies most formulations of coumaphos as General Use Pesticides. The formulations 11.6% EC and 42% flowable concentrate end-use products have been classified as Restricted Use Pesticides because they pose a hazard of acute poisoning from ingestion. No Occupational Exposure Limits were identified for coumaphos.

Organophosphorus Compounds
Jan E. Storm, Ph.D

5.0 Demeton
5.0.1 CAS Number:
[*8065-48-3*]
5.0.2 Synonyms:
O,*O*-diethyl *O* (and *S*)-2-(ethylthio)ethyl phosphorothioate mixture; Systox; Bayer 8169; Demeton-o + Demeton-s; Demox; E-1059; phosphorothioic acid *O*,*O*-diethyl *O*-2-(ethylthio)ethyl ester, mixed with *O*,*O*-diethyl-*S*-2-(ethylthio)ethyl phosphorothioate; Denox; Systemox; phosphorothioic acid *O*,*O*-diethyl *O*-[2-(ethylthio)ethyl] ester mixture with *O*,*O*-diethyl *S*-[2-(ethylthio)ethyl] phosphorothioate; phosphorothioic acid *O*,*O*-diethyl *O*-[2-(ethylthio)ethyl] ester, mixed. with *O*,*O*-diethyl *S*-[2-(ethylthio)ethyl] phosphorothioate; demeton+; Demeton (O-isomer and S-isomer); diethyl *O*-(and *S*-)(2-(ethylthio)ethyl) phosphorothioate (mixed isomers); phosphorothioic acid, *O*,*O*-diethyl *O* (and *S*)-(ethylthio)ethyl esters; Demeton O(35%)+S(56%)
5.0.3 Trade Names:
Demox®; Mercaptofos®; Systox®; Bay 10756; Bayer 8169; ENT 17,295
5.0.4 Molecular Weight:
258.34
5.0.5 Molecular Formula:
$C_8H_{19}O_3PS_2$
5.1 Chemical and Physical Properties
Demeton is a light brown to pale yellow, oily liquid. Demeton is the common name for a mixture of *O*,*O*-diethyl-*O*-2-ethylthioethyl phosphorothioate (demeton-O) and *O*,*O*-diethyl-*S*-2-ethylthioethyl phosphorothioate (demeton-S) in a ratio of approximately 2:1. Demeton decomposes to toxic gases and vapors such as sulfur dioxide, phosphoric acid mist, and carbon monoxide. Contact with strong oxidizers may cause fire and explosions.

Specific gravity	1.18 at 20°C
Melting point	>–25°C
Boiling point	134°C at 2 mmHg
Vapor pressure	3.4×10^{-4} mmHg at 20°C (mixture)
Solubility	slightly soluble in water; soluble in most organic solvents

5.1.2 Odor and Warning Properties Pronounced mercaptan-like odor.
5.2 Production and Use
Demeton is a systemic insecticide effective against sap-feeding insects and mites. Before 1989 when it was discontinued by the manufacturer, it was available as emulsifiable concentrates of varying active ingredient content (1). Because demeton is no longer an active ingredient in any registered pesticide product, its registration has been canceled by the U.S. EPA (45).
5.4 Toxic Effects
5.4.1.1 Acute Toxicity Demeton is a highly toxic organophosphate compound that has oral LD_{50}s of

2–6 mg/kg (64a, 248, 249). The oral LD_{50} for the P–S isomer (demeton-O) in rats was 7.5 mg/kg and for the P–O (demeton-S) isomer was 1.5 mg/kg (250). The sulfoxide and sulfone metabolites of demeton are as lethal as demeton itself; they have oral LD_{50}s in rats of 1.9 to 2.3 mg/kg (251).

The dermal LD_{50}s are 8.2–14 mg/kg in rats, nearly equivalent to its acute oral toxicity (64a). However, formulation impacts the dermal toxicity of demeton. An equal volume of emulsifier changed the LD_{50} from less than 24 to 620 mg/kg, whereas dilution of the mixture to the strength used for spraying greatly increased the toxicity, so that a lethal dose was about 5 mg/kg (478).

A single 2-hour exposure to 18 mg/m^3 demeton was fatal within 50–90 minutes to all of a group of six rats (250). Rats exposed to 3 mg/m^3 demeton for 2 hours/day experienced "no signs of illness during the first exposure" (sic), tremors during the second exposure, lacrimation and more severe tremors during the third exposure, and mortality in 10 of 17 rats during the fourth exposure. Rats exposed to 3 mg/m^3 demeton for only 1 hour/day experienced no signs of intoxication after two days; mild tremors after 4 days; marked tremors, lacrimation, and 5% mortality (1/20) after 6 days; and 37% mortality (7/19) after 12 days. One and four-hour LC_{50} values of 175 and 47 mg/m^3 were obtained for rats (123).

Demeton was not associated with signs of organophosphate-induced delayed neuropathy when administered subcutaneously to atropinized chickens at doses that ranged from 5–80 mg/kg and were then observed for 30 days (190).

5.4.1.2 Chronic and Subchronic Toxicity When rabbits were given greens sprayed with demeton so that intake was 2.3, 1.5, 0.5, 0.1, or 0.07 mg/kg/day for 40, 30, 100, 98, and 94 days, respectively, no effects occurred in the 0.07- or 0.1-mg/kg/day groups, one of six rabbits fed 0.5 mg/kg/day died after 64 days, four of six rabbits fed 1.5 mg/kg died, and three of six rabbits fed 2.3 mg/kg/day died (250).

Rats fed diets that contained 50 ppm demeton containing 48% of the more potent P□O isomer (equivalent to 2.6 mg/kg) for 11–16 weeks exhibited cholinergic toxicity (fasciculations, weakness, tremors, lacrimation, and salivation) at 11 weeks, but by 16 weeks they were exhibiting no signs of cholinergic toxicity despite severe brain cholinesterase inhibition (253). No cholinergic signs were observed in rats given diets that contained 1, 3, or 20 ppm demeton for 11–16 weeks. When rats were given 0.4, 0.66, 0.9, and 1.89 mg/kg/day demeton by gavage for 65 days during a 90-day period, signs of cholinergic toxicity (hyperexcitability, tremors) occurred in rats given the two highest doses after 21 days (250). There was one death in the group fed 1.89 mg/kg.

In dogs given diets that contained 1, 2, or 5 ppm demeton (0.025, 0.047, or 0.149 mg/kg/day) for 24 weeks, plasma cholinesterase activity was maximally inhibited after about 12 weeks in dogs given the 5-ppm diet and after 16 weeks in dogs given the 2-ppm diet (193). RBC cholinesterase activity was unaffected by the 1- or 2-ppm diets and was slightly inhibited by the 5-ppm diet. When demeton and parathion were in the same diet at levels necessary for cholinesterase inhibition, the effects were additive (193). In an unpublished study submitted to EPA, overt cholinergic toxicity reportedly occurred in rats fed a diet that delivered 0.9 mg/kg/day demeton but not 0.7 mg/kg/day (95). In another unpublished study, cholinsterase inhibition (*sic*) reportedly occurred in female rats fed diets that contained 3 ppm demeton for 77–112 days but not in rats fed 1 ppm). Cholinergic effects evidently occurred at 20 ppm but not at 10 ppm (95).

5.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The principal metabolic pathway for both the O- and S-isomers is oxidation of the 2-ethylthioether to sulfoxide and sulfone. In the case of demeton-O, a secondary pathway involves oxidation of P□S to P□O and subsequent oxidation to sulfoxide and sulfone (257). These oxidation products are more potent inhibitors of

acethylcholinesterase than the parent compound. Studies in mice are consistent with the notion that oxidation of the mercapto sulfur of the ethylmercaptoethyl portion of demeton and the P–O isomer to the corresponding sulfoxide and finally to the sulfone is an important metabolic pathway for demeton (258).

5.4.1.4 Reproductive and Developmental Administration of 7 or 10 mg/kg demeton to mice as a single intraperitoneal dose or as three consecutive doses of 5 mg/kg each between days 7 and 12 of gestation was embryo toxic, as evidenced by decreased fetal weight and slightly higher mortality of the young (254). Fetuses that had intestinal hernias were found at 16 but not at 18 days. The high dose (10 mg/kg) administered on days 8, 9, or 10 of gestation had no effect on litter size at birth or on the survival rate of the young.

Ducklings hatched from eggs innoculated with demeton at the rate of 0.01 mg/egg on day 13 of incubation had partial to complete loss of voluntary control of one or both hind legs. Some were excitable and ataxic. The difficulties gradually disappeared about 1 week after hatching, but the growth of treated ducklings remained retarded. Histological examination of the skeletal muscles revealed areas of degenerative change and other areas of marked regenerative activity (255, 256).

5.4.1.5 Carcinogenesis No published studies of the chronic toxicity or oncogenicity of demeton were identified. In an unpublished study submitted to the EPA, dogs were fed diets that contained demeton (all levels not specified) for 24 weeks (95). RBC cholinesterase was inhibited at a dietary concentration of 5 ppm (about 0.125 mg/kg/day), and plasma cholinesterase was inhibited at a dietary concentration of 2 ppm (about 0.05 mg/kg/day). A dietary level of 1 ppm (0.025 mg/kg/day) was without effect on either on either plasma or RBC cholinesterase. In another unpublished study submitted to EPA, cholinesterase (*sic*) was reportedly inhibited at 0.5 mg/kg/day but not at 0.15 mg/kg/day in rabbits that were given demeton orally for 106 days (95).

5.4.1.6 Genetic and Related Cellular Effects Studies Demeton was reportedly both positive and negative in *in vitro* tests of bacterial mutagenicity and negative in a sex-linked lethal mutation assay using *D. melanogaster* (545).

5.4.2 Human Experience 5.4.2.2 Clinical Cases Demeton has been associated with numerous deaths after high accidental and intentional exposures and from occupational exposures (1). Estimates of exposure are not available. A man who spilled 60 mL of concentrated liquid demeton on his thigh, then rinsed his thigh with water but continued wearing the pants, suddenly experienced nausea, vomiting and, weakness after about 9 hours, was treated with atropine, and recovered uneventfully (1).

Twelve of fourteen agricultural workers exposed to about 1 mg/m^3 demeton reportedly had lowered cholinesterase levels (*sic*) but displayed no clinical evidence of poisoning (*sic*) (259). In another study, air concentrations of up to 6 mg/m^3 were reportedly without clinical effect, although they were associated with reduced serum cholinesterase activity (259).

Eighteen different doses of demeton were evaluated in men who were given oral doses of demeton that began at 0.75 mg per day for 30 days (260). Doses of 4.5 to 6.375 mg/day (equivalent to about 0.06 to 0.09 mg/kg/day assuming a 70-kg body weight) produced average inhibition of plasma cholinesterase that was indistinguishable from normal variation. Doses of 6.75 mg/day (0.10 mg/kg/day) produced an average temporary inhibition of plasma cholinesterase, and a dose of 7.124 mg/day (0.10 mg/kg/day) produced an average of 40% inhibition by day 25. This dose was also associated with an average 16% inhibition of RBC cholinesterase inhibition. However, one of five test subjects had a marked decrease in plasma and RBC cholinesterase activities of 59% and 29%, respectively, after 24 days when given 4.125 mg/day (equivalent to 0.06 mg/kg/day). No clinical signs were observed or reported at any exposure level.

Three volunteers were exposed for two consecutive days to 9–27 mg/m^3 Metasystox (30% demeton-*S*-methyl, 70% demeton-*O*-methyl) while spraying with a hand-held nebulizer. Exposure lasted for 3 and 6 hours on the first and second days, respectively. Plasma and RBC cholinesterase activities measured up to 14 days after exposure did not show significant decreases (262).

5.5 Standards, Regulations, or Guidelines of Exposures

Demeton is not registered for use by the U.S. EPA. The ACGIH TLV for demeton is 0.11 mg/m^3 with a skin notation (154). The OSHA PEL-TWA is also 0.1 mg/m^3 with a skin notation. NIOSH established an IDLH of 10 mg/m^3 and REL-TWA of 0.1 mg/m^3 with a skin notation. Many other countries have also established Occupational Exposure Limits (OELs) of 0.1 mg/m^3 for demeton with a skin notation (Australia, Austria, Belgium, Denmark, Finland, France, Germany, India, The Netherlands, The Philippines, Switzerland, Thailand, and Turkey).

Organophosphorus Compounds
Jan E. Storm, Ph.D

6.0 Demeton-**S**-methyl

6.0.1 CAS Number:

[*919-86-8*]

6.0.2 Synonyms:

Ethanethiol, 2-(ethylthio)-*S*-ester with *O*,*O*-dimethyl phosphorothioate; BAY 18436; Bayer 25/154; phosphorothioic acid *S*-[2-(ethylthio)ethyl] *O*,*O*-dimethyl ester; Metasystox (I); metasytox thiol; *S*-(2-(ethylthio)ethyl) *O*,*O*-dimethyl phosphorothioate; Methyl-*S*-Demeton

6.0.3 Trade Names:

Demetox®; DEP 836 349; Duratox®; Isometasystox®; Isomethylsystox®; Metaisoseptox®; Metaisosytox; Metasystox (I)®

6.0.4 Molecular Weight:

230.3

6.0.5 Molecular Formula:

$C_6H_{15}O_3PS_2$

6.0.6 Molecular Structure:

6.1 Chemical and Physical Properties

Demeton-*S*-methyl is an oily, colorless to pale yellow liquid. It is hydrolyzed by alkali and oxidized to the sulfoxide (oxydemeton-methyl) and sulfone (demeton-*S*-methylsulfone).

Specific gravity	1.21 at 20°C
Boiling point	74°C at 0.15 mmHg; 92°C at 0.2 mmHg; 102°C at 0.40 mmHg; 118°C at 1 mmHg
Vapor pressure	1.6×10^{-4} mmHg at 10°C; 4.8×10^{-4} at 10°C; 1.45×10^{-3} at 30°C; 3.8×10^{-3} mm Hg at 40°C
Solubility	soluble in water (3.3 g/L); readily soluble in most organic solvents (e.g., dichloromethane, 2-propanol, toluene); limited solubility in petroleum solvents

6.1.2 Odor and Warning Properties Unpleasant odor.

6.2 Production and Use

Demeton-*S*-methyl was first marketed in 1957. It replaced technical grade methyl demeton which had been introduced in 1954 and was a 70:30 mixture of *O*,*O*-dimethyl-*O*-ethylthioethyl phosphorothioate (demeton-*O*-methyl or O-isomer) and *O*,*O*-dimethyl-*S*-ethylthioethyl phosphorothioate (Demeton-*S*-methyl or S-isomer). Demeton-*S*-methyl is a systemic and contact insecticide and acaricide used to control aphids, red spider mites, whiteflies, leafhoppers, and sawflies on garden crops, fruit, and hops (155). It is applied as an emulsifiable concentrate formulation, mainly as a spray, and usually at a concentration of 0.025% active ingredient.

6.4 Toxic Effects

6.4.1.1 Acute Toxicity Demeton-*S*-methyl is an organophosphate that has high oral toxicity with oral LD_{50}s of 33–130 mg/kg (262). The toxicity of demeton-*S*-methyl is markedly increased when it is allowed to age and forms sulphonium derivatives (263) Intravenous and oral LD_{50}s for the sulfoxide and sulfone derivatives of demeton-*S*-methyl were 22–47 mg/kg and 32–65 mg/kg, respectively (261). Intraperitoneal LD_{50}s of 7.5 and 10 mg/kg were also reported for demeton-*S*-methyl, suggesting that oral absorption may be slightly limited and/or that bypassing first-pass hepatic metabolism enhances toxicity (262). Dermal LD_{50}s from 45 to 200 mg/kg, depending on formulation and duration of exposure, were reported for rats, indicating that dermal exposures are about as potent as oral exposures on a milligram per kilogram basis (262). Dermal application of 10 mg/kg to the backs of cats caused mild signs (*sic*); application of 20 or 100 mg/kg caused death (no other details provided) (IPSC 1997). Four hour LC_{50}s for rats were 210–500 mg/m^3 (545).

Demeton-*S*-methyl applied to the shaved skin of rabbits for four hours caused mild erythema and edema that disappeared after three days (262). No signs of eye irritation occurred in rabbits whose eyes were treated with a 0.5% aqueous solution of demeton-*S*-methyl, but an undiluted formulation caused severe lacrimation and miosis. Mild corneal opacity and discrete redness and edema of conjunctivae were observed that disappeared within about 7 days (262).

Demeton-*S*-methyl had skin sensitizing potential when assessed using the guinea pig mazimization test but did not have skin sensitizing potential when assessed using the Buehler epidermal patch test on guinea pigs (262).

6.4.1.2 Chronic and Subchronic Toxicity When groups of six rats were fed diets that contained 50, 100, or 200 ppm (aged) demeton-*S*-methyl (5, 10, and 20 mg/kg/day, respectively) for six months, cholinergic signs (slight tremors, fasciculations) occurred at 200 ppm during the first 5 weeks (263). Decreased body weight gain in the 10- and 20-mg/kg/day rats and decreased brain and RBC cholinesterase activities occurred at 5 ppm and higher.

6.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Demeton-*S*-methyl is completely absorbed and very rapidly eliminated following either oral or intravenous administration. Blood concentration decreased, and the half-life was about 2 hours during the first 6 hours and then about 6 hours for the next 48 hours following oral administration of demeton-*S*-methyl to rats. The half-life thereafter was even longer. The half-life of urinary elimination was 2–3 hours during the first 24 hours and 1.5 days thereafter. Elimination through feces and exhaled air was minimal and accounted for 0.5–2% and about 0.2% of the dose, respectively. Except for RBCs which tended to bind the demeton-*S*-methyl, it was distributed uniformly in various body tissues and organs. At 2, 24, and 48 hours after dosing, about 60%, 1%, and 0.5% of the administered dose, respectively, remained in the body. By 10 days, demeton-*S*-methyl was almost undetectable in most organs except in the RBCs (262).

The main metabolic route of demeton-*S*-methyl is oxidation of the side chain leading to the formation of the corresponding sulfoxide, oxydemeton methyl, and to lesser extent, after further oxidation, the sulfone (262). O-demethylation also occurs. Neither glucuronide nor sulfate conjugates have been identified (262).

6.4.1.4 Reproductive and Developmental Pup viability, lactation index, and body weight gain were reduced in F1 offspring when rats were fed a diet that contained 25 ppm demeton-*S*-methyl for two generations (202). Offspring of rats fed 1 or 5 ppm were unaffected. No compound-related malformation was found in animals of any of the treatment groups.

No alterations of physical appearance or behavior occurred in dams or fetuses from dams given 0, 0.3, 1, or 3 mg/kg demeton-*S*-methyl by gavage on days 6 to 15 of gestation (262). The numbers of live fetuses and resorptions, fetal weight, number of fetuses with malformations, and number of implants were comparable in all groups. No treatment-related visceral or skeletal abnormalities were observed (262). No abortions or increases in the numbers of implantations per day, preimplantation losses, postimplantation losses, resorptions, living and dead fetuses, or sex ratios occurred in rabbits given 3, 6, and 12 mg/kg/day demeton-*S*-methyl by gavage on gestation days 6 to 18. Diarrhea, decreased food consumption, and decreased fetal body weight occurred in the 12 mg/kg/day treated animals. There was no treatment-related increase in gross, skeletal, or visceral malformations (262).

6.4.1.5 Carcinogenesis When dogs were fed diets containing 1, 10, or 100 ppm (day 1–36) followed by 50 ppm (day 37-termination) demeton-*S*-methyl (equivalent to 0.036, 0.36, and 4.6 followed by 1.5 mg/kg/day), diarrhea and vomiting occurred at all levels (262). Multifocal slight/moderate atrophy and/or hypertrophy of proximal renal tubules also occurred in the high dose group. Plasma and RBC cholinesterase activity was reduced at 10 and 100 ppm, and, brain cholinesterase activity was reduced at 10 ppm.

There was no evidence of carcinogenicity in mice given diets with 1, 15, or 75 ppm demeton-*S*-methyl (0.24, 3.47, or 17.81 mg/kg/day (males); 0.29, 4.18, or 20.0 mg/kg/day (females)) for two years (271). Cholinergic signs were not observed at any level nor did mortality differ among groups. Plasma, RBC, and brain cholinesterase activity decreased in mice at 15 and 75 ppm. There was no evidence of carcinogenicity in rats given 1, 7, or 50 ppm demeton-*S*-methyl in their feed (0.05, 0.31, or 2.59 mg/kg/day (males); 0.06, 0.41, or 3.09 mg/kg/day (females)) for 24 months (262). Hair loss and diarrhea occurred more frequently at 50 ppm. Body weight was reduced in males at 7 ppm and in both males and females at 50 ppm. Plasma, RBC, and brain cholinesterase activites decreased in groups given the 7- or 50-ppm diet. Increased incidence of retinal atrophy and keratitis was observed in mice given the 50-ppm diet.

6.4.1.6 Genetic and Related Cellular Effects Studies Available information is insufficient to permit an adequate assessment of the genotoxic potential of demeton-*S*-methyl (262). Demeton-*S*-methyl did not induce DNA damage in the Pol test in *E. coli* with or without metabolic activation, but it did increase mutation rates in the Ames test and in the mouse lymphoma forward mutation assay with or without metabolic activation. In *in vivo* tests, no sister chromatid exchanges (SCEs) were found in the bone marrow of Chinese hamsters treated with high doses of demeton-*S*-methyl, and, bone marrow micronucleus and dominant lethal tests in mice treated with demeton-*S*-methyl gave negative results. However, chromosomal aberrations were found in the bone marrow of Syrian hamsters treated with a commercial formulation of demeton-*S*-methyl (262).

6.3.5 Biomonitoring/Biomarkers Urinary levels of the metabolite dimethyl phosphorothiolated potassium salt (DMPThK) and plasma and whole blood cholinesterase activities were monitored in agricultural workers exposed to demeton-*S*-methyl for 3 consecutive days (262). Exposed subjects were identified as either mixers, sprayers, or others not directly involved in handling the pesticide. Levels of DMPThK in urine from mixers had a medium (*sic*) value of 83 mg/liter and a range of 0–822 mg/liter (neither corrected for creatinine nor for urine volume); urine from sprayers had a mean value of 30 mg/liter (limit of detection) and a range of 0–208 mg/liter, and urine from other subjects not directly exposed had a mean value of 30 mg/liter and a range of 0–100 mg/liter. Whole blood cholinesterase activity was not affected by exposure, and plasma cholinesterase activity was slightly reduced compared to preexposure levels in mixers. No correlation was found between DMPThK levels and plasma cholinesterase activity (269).

6.4.2 Human Experience 6.4.2.2 Clinical Cases Six hundred seventy-three occupational cases of organophosphate poisoning, including three deaths, reportedly occurred in Egypt about 1 week after demeton-*S*-methyl began to be used for spraying cotton (265). Two children evidently accidentally exposed to demeton-*S*-methyl via inhalation while waiting for their father (a sprayman) to finish work, became unconscious for a few minutes. When aroused, they vomited and complained of abdominal colic. Another girl who evidently ate beans contaminated during spraying also vomited and suffered abdominal colic.

One woman attempted suicide by ingesting "1 or 2 mouthfuls" of Metasystox I (25% demeton-*S*-methyl). On admission to hospital she was comatose, sweating, salivating and had pinpoint pupils. Plasma and RBC cholinesterase activites were less than 10% of normal. She was successfully treated and released after 30 days at which time plasma cholinesterase values had returned to normal, but RBC cholinesterase activity was still below normal (262). In another suicide attempt, a 41-year-old pregnant woman was admitted to a hospital about 3.5 hrs after ingesting an estimated 12 g of methyl demeton. Upon admission, blood (*sic*) cholinesterase was 10% of normal. About 12 hours after admission, she became comatose and was treated with atropine, odoxime, haemoperfusion, and artificial ventilation. She recovered and was discharged 24 days later (262).

A man who had been an agricultural applicator for five years worked with demeton-*S*-methyl, mainly as a flagman in aerial spraying but also in preparing the spray and in cleaning containers after spraying. For about a month and half, he was potentially exposed for periods that varied from 20 minutes to 6¾ hours. Symptoms (headaches, nausea, dizziness) gradually increased in severity during the week and subsided during the weekend. Later, he developed anorexia and loss of ability to concentrate. At the end of 6 weeks, his symptoms became worse while he was driving a tractor applying disulfoton. After 2 hours, he became dissatisfied with his control of the machine and sought medical aid. Clinical findings were normal, but cholinesterase activity was low (266). The author concluded that the man had suffered from gradually worsening organophosphate poisoning primarily due to absorption of demeton-*S*-methyl through the skin (despite the use of required protective clothing) that began about 2–3 weeks after initial exposure.

Organophosphate poisoning following demeton-*S*-methyl exposure was described in six men engaged in packaging bulk loads of demeton-*S*-methyl concentrate (500 g/L) into one liter containers (267). The first poisoned worker experienced cholinergic symptoms (nausea, dizziness, weakness, difficult breathing, and diarrhea) after working 1 day filling containers; the second experienced symptoms (giddiness, nausea, weakness, sweating, and cramps) after 72 hours. The filling procedure was modified to decrease worker exposure by requiring more protective clothing and performing operations in a fume "cupboard," but a third worker experienced symptoms (nausea, abdominal cramps, and weakness) after working 2 days using the revised procedure. Plasma and RBC cholinesterase activities measured 15–30 days after exposure were below the lower limit of the normal range and did not completely recover to the normal range until 60 days after exposure. Chemical analysis of vapor in the fume hood and of residue on gloves and other clothing indicated that exposure had occurred primarily via dermal absorption that resulted from contamination of external and internal surfaces of gloves.

Six workers engaged in hop cultivation using Metasystox I (reported to contain demeton-*O*-methyl instead of demeton-*S*-methyl as the commercial name implies) were monitored. They sprayed up to 2400 liters of a 0.1% solution (in water) of the insecticide in 1 day. No significant inhibition of blood acetylcholinesterase was observed at the end of exposure or 1 or 2 days later. One subject, who was exposed twice, showed a 29% decrease in blood (sic) acetylcholinesterase after the second exposure. No cholinergic toxicity was observed in these workers (262).

In a group of men who sprayed cotton fields with demeton-*S*-methyl, signs and symptoms of cholinergic toxicity (gastrointestinal disturbances, dizziness, persistent general weakness and fatigue, respiratory manifestations, headache, sweating, salivation or lacrimation, tremors of outstretched

hands, intention tremors, ataxia, exaggerated superficial and deep reflexes, hiccough, and muscular fasciculations) occurred after 1–18 days of exposure, and the mean latency period was 3 days (265). Serum cholinesterase activity estimates were performed within 24 hours after the onset of symptoms in some patients and after the cessation of symptoms in some others. In most cases, they were repeated two to three times at various intervals up to 40 days from the onset of symptoms. In general, serum cholinesterase activity underwent a marked initial fall followed by a rise above normal levels after about 30–40 days (265).

6.5 Standards, Regulations, or Guidelines of Exposure

Demeton-*S*-methyl is not registered by the EPA for use. It is anticipated that most other national registrations for demeton-*S*-methyl were probably transferred soon after 1998 to oxydemeton-methyl (262). No Occupational Exposure Limits were identified for demeton-*S*-methyl. In the 2000 ACGIH TLVs, in the notice of intended changes, ACGIH proposes a TLV of 0.05 mg/m^3, for demeton-*S*-methyl.

Organophosphorus Compounds
Jan E. Storm, Ph.D

7.0 Diazinon

7.0.1 CAS Number:

[*333-41-5*]

7.0.2 Synonyms:

O,*O*-diethyl *O*-2-diethyl *O*-2-isopropyl-4-methyl-6-pyrimidinyl thiophosphate; phosphorothioic acid, *O*,*O*-diethyl-*O*-(2-isopropyl-6-methyl-4-pyrimidinyl)ester; Dimpylate; *O*,*O*-diethyl *O*-(2-isopropyl-6-methyl-4-pyrimidinyl), phosphorothioate; *O*,*O*-diethyl *O*-(6-methyl-2-(1-methylethyl)-4-pyrimidinyl) phosophorothioatae; phosphorothioic acid *O*,*O*-diethyl *O*-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl] ester; thiophosphoric acid 2-isopropyl-4-methyl-6-pyrimidyl diethyl ester; *O*,*O*-diethyl *O*-2-isopropyl-4-methyl-6-pyrimidyl thiophosphate; Knox Out; dianon; gardentox; kayazinon; g-24480; diethyl 2-isopropyl-6-methyl-4-pyrimidinyl phosphorothionate; *O*,*O*-diethyl *O*-(6-methyl-2-(1-methylethyl)-4-pyrimidinyl) phosphorothioate; Dipofene; Diazitol; AG-500; Antigal; Dacutox; Dassitox; Dazzel; Diagran; Diaterr-fos; Diazajet; Diazide; Diazol; diethyl 2-isopropyl-4-methyl-6-pyrimidinyl phosphorothionate; diethyl 2-isopropyl-4-methyl-6-pyrimidyl thionophosphate; diethyl *O*-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate; Dimpylatum; Drawizon; Dyzol; Exodin; Fezudin; Flytrol; Galesan; isopropylmethylpyrimidyl diethyl thiophosphate; Kayazol; Knox out 2FM; Neocidol; Nipsan; Nucidol; Sarolex; Dizinon; *O*,*O*-diethyl *O*-(2-isopropyl-4-methyl-6-pyrimidinyl) thiophosphoric acid

7.0.3 Trade Names:

Spectracide®, Basudin®, Diazitol®, Dipofene®, Neocidol®, Nucidol®

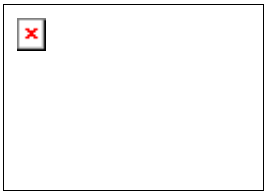
7.0.4 Molecular Weight:

304.36

7.0.5 Molecular Formula:

$C_{12}H_{21}N_2O_3PS$

7.0.6 Molecular Structure:



7.1 Chemical and Physical Properties

Diazinon is a colorless liquid.	
Specific gravity	1.116–1.118 at 20°C
Boling point	83–84°C at 0.002 torr
Melting point	>120°C (dec)
Vapor pressure	1.4×10^{-4} mmHg at 20°C
Solubility	slightly soluble in water (0.004 g/100 mL); freely soluble in petroleum solvents; miscible with alcohol, ether, benzene, and similar hydrocarbons

7.1.2 Odor and Warning Properties Faint ester-like odor.
7.2 Production and Use
Diazinon is a nonsystemic insecticide used on a wide variety of agricultural crops such as rice, fruit trees, corn, tobacco, and potatoes and to control fleas and ticks. Various types of formulations are available, including dusts, emulsifiable concentrates, impregnated material, granules, microencapsulated forms, pressurized sprays, soluble concentrates, and wettable powders (55).
7.4 Toxic Effects
7.4.1.1 Acute Toxicity Diazinon is a moderately toxic organophosphate compound that has oral LD_{50}s of 250–466 mg/kg (64a). Oral LD_{50}s for an impure formulation were 76–108 mg/kg (Gaines, 1960). The dose–lethality curve is steep as illustrated by the observation that acute LD_{01}s are only 30–36% smaller than LD_{50}s (64a) and that an acute oral dose of 528 mg/kg was lethal to rats whereas a dose of 264 mg/kg was not (55). Dermal LD_{50}s were 455–900 mg/kg (64a, 268). The dermal LD_{50} for male rats of a sample allowed to completely crystallize in air for several weeks was 34 mg/kg, demonstrating that acute dermal toxicity increases significantly with an impure diazinon formulation (268). Onset of symptoms and death following acute exposures to diazinon occurs between 1 and 6 hours from oral exposures (81, 271) but may be delayed following dermal exposure by about 10 hours (272).

A 4-hour LC_{50} of 3500 mg/m^3 was reported for rats; a 4-h LC_{50} of 1600 mg/m^3 was reported for mice, and a 4-hour LC_{50} of 55,500 mg/m^3 was reported for guinea pigs (545). No deaths occurred among rats exposed to 2330 mg/m^3 diazinon for 4 hours in inhalation chambers and observed for 14 days, although decreased activity and increased salivation were noted (55).

No signs of organophosphate toxicity occurred in rats exposed to 0.05, 0.46, 1.57, or 11.6 mg/m^3 for 6 h/day, 5 days/week for three weeks (55). Serum cholinesterase activity decreased in females exposed to 0.46 mg/m^3 and higher and in males exposed to 1.57 mg/m^3 and higher; RBC acetylcholinesterase activity decreased in females exposed to 11.6 mg/m^3, and brain acetylcholinesterase activity decreased in females exposed to 1.57 and 11.6 mg/m^3.

Among male rats that were given single doses of 100, 200, or 400 mg/kg diazinon by gavage, cholinergic signs (lacrimation, salivation, miosis, hypoactivity, ataxia, increased landing foot splay, decreased tail-pinch response, tremors, chewing (smacking), and hypothermia) peaked at 4 hours in the 400-mg/kg group and were still present at 24 hours, but had disappeared by 72 hours after dosing (55). Cholinergic toxicity also occurred in the 200-mg/kg group, and only hypoactivity and decreased defecation occurred in the 100-mg/kg group. Among rats given single oral doses of 2, 132, 264, or 528 mg/kg diazinon, cholinergic signs (autonomic (smacking), neuromuscular (ataxia, abnormal gait)) occurred at 132 mg/kg and higher (55). Serum cholinesterase and RBC

acetylcholinesterase activity was reduced at all levels (55).

Diazinon was not neurotoxic in atropinized hens given 11.3 mg/kg twice orally, 21 days apart (55).

7.4.1.2 Chronic and Subchronic Toxicity No cholinergic toxicity occurred in rats fed diets that contained up to 1000 ppm technical diazinon for four weeks (82), in rats or mice fed diets that contained up to 1600 ppm for 13 weeks (87), in rats given diets that contained up to 25 ppm diazinon for up to 92 days (79, 80) or in rats fed diets, that contained up to 125 ppm diazinon for 15–16 weeks (81). Subchronic exposures in the 3- to 100-ppm range were associated with inhibition of RBC acetylcholinesterase activity, and exposures to 1000 ppm were associated with brain acetylcholinesterase inhibition (79–82). Six week exposures of rats to up to 180 mg/kg/day via their diet caused no cholinergic toxicity, although RBC acetylcholinesterase activity was inhibited at doses of 8 or 9 mg/kg/day (83). Thirteen-week exposures of rats to 168 or 212 mg/kg/day resulted in cholinergic signs (soft stools and hypersensitivity to touch and sound), although RBC acetylcholinesterase activity was inhibited at doses as low as 15 mg/kg/day (83).

No cholinergic toxicity occurred in dogs given diazinon via their diet (0.25, 0.75, or 75 ppm) for 12 weeks, although RBC acetylcholinesterase activity was inhibited for 6 weeks after termination of dosing to dogs given the 75-ppm diet (84). When dogs were given diets that contained 0.1, 0.5, 150, and 300 ppm diazinon for 13 weeks, cholinergic signs (emesis and diarrhea) occurred but were not dose-related (90). Significant reductions in RBC and brain acetylcholinesterase levels occurred in rats fed the 150-ppm diet.

7.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Absorption of diazinon following oral exposures is rapid and complete. Nearly 100% of orally administered diazinon was recovered in urine (70–80%) and feces (16–24%) within 168 hours in rats (98). Diazinon was not detected later than 2 days after a final repeated dose of diazinon, demonstrating that it does not accumulate in tissues (98). The biological half-life of diazinon was 12 hours. In dogs, absorption was at least 85% after a single oral dose (99). About 68% of an oral dose of diazinon was detected in urine 60 minutes after dosing in mice. In all cases, diazinon is widely distributed to tissues, especially adipose tissue, muscle, brain, and liver (101). Similar results were observed in dogs, guinea pigs, goats, sheep, and cows (55).

The pharmacokinetics of diazinon following inhalation exposure has not been studied. However, pharmacokinetic studies following intravenous administration of diazinon to dogs indicated rapid absorption and an elimination half-life of 6 hours (99). Recovery in urine was 58% of the administered dose after 24 hours and was primarily diethyl phosphoric and phosphorothioic acid. In rats given diazinon intravenously, plasma diazinon levels declined rapidly during the distribution phase and more slowly during the elimination phase and were characterized by an elimination half-life of about 6 hours (102). In another study that examined the toxicokinetics of diazinon in rats following oral and intravenous exposure, the elimination half-lives were 1.8 and 4.7 hours, respectively, suggesting that hepatic metabolism enhances elimination (102). In four rhesus monkeys dosed intravenously with 32 mg diazinon, about 56% was excreted in urine, and 23% was eliminated in feces after 7 days, accounting for about 70% of the total dose. Most of the dose was excreted in urine on day 1 (103).

Total dermal absorption of diazinon was estimated at about 3–4% of the dose applied to the forearm or abdomen (2 mg/cm^3) of humans during 7 days regardless of whether the vehicle was acetone or lanolin (103). Absorption measured in human skin placed in an *in vitro* diffusion cell was about 14%.

The metabolism of diazinon is complex. The primary pathways are desulfuration by cytochrome P450 enzymes to the metabolite diazoxon which then either binds to acetylcholinesterase and other esterases or is further metabolized to diethyl phosphoric acid and oxidative products such as 2-

isopropyl-4-methyl-6-hydropyrimidine (104, 105). Alternatively, diazinon is dearylated and hydrolyzed by cytochrome P450 enzymes to diethyl phosphorothioic and phosphoric acid and other oxidation products (e.g. 2-isopropyl-4-methyl-6-hydropyrimidine) which are excreted mostly in urine, although minor amounts of these metabolites and some unchanged diazinon have been detected in feces (98, 100, 104).

7.4.1.4 Reproductive and Developmental Diazinon did not cause adverse effects on fertility in rats fed 0.05 mg/kg/day diazinon in the diet for 60 days before weaning for four generations (89). No gross or histological treatment-related damage to reproductive tissues occurred in rats given up to 168 mg/kg/day (males) or 212 mg/kg/day (females) diazinon for 13 weeks (83), in rats given up to 10 mg/kg/day (males) or 12 mg/kg/day (females) for 98 weeks (86), or in dogs given up to 11 mg/kg/day for 13 weeks (90). In another study, testicular atrophy and arrested spermatogenesis were observed in one dog given 10 mg/kg/day and in all dogs given 20 mg/kg/day for 8 months via corn oil capsule (85).

No teratogenic or fetotoxic effects occurred in rabbits given 7–100 mg/kg/day diazinon by gavage during gestation (91, 92). Cholinergic signs occurred in dams given 30 mg/kg or more. In hamsters, no embryo- or teratogenicity occurred at doses up to 0.25 mg/kg/day during gestation, although cholinergic toxicity occurred in parents (diarrhea, salivation, and incoordination). In another study, however, diazinon caused an increased incidence of stillbirths in dogs given 1.2 or 5 mg/kg/day by gavage (85). In rats, doses greater than or equal to 70.6 mg/kg/day during gestation increased fetal resorptions when given on days 8 to 12 or 12 to 15; no effects occurred at doses less than 70.6 mg/kg/day (93). In another study, no differences were observed in litter size, fetal body weight, fetal brain weight, number of resorptions, or corpora lutea among rats given diazinon via peanut oil gavage at 0, 40, 50, 60, or 75 mg/kg/day on gestation days 7 through 19 (94).

Pregnant mice given 0, 0.18, or 9 mg/kg/day diazinon throughout gestation (18 days) gave birth to viable offspring, although pups exposed to 9 mg/kg grew more slowly than controls (590). Mature offspring of both treated groups displayed impaired endurance and coordination on rod cling and inclined place tests of neuromuscular function. Morphological abnormalities in brain occurred among offspring of dams exposed to 9.0 mg/kg/day.

7.4.1.5 Carcinogenesis No signs of cholinergic toxicity occurred in rats given diets containing 10 to 1000 ppm diazinon for 72 weeks or in dogs given up to 4.6 mg/kg/day diazinon via capsule 6 days/week for up to 46 weeks (82). Doses of 4.3 to 4.6 mg/kg/day, however, caused significant RBC cholinesterase inhibition in dogs after two week (82). Cholinergic signs (soft stools) occurred in dogs given 9.3 mg/kg by 30 days and excitability and tremors occurred in one dog given 25 mg/kg/day for 6 days. In dogs given 2.5, 5.0, 10.0, or 20.0 mg/kg/day diazinon by gavage for 8 months, cholinergic signs were observed in one dog given 10 mg/kg/day and emesis, fasciculation and mortality occurred in dogs given 20.0 mg/kg/day (85). No cholinergic toxicity occurred in pigs given 1.25 mg/kg/day for eight months; but cholinergic signs were observed pigs given 2.5–10 mg/kg/day (85).

No signs of cholinergic toxicity occurred in rats given diazinon via their diet at doses of 0.004, 0.06, 5, or 10 mg/kg/day (males) and 0.005, 0.07, 6, or 12 mg/kg/day (females) for 52 or 98 weeks (86). After 1 year, RBC acetylcholinesterase activity decreased in males given 5 and 10 mg/kg/day and in females given 6 or 12 mg/kg/day; brain acetylcholinesterase activity was unchanged in males but decreased in females given 6 or 12 mg/kg/day. During a 4-week recovery period, RBC acetylcholinesterase activity returned to normal in males, whereas that of females dosed at 12 mg/kg/day remained decreased; brain acetylcholinesterase activity returned to normal in females. Results were similar at 98 weeks.

Diazinon was not carcinogenic in rats or mice when they were given diets containing 400 or 800 ppm diazinon (rats) or 100 or 200 ppm diazinon (mice) for 2 years (87). However, clinical signs of hyperactivity were noted in low- (males) and high-dose (males and females) rats and in all dosed mice (*sic*). Bloating, vaginal bleeding, and vaginal discharge were also noted in the dosed female

rats.

No cholinergic, hematological, clinical chemistry, or histopathological signs occurred at any dose in monkeys given oral doses of 0, 0.05, 0.5, or 5 mg/kg diazinon 6 days/week for two years via gavage, although serum and RBC cholinesterase activities were inhibited in monkeys given 0.5 or 5 mg/kg/day (88).

7.4.1.6 Genetic and Related Cellular Effects Studies The genotoxicity of diazinon is equivocal. *In vitro* test results showed that diazinon was positive for gene mutations in the *S. typhimurium* test assay with metabolic activation and in the mouse lymphoma cell forward mutation assay without metabolic activation (55, 96). Diazinon was also positive for chromosomal aberrations in Chinese hamster cells with metabolic activation (55). But in other tests, diazinon was negative for gene mutations in the *S. typhimurium* test assay (97) and in the rec assay utilizing strains of *Bacillus subtilis* (55) both of which were conducted without metabolic activation. Tests for sister chromatid exchange in Chinese hamster V79 cells with and without metabolic activation (55) and for chromosomal aberrations in human peripheral blood lymphocytes (55) were also negative.

7.4.2 Human Experience 7.4.2.2 Clinical Cases Ingestion of diazinon causes typical organophosphate poisoning that varies in intensity with dose (107–109). Lethality followed adult ingestion of an estimated 293 mg/kg diazinon (110) and child ingestion of 20 mg/kg (111), although the latter estimate may have been complicated by the possible simultaneous ingestion of parathion and/or chlordane. A summary of 76 fatal cases of diazinon poisoning indicated a high incidence of miosis, froth from nose and mouth, acute pulmonary edema and congestion, acute ulcers, blood stained gastric contents, CNS hemorrhage, and evidence that death was due to asphyxiation (109). No estimates of exposure levels were provided.

Cholinergic symptoms (nausea, epigastric pain, headache, miosis and unreactive pupils, tachycardia) occurred in a woman who ingested an estimated 1.5 mg/kg diazinon (112). Severe toxicity (bradycardia, tachycardia, clonus, stupor, profuse diaphoresis, sialorrhea, miosis, hyperreflexia, weakness, dysdiadokinesis, abdominal pain, nausea, coma, twitching, restlessness, and bronchospasm) was reported in five individuals who intentionally ingested estimated doses of 240 to 986 mg/kg diazinon and recovered (113). Signs of organophosphate poisoning (profuse sweating, nausea, vomiting, and abdominal cramps) were reported in children who had eaten oatmeal contaminated with about 2.5–244 ppm diazinon (114). An earlier report indicated that oatmeal contaminated by home spraying with a 25% concentrate of diazinon caused organophosphate poisoning (nausea, vomiting, abdominal cramps, diaphoresis, muscular weakness, rolling eye movements, ataxia, and muscle cramps) in eight children from two different families (115).

A man died from cardiac arrest, despite atropine therapy, following inhalation exposure to a commercial insecticide formulation containing diazinon and malathion, but no estimate of exposure was provided (115a). Inhalation exposures to a diazinon spray used to kill cockroaches in an adjoining apartment were implicated in the organophosphate poisoning of twin infants (116).

Depressed serum cholinesterase activities were only sometimes accompanied by signs of cholinergic toxicity in individuals occupationally exposed to diazinon primarily via inhalation (117). However, cholinergic symptoms (headache, blurred vision, dizziness, fatigue, nausea, and vomiting) began within 15 minutes in mushroom workers exposed to diazinon when it was sprayed around the only entrance to a room in which they were working. Reduced serum and RBC cholinesterase activities also occurred within 48 hours, and serum cholinesterase activities remained depressed for 15 days (118). Based on comparison with stabilized cholinesterase measurements taken in affected individuals 15 days after exposure, the authors estimated that plasma cholinesterase activities had been inhibited by about 30–34% and RBC acetylcholinesterase activities had been inhibited by about 27–34%.

In another report that involved multiple routes of exposure, several family members experienced

diazinon poisoning (headache, vomiting, fatigue, and chest heaviness) associated with slightly depressed serum cholinesterase activities for several months after their home had been treated with diazinon (118a). Surface concentrations in the home ranged from 126 to 1051 mg/m^2, air concentrations were between 5 and 27 mg/m^3, and some clothing showed contamination (0.5 to 07 mg/g).

Dermal exposure to diazinon caused cholinergic signs (cyanosis, forthing at the mouth, drowsiness, nausea, vomiting, abdominal colic, diarrhea, tachpnea, miosis, and sinus tachycardia) in two female gardeners (119), but estimates of exposure were not available.

Exposure to diazinon via multiple routes was estimated at an average of 0.02 mg/kg/day in 99 workers exposed to diazinon granules 8 h/day for 39 days during an insecticide application program. Slight neurological functional deficits (postshift symbol-digit speed and pattern memory accuracy) were reported among the workers, but these effects were not statistically significant (120).
7.5 Standards, Regulations, or Guidelines of Exposure
Diazinon is under reregistration by the EPA (78).

The ACGIH TLV for diazinon is 0.1 mg/m^3 with a skin notation (154). The OSHA PEL-TWA and NIOSH REL-TWA are 0.1 mgm^3 with a skin notation. Most other countries have also established an Occupational Exposure Limit of 0.1 mg/m^3 for diazinon (Australia, Belgium, Denmark, Finland, France, Germany, India, The Netherlands, and the United Kingdom).

Organophosphorus Compounds
Jan E. Storm, Ph.D

8.0 Dichlorvos
8.0.1 CAS Number:
[*62-73-7*]
8.0.2 Synonyms:
O,*O*-dimethyl-*O*-2,2-dichlorvinyl dimethyl phosphate; 2,2-dichlorovinyl dimethylphosphate; DDVP; dichlorophos; Equigand; No-Pest Strip; 2,2-dichlorovinyl-*O*,*O*-dimethyl phosphate; phosphoric acid 2,2-dichloroethenyl dimethyl ester; phosphoric acid 2,2-dichlorovinyl dimethyl ester; SD 1750; Astrobot; Atgard; Canogard; Dedevap; Dichlorman; Divipan; Equigard; Equigel; Estrosol; Herkol; Nogos; Nuvan; 2,2-dichloroethenyl dimethyl phosphate; 2,2-dichlorovinyl dimethyl phosphoric acid ester; 2,2-dichloroethenyl phosphoric acid dimethyl ester; dimethyl 2,2-dichloroethenyl phosphate; dimethyl 2,2-dichlorovinyl phosphate; *O*,*O*-dimethyl dichlorovinyl phosphate; *O*,*O*-dimethyl *O*-2,2-dichlorovinyl phosphate; 2,2-dichlorovinyl alcohol dimethyl phosphate; apavap; atgard c; atgard v; bay-19149; benfos; bibesol; brevinyl; brevinyl e50; chlorvinphos; deriban; derribante; devikol; duo-kill;duravos; estrosesel; fecama; fly-die; fly fighter; herkal; krecalvin; MAFU; mafu strip; marvex; mopari; nerkol; nogos 50; nogos g; no-pest; NUVA; nuvan 100ec; OKO; OMS 14; phosvit; szklarniak; TASK; Tenac; task tabs; tetravos; UDVF; unifos; unifos 50 ec; vaponite; vapora ii; verdican; verdipor; vinylofos; vinylophos; bayer 19149; *O*,*O*-dimethyl 2,2-dichlorovinyl phosphate; fekama; insectigas d; nefrafos; nogos 50 ec; novotox; nuvan 7; panaplate; winylophos; 2,2-dichloroethenol dimethyl phosphate; Cekusan; Cypona; Delevap; Derriban; Dichloroethenyl dimethyl phosphate; Equiguard; Prentox; Verdisol; DichlorvosI [Dimethyl Dichlorovinyl Phosphate]
8.0.3 Trade Names:
Vapona®
8.0.4 Molecular Weight:
220.98
8.0.5 Molecular Formula:

$C_4H_7Cl_2O_4P$

8.0.6 Molecular Structure:

8.1 Chemical and Physical Properties

Dichlorvos is a colorless to amber, oily liquid. It hydrolyzes at a rate of 3% per day in saturated aqueous solution at room temperature; at high pH or in boiling water, it completely hydrolyzes in 1 hour. Dichlorvos decomposes to toxic gases and vapors (such as hydrogen chloride gas, phosphoric acid mist, and carbon monoxide)

Specific gravity	1.415 g/ml at 25°C
Boiling point	140°C at 20 mmHg; 221°C at 760 mmHg
Melting point	–60°C
Vapor pressure	0.012 torr at 20°C
Solubility	slightly soluble in water (1 g/100 mL at 20°C); miscible with aromatic and chlorinated hydrocarbon solvents and alcohols

8.1.2 Odor and Warning Properties Mild chemical odor.

8.2 Production and Use

Dichlorvos is used against a wide variety of insects in greenhouses, outdoor fruit and vegetable crops, and is also used in aquaculture to rid fish of various skin parasites. In addition, it is used to control severe internal and external parasite infestations in animals and humans (57). It is a available as soluble concentrates and aerosols and is also formulated with other pesticides.

8.4 Toxic Effects

8.4.1.1 Acute Toxicity Dichlorvos is an organophospahte that has high oral toxicity, oral LD_{50}s of 56–98 mg/kg in rats, and oral LD_{50}s 133–139 mg/kg in mice (57). Dose–lethality curves are steep; oral LD_{01}s are about one-half or less the LD_{50} value (62, 64a), and death occurs quickly within minutes. Cholinergic signs occurred within 7–15 minutes in dogs given a single oral dose of 11 or 22 mg/kg dichlorvos (62a). Three of 12 dogs given 22 mg/kg died within 10–155 minutes of treatment. Similar effects occurred when dogs were given 2–11 mg/kg dichlorvos intravenously, but death occurred slightly more rapidly, by 7 minutes in one case. When rats were given single oral doses of 0.5, 35, or 70 mg/kg dichlorvos by gavage, the 35- and 70-mg/kg groups exhibited cholinergic signs within 15 minutes after dosing (120a). Several animals in the 70-mg/kg group died. No signs of toxicity were apparent in any rats given 0.5 mg/kg or in any of the 35- or 70-mg/kg treated rats that survived 7 days after dosing (120a). Severe cholinergic signs occurred in dogs given 15–30 mg/kg/day for 12–24 days via corn oil capsule, and less severe cholinergic signs occurred in dogs given 1–10 mg/kg/day for 16–24 days (95). Doses of 0.1 mg/kg/day for up to 24 days had no effect.

Dermal LD_{50}s are 75–107 mg/kg in rats (64a). Cholinergic signs and death occurred in monkeys after a single 100 mg/kg dermal dose, after eight 50-mg/kg/day doses during 10 days, and after ten 75-mg/kg doses during 12 days, suggesting that dermal exposures may be cumulative (121).

Inhalation exposures are more potent on the basis of body weight than oral exposures (122). Four and one-hour LC_{50}s for dichlorvos in rats are 455 and 340 mg/m^3 (123). A saturated atmosphere of

dichlorvos (230–341 mg/m^3) caused deaths among rats after 7 to 62 hours (121). Rabbits are more sensitive than rats or mice to dichlorvos vapor. Deaths occurred in 9 of 16 rabbits exposed to 6.25 mg/m^3 and in 6 of 20 rabbits exposed to 4 mg/m^3 for 23 h/day for 28 days during gestation (37), whereas no deaths occurred in mice or rats exposed to the same concentrations. Even exposures up to 56 mg/m^3 for 14 days did not cause deaths in rats (124). No deaths occurred in mice exposed to 30–55 mg/m^3 for 16 hours (125) or in pregnant mice or rabbits exposed to 4 mg/m^3 for 7 h/day (126). No adverse effects occurred in rhesus monkeys exposed to 0.48, 2.3, 2.6, or 12.9 mg/m^3 for 2 h/day for 4 days, although RBC cholinesterase was inhibited in monkeys exposed to 12.9 mg/m^3 (127).

Delayed neuropathy occurred in chickens after 35 days treatment with 6.1 mg/kg/day dichlorvos; 3.1- and 4.4-mg/kg/day doses were ineffective (128). Two doses of 16.5 mg/kg dichlorvos 21 days apart to hens did not cause acute delayed neurotoxicity, although signs of cholinesterase inhibition were apparent shortly after dosing (120a).

In a guinea pig mazimization test, induction with dichlorvos by intradermal injection and topical application and subsequent challenge with topical dichlorvos solutions showed sensitization (129).

8.4.1.2 Chronic and Subchronic Toxicity A 90-day LD_{50} > 70 mg/kg was determined in rats fed dichlorvos in their diet for 90 days (196). Because this value was more than the single dose LD_{50} of 56 mg/kg, it was concluded that dichlorvos does not have a cumulative effect. When rats were given feed that delivered 0–360 mg/kg/day for 6 weeks, all rats that consumed 180 mg/kg or more died whereas none that consumed 90 mg/kg/day or less died (130). When mice were given feed that delivered 0–1080 mg/kg/day for six weeks, four of five females given 720 mg/kg/day died; all mice given 1080 mg/kg/day died (130).

Cholinergic signs occurred in dogs given 0.625 or 1.25 mg/kg/day dichlorvos by capsule for 70–90 days (65). RBC and brain cholinesterase activities were inhibited in dogs given 0.625 mg/kg/day. Ninety-day studies of dichlorvos in rats have shown that dietary levels up to 1000 ppm (about 70 mg/kg/day) do not result in overt cholinergic toxicity, although exposures to levels of 200 ppm or greater inhibit RBC cholinesterase (56, 57). Oral gavage studies show lower effect levels. Daily administration of 7.5 mg/kg/day or more to rats via gavage for 13 weeks is associated with cholinergic toxicity (131) as well as significant RBC and brain acetylcholinesterase inhibition. Daily administration of 160 mg/kg/day by gavage for 13 weeks caused death in mice (131) as well as significant RBC and brain acetylcholinesterase inhibition. Gavage doses up to 40 mg/kg/day had no effect.

8.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms At least 85% of an oral dose of dichlorvos is absorbed (145). Dichlorvos is well absorbed following inhalation exposure based on the occurrence of toxic symptoms associated with inhalation exposures and the detection of specific dichlorvos metabolites (dichloroethanol and dimethyl phosphate) in urine of individuals exposed to dichlorvos (137, 138). Excretion is very rapid based on the observation that dichlorvos could not be detected in the blood of two male volunteers immediately after exposure to dichlorvos vapor (145). An elimination half-life of 13.5 minutes was estimated based on dichlorvos concentration in rat kidney after 2 or 4 hours exposure to 5 mg/m^3 (145). In mice and rats given single oral doses of dichlorvos, 59–65% was eliminated in urine, 3–7% was eliminated in feces, 14–18% was eliminated as CO_2 by 4 days after dosing, and the vast majority was eliminated by 24 hours (138). Retained dichlorvos following either oral or inhalation exposures is high because it is incorporated into intermediary metabolism (139).

Dichlorvos binds to acetylcholinesterase forming dimethoxy-phosphorylated acetycholinesterase and dichloroacetaldehyde (140). Alternatively, it is metabolized (primarily in the liver but also in the

blood, adrenal, kidney, lung, and spleen) via two pathways (141). The major pathway is catalyzed by A-esterases and produces dimethyl phosphate and dichloroacetaldehyde (140). Dichloroacetaldehyde is converted to dichloroethanol which is then excreted as the glucuronide. Alternatively, dichloroacetaldehyde is dehalogenated and the carbon atoms are incorporated into normal tissue constituents via intermediary metabolism (137, 138, 141). The second minor pathway is catalyzed by glutahione-*S*-transferase and produced desmethyl dichlorvos and *S*-methyl glutathione. Subsequent degradation of desmethyl dichlorvos to dichloroacetaldehyde and monomethyl phosphate is catalyzed by A-esterases. *S*-methyl glutathione is broken down to methylmercapturic acid and excreted in urine. CO_2 is also the major metabolite following inhalation exposures. The major urinary metabolite following either oral or inhalation exposures is dichloroethanol glucuronide.

Dichlorvos is rapidly metabolized in human blood by A-esterases (142, 143). Unlike paraoxonse which exhibits polymorphism in the human population (144), dichlorvos A-esterase appears to be normally distributed. Half-lives for degradation of dichlorvos in whole blood after inhalation were 8.1 minutes for men and 11.2 minutes for women (145).

8.4.1.4 Reproductive and Developmental Several studies indicated that dichlorvos is not a reproductive or developmental toxin. No impairment of male fertility occurred in mice exposed to 30 or 55 mg/m^{3}dichlorvos for 16 hours or to 2.1 or 5.8 mg/m^3 for 23 hours daily for 4 weeks (37). However, estrus was delayed 10 days in female rats that were continuously exposed from birth to 2.4 mg/m^3 dichlorvos vapors from a Shell “No-pest Strip” (132). Number, viability, and growth rate were normal in offspring of swine fed up to 37 months on diets containing 200–500 ppm dichlorvos (133). No maternal or reproductive toxicity occurred in rats given dichlorvos for three generations at a dietary level of 0.1–500 ppm (about 0.005–25 mg/kg/day) (95).

No adverse effect on fetuses occurred when pregnant rats were given injections of 15 mg/kg dichlorvos on gestation day 11 (379), 0.1–21 mg/kg/day dichlorvos on gestation days 6 through 15 (95), or were exposed to 0.25–6.25 mg/m^3 dichlorvos vapor for 23 h/day on gestation day 1 through 20 (37). No adverse effect on fetuses occurred when pregnant mice were given the maximal tolerated dose of dichlorvos (60 mg/kg) on gestation days 6 through 15 or were exposed to 4 mg/m^3 dichlorvos vapor for 7 h/day (126). No adverse effect occurred on fetuses when pregnant rabbits were administered doses of 0.1 to 7.0 mg/kg/day dichlorvos by gavage on gestation days 7 through 19 (120a) or when rabbits were exposed for 23 h/day to 0.25 to 6.25 mg/m^3 dichlorvos vapor on gestation days 1 through 28 (37).

8.4.1.5 Carcinogenesis Dichlorvos was not carcinogenic when rats were exposed to 0.05, 0.48, or 4.70 mg/m^3 dichlorvos for 23 h/day, 7 days/week for up to two years (136). Nor were any cholinergic signs observed in any group. The EPA's Carcinogenicity Peer Review Committee (CPRC) considered this study sufficient evidence that dichlorvos does not cause cancer via inhalation (68).

Carcinogenicity was not observed in rats given diets of 0, 150, or 326 ppm dichlorvos (equivalent to doses of about 8–14 and 16–29 mg/kg/day) for 80 weeks and then observed for an additional 30 weeks (130). The results of this study, however, were questioned because of an extraordinarily high mortality rate in control rats. Therefore, the chronic toxicity and carcinogenicity of dichlorvos was reevaluated in rats dosed with dichlorvos by gavage at levels of 0, 4, or 8 mg/kg/day dichlorvos for 5 days/week for 103 weeks (131). Cholinergic signs of toxicity occurred and RBC acetylcholinesterase activity decreased in both groups. Significant increase in mammary gland neoplasms in females and a significant trend (not dose related) for mononuclear cell leukemia was observed in males. Peer review panels characterized these results as “some evidence” of carcinogenic activity in males and equivocal evidence” in females (131). EPA's CPRC concluded that increased incidence of leukemia in rats may not be biologically significant (68, 120a).

Carcinogenicity was not observed in mice given diets that delivered 57 or 114 mg/kg/day dichlorvos for 80 weeks (130). However, a positive trend for squamous cell papilloma and carcinomas of the forestomach was observed in mice given 10–40 mg/kg/day dichlorvos by gavage for 5 days/week for 102 weeks (131). Significantly decreased RBC acetylcholinesterase activity was also observed at all levels. Peer review panels characterized these results as "some evidence" of carcinogenicity in male mice and "clear evidence" in female mice (131). However, the relevance of forestomach tumors to humans is questionable. Carcinogenicity was not reported in male or female mice given 58 or 95 mg/kg/day or 56 or 102 mg/kg/day, respectively, in their drinking water for 2 years (95). However, there was a dose-related decrease in absolute and relative weight of the gonads of males, and testicular atrophy increased in males given the high dose (95 mg/kg/day). The absolute and/or relative weight of the pancreas also decreased in treated females.

When dogs were given dichlorvos by capsule for 52 weeks at doses of 0, 0.1, 1.0, or 3.0 mg/kg/day, one male in the 3.0 mg/kg/day group exhibited cholinergic toxicity only at week 33 (57). RBC cholinesterase was inhibited at doses of 0.1 mg/kg/day and higher, and brain cholinesterase was inhibited in the 1.0-mg/kg/day (males only) and 3.0-mg/kg/day groups.

8.4.1.6 Genetic and Related Cellular Effect Studies Dichlorvos is not genotoxic when tested in *in vivo* system but is generally genotoxic or mutagenic in *in vitro* test when metabolizing enzymes are not present (57). Dichlorvos increased the frequency of chromosomal damage and micronucleus formation in Chinese hamster ovary cells; induced sister chromatid exchange, chromosomal aberrations, and transformation in cultured rat tracheal epithelial cells; induced DNA single-strand breaks in isolated rat hepatocytes; and caused increases in cell transformation of hamster embryo cells (134).

Dichlorvos was negative in the sex-linked lethal mutation test in *Drosophila*. However, increased mutations and chromosomal abnormalities occurred in flies given dichlorvos-contaminated food. Dominant lethal mutations did not occur in mice given an intraperitoneal dose or oral doses of 5 or 10 mg/kg dichlorvos or in mice exposed to dichlorvos via inhalation (30 or 55 mg/m^3). No chromosome damage occurred in mice given drinking water containing 2 mg/L dichlorvos for 7 weeks, no aberration in chromosomal structure or number occurred in bone marrow cells of mice given intraperitoneal injections of dichlorvos for 2 days, and no chromosomal abnormalities occurred in mice exposed to 64–82 mg/m^3 dichlorvos for 16 h or to 5 mg/m^3 for 21 days (134). There is a report that intraperitoneal injection of mice with lethal (LD_{50}, ½ LD_{50}) amounts of dichlorvos causes chromosomal aberrations in bone marrow (146). However, the usefulness of this study in predicting *in vivo* genotoxicity has been challenged because of the toxic dose administered (134). In other *in vivo* studies, an increase in the percentage of hair follicles that contained nuclear aberrations occurred in mice 24 hours after a single dermal dose of dichlorvos (134a) and an increase in the incidence of micronuclei occurred in cultured skin cells from mice given a single dermal dose of dichlorvos (135).

It has been suggested that dichlorvos is not genotoxic *in vivo*, despite its methylating ability, because the phosphorus atom of the molecule is a stronger electrophile than the methyl carbons. Hence, *in vivo*, dichlorvos is much more likely to react with A-type esterases, serum cholinesterase, or acetylcholinesterase than with DNA (57, 134).

8.3.5 Biomonitoring/Biomarkers The major metabolites of dichlorvos, dimethyl phosphate, and the glucuronide conjugate of dichloroethanol, are rapidly excreted in urine and could conceivably be used to monitor acute dichlorvos exposure. However, because other organophosphates, naled and trichlorphon, are metabolized to dichlorvos, exposure to them would have to be ruled out before a definitive exposure of dichlorvos could be made.

8.4.2 Human Experience 8.4.2.2 Clinical Cases Death has followed accidental or intentional ingestion of liquid dichlorvos or cake-like baits containing both malathion and dichlorvos (504).

Two workers in Costa Rica died after splashing a concentration formulation of dichlorvos on their bare arms and failing to wash it off (504). Persistent contact dermatitis has also been reported following skin contact with dichlorvos (148).

RBC acetylcholinesterase activity marginally decreased in one of two dichlorvos applicators exposed to an estimated level of 0.02 mg/m^3 for about 25.5 minutes and 0.028 mg/kg/hr dermally (149). RBC acetylcholinesterase activity was reduced in some residents exposed to an estimated level of 0.2 mg/m^3 dichlorvos for about 15.8 hours, and some residents complained of headache (149). Average air concentrations of 0.13 mg/m^3 resulting from the use of resin strips in residences had no effect on RBC acetylcholinesterase activity (149a). Airbone levels of dichlorvos that caused slight to moderate RBC cholinesterase depression were 0.7 mg/m^3 averaged over 1 year in factory workers who produced dichlorvos vaporizers (149b). No significant change in RBC acetylcholinesterase activity occurred in babies exposed to an estimated 0.05 to 0.16 mg/m^3 dichlorvos for 18 h/day for 5 days (150).

Exposure of men to 0.1 to 0.3 mg/m^3 dichlorvos in 39 half-hour periods during 14 days had no effect on RBC, plasma cholinesterase, or physiological function (151). When the intensity of exposure was kept the same but the frequency of exposure increased to 96 half-hour exposures during 21 days, plasma cholinesterase activity slightly decreased, and when exposure concentration was increased to 0.4 to 0.5 mg/m^3, plasma cholinesterase activity significantly decreased. RBC cholinesterase activity was unaffected under any exposure conditions. No cholinergic signs or RBC acetylcholinesterase inhibition occurred in men exposed to average dichlorvos concentrations of 0.49 or 2.1 mg/m^3 for 1 or 2 hours on 4 consecutive days in a simulated aircraft cabin (127).

No cholinergic signs or RBC acetylcholinesterase inhibition occurred in men given 1- to 2.5-mg doses of dichlorvos via two corn oil capsules daily for up to 28 days (152) or in men given 0.9 mg dichlorvos three times a day for 21 days (152a). No adverse clinical signs or RBC acetylcholinesterase inhibition occurred in men given two oral doses of 35 mg dichlorvos (0.5 mg/kg/day), 12 or 15 daily doses of 21 mg dichlorvos (0.3 mg/kg/day), or 21 daily doses of 7 mg/kg dichlorvos (0.1 mg/kg/day) (120a). When the same individuals were given 70 mg dichlorvos for 14 days, however, RBC acetylcholinesterase was significantly inhibited. Cholinergic toxicity did not occur in volunteers given single oral doses of dichlorvos in slow release polyvinyl resin pellets ranging from 0.1 to 32 mg/kg, despite the fact that RBC acetylcholinesterase was dose-dependently inhibited because it was maximal at 24 mg/kg (153). Repeated daily administration of 8 to 38 mg/kg for 7 days caused cholinergic toxicity and dramatically decreased RBC acetylcholinesterase activity, so the experiment was terminated in most subjects in less than 7 days.

Six of 59 males and 9 of 48 females in an occupational study of flower growers showed positive reactions on patch testing of dichlorvos for an overall rate of 14%. Twelve of 18 subjects who had positive skin patch test reactions to triforine (1,4-bis (2,2,2-trichlor-1-formamidoethyl)piperazine) also showed positive reactions to dichlorvos (129).

8.5 Standards, Regulations or Guidelines of Exposure

Dichlorvos is undergoing reregistration by the EPA (9a). The ACGIH TLV for dichlorvos is 0.9 mg/m^3 with a skin notation (154). The OSHA PEL-TWA and NIOSH REL-TWA are 1 mg/m^3 with a skin notation. Most other countries have established OELs of 0.1 ppm as well (Republic of Egypt, Australia, Austria, Belgium, Denmark, Finland (1 mg/m^3) (Jan. 93), France, Germany 0.11 ppm (1 mg/m^3), Hungary STEL 0.2 mg/m^3 (Jan. 93), India, The Netherlands, The Philippines 1 mg/m^3 (Jan. 93), Poland 1 mg/m^3 (Jan. 93), Russia 0.2 mg/m^3 (Jan. 93), Switzerland, Thailand, United Kingdom 0.1 ppm (0.92 mg/m^3).

Organophosphorus Compounds
Jan E. Storm, Ph.D

9.0 Dicrotophos
9.0.1 CAS Number:
[*141-66-2*]
9.0.2 Synonyms:
O,*O*-dimethyl-*O*-(3-dimethylamino-1-methyl-3-oxo-1-propenyl) phosphate; 3-dimethoxyphosphinyloxy-*N,N*-dimethylisocrotonamide; Bidirl; C709; Diapadrin; SD3562; phosphoric acid (E)-3-(dimethylamino)-1-methyl-3-oxo-1-propenyl dimethyl ester; dimethyl 1-methyl-3-(*N,N*-dimethylamino)-3-oxo-1-propenyl phosphate, (*E*)-; Penetrex; Chiles' Go-Better; Mauget Inject-A-Cide B; phosphoric acid, 3-(dimethylamino)-1-methyl-3-oxo-1-propenyl dimethyl ester, (*E*)-; phosphoric acid, dimethyl ester, ester with 3-hydroxy-*N,N*-dimethylcrotonamide, (*E*)-;Carbomicron; crotonamide, 3-hydroxy-*N,N*-dimethyl-, *cis*-, dimethyl phosphate; dimethyl *cis*-2-dimethylcarbamoyl-1-methylvinyl phosphate; dimethyl *O*-(*N,N*-dimethylcarbamoyl-1-methylvinyl) phosphate; dimethyl phosphate ester with 3-hydroxy-*N,N*-dimethyl-*cis*-crotonamide; dimethylcarbamoyl-1-methylvinyl dimethylphosphate; hydroxy-*N,N*-dimethyl-*cis*-crotonamide dimethyl phosphate; Karbicron; Oleobidrin
9.0.3 Trade Name:
Bidrin®; Carbicron®; Ektafos®
9.0.4 Molecular Weight:
237.21
9.0.5 Molecular Formula:
$C_8H_{16}NO_5P$
9.0.6 Molecular Structure:

9.1 Chemical and Physical Properties
Pure dicrotophos is an amber liquid; the commercial grade which consists of 85% E-isomer is brown in color. Dicrotophos is stable when stored in glass or polyethylene containers up to 40°C but decomposes after 31 days at 75°C or after 7 days at 90°C. Dicrotophos emits toxic fumes of phosphorus and nitrogen oxides when heated to decomposition.

Specific gravity	1.216 at 15°C; 8.6×10^{-5} mmHg at 20°C
Boiling point	440°C at 760 mmHg
Vapor pressure	1×10^{-4} mmHg at 20°C
Solubility	slightly soluble in xylene, kerosene, and diesel fuel; miscible with water, acetone, alcohol, 2-propanol, and other organic solvents

9.1.2 Odor and Warning Properties A mild ester odor.
9.2 Production and Use
Dicrotophos was introduced in 1956 as a systemic and contact organophosphorus insecticide effective against sucking, boring, and chewing pests and is recommended for use on coffee, cotton, rice, pecans, and other crops. It is also used to control ticks and lice on cattle (155). Dicrotophos is available as 24% and 85% concentrates, as 40% and 50% emulsifiable concentrates, water-soluble concentrates, and ultra low volume formulations (155).

9.4 Toxic Effects

9.4.1.1 Acute Toxicity Dicrotophos is an organophosphate that has high oral toxicity and oral LD_{50}s of 16–21 mg/kg (64a). The dermal LD_{50} of dicrotophos is 42–43 mg/kg in rats (64a) and 225 mg/kg in rabbits (155). A 4-hour LC_{50} of 90 mg/m^3 and a 1-hour LC_{50} of 610–910 mg/m^3 was reported for rats (545).

9.4.1.2 Chronic and Subchronic Toxicity Cholinergic toxicity did not occur in rats fed diets that contained 0, 15, or 150 ppm dicrotophos for 4 weeks, although whole blood and plasma cholinesterase activites were markedly inhibited at both dose levels (156).

9.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The oral, intraperitoneal, and intravenous LD_{50}s for dicrotophos are equivalent (ranging from 9–17 mg/kg), indicating that it is essentially completely absorbed orally. Experimental studies show it is well absorbed via other routes of exposure as well.

After 6 hours, 65% of a subcutaneously injected dose (10 mg/kg) was excreted, and after 24 hours, 83% was excreted in the urine alone (159). Similar results were obtained in other studies of rats and other species (160).

Dicrotophos is metabolized in part to monocrotophos, and the concentration of monocrotophos in tissues may be higher than that of the parent compound a few hours after administration, as reflected by analysis of rat urine and goat milk (1). Residues of both compounds are dissipated almost entirely within 24 hours, as indicated by a rapid decrease in unhydrolyzed metabolites in urine or milk.

Hydrolysis of the vinyl phosphate bond of dicrotophos and/or its oxidative metabolites (monocrotophos) to produce dimethyl phosphate is the predominant metabolic reaction (159). The proportion of dimethyl phosphate in the urine of rats increases rapidly after dosing and reaches 50% of all metabolites present in less than 4 hours and more than 80% in 20 hours. During this interval, there is a correspondingly rapid decrease in the excretion of the parent compound and its oxidation products. Desmethyl dicrotophos and inorganic phosphate are also found in minor concentrations in the urine of treated rats (159). Dimethyl phosphate has been confirmed in the urine of an individual who accidentally ingested dicrotophos (161).

9.4.1.4 Reproductive and Developmental When rats were fed diets that contained 2, 5, 15, or 50 ppm dicrotophos (0.1, 0.25, 0.75, and 2.5 mg/kg/day) for two generations, decreased pup survival was observed at 5 ppm (95). Other effects (weakness, emaciation, and CNS effects) were seen at 50 ppm. No effects occurred at 2 ppm.

No morphological anomalies occurred in offspring of pregnant mice given intraperitoneal injections of 1, 2, 4, or 7.5 mg/kg dicrotophos on gestation day 11, 13, or days 10–12 (157). In other mice, a dose of 5 mg/kg/day on gestation days 8 though 16 did not change the developmental patterns of brain acetylcholinesterase or choline acetyltransferase in offspring through day 42, even though this dose on day 11 reduced embryonic or fetal acetylcholinesterase to 1.8% of control levels (157). The fetal brain enzyme level returned to normal by day 19 following dosing of the mother on days 8 through 16 of gestation.

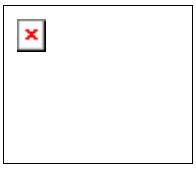
9.4.1.5 Carcinogenesis When rats were fed dicrotophos in their diets at concentrations of 0, 1, 10, or 100 ppm for two years, there were no detectable effects at the 1-ppm concentration (95). Plasma cholinesterase was inhibited at 1 ppm (95). At 10 and 100 ppm, decreased body weights and reduced cholinesterase (RBC, plasma, brain not specified) activities occurred. Dogs given dicrotophos in their diets at 0, 0.16, 1.6, or 16 ppm for two years showed some instances of slightly excessive salivation (95). At 16 ppm, both plasma and RBC cholinesterase activity was decreased.

9.4.1.6 Genetic and Related Cellular Effects Studies Dicrotophos is considered mutagenic on the basis of its similarity in structure to monocrotophos and the observation that it induced increases in sister chromatid exchanges in cultures of Chinese hamster ovary cells (158).

9.4.2 Human Experience An individual who inhaled a spray that contained dicrotophos and was being used to control mosquitoes in the home developed organophosphate poisoning (162). Upon hospital admission, he had abdominal cramps, nausea, vomiting, and diarrhea; the next day he exhibited increased sweating, salivation, dyspnea, coarse tremor of both legs, and generalized weakness. Plasma and RBC cholinesterase activities were nonexistent. The patient responded to atropine and pralidoxime. However, on the sixth day, respiratory paralysis occurred (typical of "intermediate syndrome"), and he required an artificial respirator for 5 days. He was discharged on day 22. In another case, a 52-year-old man accidentally drank a solution that contained dicrotophos in turpentine (163). He was brought to the hospital where he was treated effectively with atropine and pralidoxime chloride, but he required assisted respiration for more than a week.
9.5 Standards, Regulations, or Guidelines of Exposure
Dicrotophos is undergoing reregistration by the EPA (9a). Dicrotophosis a Restricted Use Pesticide (RUP) which can be purchased and used only by certified applicators. Some specific state restrictions may apply. The ACGIH TLV for dicrotophos (intended change in the 2000 TLVS is 0.05 mg/m^3) and monocrotophos is 0.25 mg/m^3 with a skin notation (154). The NIOSH TWA-REL is also 0.25 mg/m^3 with a skin notation.

Organophosphorus Compounds
Jan E. Storm, Ph.D

10.0 Dioxathion
10.0.1 CAS Number:
[*78-34-2*]
10.0.2 Synonyms:
2,3-*p*-Dioxanedithion *S,S*-bis-(*O*,*O*-diethyl phosphorodithioate); Hercules AC528; Ruphos; Navadel; Delnatex; Delnav; 1,4-dioxan-2,3-diyl-bis(*O*,*O*-diethyl phosphorothiolothionate); Delanov; Delnav (R); Phosphorodithioic acid *S,S*′-1,4-dioxane-2,3-diyl *O,O,O′,O*′-tetraethyl ester; phosphorodithioic acid *S,S*′-*p*-dioxane-2,3-diyl *O,O,O′,O*′-tetraethyl ester; AC 528; dioxation; 1,4-dioxan-2,3-diyl *O,O,O′,O*′-tetraethyl di(phosphoromithioate); 2,3-*p*-dioxane *S,S*-bis(*O*,*O*-diethylphosphorodithioate); *p*-dioxane-2,3-dithiol, *S,S*-diester with *O*,*O*-diethyl phoshorodithioate; *p*-dioxane-2,3-diyl ethyl phosphorodithioate; dioxothion; hercules 528; kavadel; deltic; 2,3-*p*-dioxanedithiol *S,S*-bis(*O*,*O*-diethyl phosphorodithioate); *S,S*′-1,4-dioxane-2,3-diyl *O,O,O′,O*′-tetraethyl phosphorodithioate; Cooper Del-Tox Delnav; Dextrone X; 1,4-dioxane-2,3-dithiol, *S,S*-diester with *O*,*O*-diethyl phosphorodithioate; 1,4-dioxane-2,3-diyl *O,O,O′,O*′-tetraethyl phosphorodithioate; 1,4-dioxanedithiol *S,S*-bis(*O*,*O*-diethyl phosphorodithioate)
10.0.3 Trade Names:
Delnav®; Hercules AC528®; Navadel®
10.0.4 Molecular Weight:
456.54
10.0.5 Molecular Formula:
$C_{12}H_{26}O_6P_2S_4$
10.0.6 Molecular Structure:



10.1 Chemical and Physical Properties

Dioxathion is a nonvolatile, chemically stable, dark amber liquid.

Specific gravity	1.257 at 26°C
Melting point	–20°C
Boiling point	60–68°C
Solubility	insoluble in water; soluble in aromatic hydrocarbons, alcohols, ethers, esters and ketones

10.2 Production and Use

Dioxathion is the common name for an organophosphate product that contains 70% cis and trans (1:2 ratio) isomers of 2,3-*p*-dioxanedithiol *S,S*-bis-(*O,O*-diethyl phosphorodithioate) as the principal ingredient (164). It was formely used in the United States on citrus, grapes, walnuts, and stone fruits. It was also used to control ticks, lice, and horn flies on cattle, goats, hogs, horses, and sheep when sprayed or dipped. Until 1989, when its manufacture and use in the United States was discontinued, dioxathion was available as a 25% wettable powder and a 48% emulsifiable concentrate (1, 155).

10.4 Toxic Effects

10.4.1.1 Acute Toxicity Dioxathion is an organophosphate compound that has moderately high oral toxicity and oral LD_{50}s of 23–64 (64a, 164). An intraperitoneal LD_{50} of 30 mg/kg was obtained for rats suggesting (by comparison with the oral LD_{50} of 23 mg/kg) that dioxathion is well absorbed orally. The oral LD_{50} for dogs is 10–40 mg/kg. The dermal LD_{50} for dioxathion is 63–235 mg/kg in rats and 85 mg/kg in rabbits (64, 545). One-hour LC_{50} values of 1398 and 340 mg/m^3 were reported for rats and mice (164). The acute symptoms of dioxathion are typical of other organophosphates, but the rate of onset is "somewhat slower" (164).

When dogs were given 0.25, 0.80, 2.5, or 8.0 mg/kg/day dioxathion by capsule for 5 days/week for two weeks, those given 8.0 mg/kg/day developed signs of cholinergic toxicity (diarrhea, hypersalivation, termors, ataxia, and depression) (*sic*). Doses of 0.8 mg/kg/day and higher significantly inhibited plasma cholinesterase, and doses of 2.5 and 8.0 mg/kg/day significantly inhibited RBC cholinesterase (164).

Dioxathion showed additive or less than additive toxicity when administered in equitoxic ratios with 15 other anticholinesterase insecticides. However, when dioxathion was administered 4 hours before malathion, potentiation as great as 5.4-fold was observed (164).

When rats were given single intraperitoneal injections of 4, 8, or 16 mg/kg, liver and plasma carboxylesterase activities were 19–55%, RBC cholinesterase activity was 76%, and, brain cholinesterase activity was 96% of control in rats given 4 mg/kg/day dioxathion (165). Thus dioxathion more effectively inhibits carboxylesterases than acetylcholinesterase. A similar tendency of dioxathion to inhibit carboxylesterases to a greater extent than acetylcholinesterase was observed when enzymatic activity was examined in rats fed diets that contained 4, 10, 20 or 40 ppm dioxathion for 7 days (165). Brain acetylcholinesterase was unaffected at any level, and RBC cholinesterase was significantly inhibited at 20 and 40 ppm; however, liver carboxylesterases were significantly inhibited at all levels. Further, rats given diets that contained 4 or 10 ppm dioxathion were more susceptible than untreated rats to inhibition of brain cholinesterase by a single 100- or 200-mg/kg dose of malathion (165).

When 75 mg/kg dioxathion was given subcutaneously to rats, they displayed muscular fibrillation at 2 hours and convulsions at 4 to 8 hours (166). Symptoms of organophosphate poisoning continued several days before recovery. Oral administration of dioxathion to rats at 5 mg/kg/day for up to 21 days resulted in plasma, RBC, and brain cholinesterase inhibition within 1 day (166).

Dioxathion produced mild, transient conjunctivitis but no transient or permanent corneal damage when 0.1 mL was instilled into the eyes of rabbits (164).

Dioxathion did not produce neurotoxicity in surviving hens that received single oral doses of 10–1000 mg/kg or subcutaneous doses of 25–200 mg/kg, even though the higher rates killed some of the birds (164). However, a slightly larger subcutaneous dose, 320 mg/kg, in hens protected by atropine produced a temporary neurotoxic effect that lasted 3–31 days (164).

10.4.1.2 Chronic and Subchronic Toxicity When rats were fed diets that contained 100 or 500 ppm dioxathion for 1–13 weeks, a dietary level of 500 ppm caused marked food refusal and loss of body weight within the first week (164). Female rats given 100 ppm (about 7.5 mg/kg/day) showed hyperexcitability and slight tremor, but males remained well. Both sexes showed marked inhibition of brain, plasma, and RBC cholinesterase activity. In another study, rats were fed diets that contained 1, 3 or 10 ppm dioxathion for 13 weeks. A dietary level of 10 ppm (0.78 mg/kg/day) produced no inhibition of brain cholinesterase but significantly reduced plasma and RBC cholinesterase activity. Dietary levels of 3 and 1 ppm (0.22 and 0.077 mg/kg/day) did not alter brain, plasma, or RBC cholinesterase activity (164).

No adverse effects occurred in dogs given 0.013, 0.025, or 0.075 mg/kg/day dioxathion for 5 days/week for 90 days via capsule (164).

10.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Dioxathion is well absorbed orally or dermally. Rats treated orally with dioxathion for 10 consecutive days excreted dioxathion primarily in the urine (about 50% of daily administered dose) and to a lesser extent in the feces (about 20% of daily administered dose) (166). Rats given 25 mg/kg of different components of the technical product excreted about 36–45% in the urine and about 6 to 25% in the feces, depending on the component administered, by 48 hours. Hydrolytic products identified in the urine included diethyl phosphoric, phosphorothioic, and phosphorodithioic acids. When rats were given 25 mg/kg dioxathion and sacrificed after 48 hours, fat had “appreciable” (*sic*) amounts of the dose. When rats were given 5 or 10 mg/kg dioxathion for several days, the maximum level in fat (0.6 ppm) was reached within 3 days and held constant through 21 days.

The metabolism of dioxathion was examined in rats treated orally and in rat liver microsomes (168). Both the trans, and cis, isomers were rapidly and extensively metabolized by rat liver microsomes in the presence of NADPH (indicating the involvement of microsomal oxidases) and by rats *in vivo* to the corresponding oxons and dioxon. The compound also underwent oxidative O-deethylation and hydroxylation of the ring resulting in ring cleavage and the loss of both phosphorus moieties. The more toxic cis isomer was metabolized more rapidly to form oxon and dioxon and also to form CO_2 from the ethoxy group (168). Of the dose administered, 80–87% was excreted by 96 hours in urine and most of this occurred in the first 24 hours. Unmetabolized dioxathion appeared in feces.

10.4.1.4 Reproductive and Developmental In a three-generation study, rats were fed diets containing 0, 3, or 10 ppm dioxathion (167). There were no measurable abnormalities among either parental animals or their progeny.

10.4.1.5 Carcinogenesis No evidence of carcinogenicity was observed in rats or mice given diets that contained dioxathion for 78 weeks and then observed for an additional 33 or 12–13 weeks, respectively (585). Time-weighted average dietary concentrations were 180 and 90 ppm for male rats, 90 and 45 ppm for female rats, 567 and 284 ppm for male mice, and 935 and 467 ppm for

female mice.

10.4.1.6 Genetic and Related Cellular Effects Studies Dioxathion was positive in the *Salmonella* assay and in cultured Chinese hamster ovary (CHO) cells for the induction of sister-chromatid exchanges but was negative in the mouse lymphoma assay and in cultured CHO cells for the induction of chromosomal aberrations (65).

10.4.2 Human Experience 10.4.2.2 Clinical Cases A 5-year-old boy, who ingested about three-quarters of a teaspoon of a 21% dioxathion formulation intended to be diluted for use as a flea dip (about 57 mg/kg) when it was mistaken for cough medicine, vomited and exhibited profuse diarrhea (169, 170). Within 2 hours, the child was mentally dull and unable to stand; he had shallow rapid respirations, muscle fasciculations, tearing, and miosis. After 12 hours of appropriate treatment, he recovered.

Volunteers were given 0.075 mg/kg/day dioxathion in divided doses three times/day, 7 days/week via capsule for 4 weeks. After 4 weeks, two of the subjects continued on this dose; other subjects received 0.150 mg/kg/day, and, the other six continued to receive 0.075 mg/kg/day dioxathion, but also received 0.150 mg/kg malathion. A dose of 0.075 mg/kg/day produced no effect on plasma or RBC cholinesterase activity. There was a slight inhibition of plasma cholinesterase activity in subjects that received 0.015 mg/kg/day. There was no effect on RBC cholinesterase activity and no clinical effect. Plasma cholinesterase measurements showed slight but statistically uncertain decreases when dioxathion was administered daily for 60 days at a rate of 0.075 mg/kg/day and malathion was given at a rate of 0.15 mg/kg/day simultaneously for the last 30 of these days (164).
10.5 Standards, Regulations, or Guidelines of Exposure
All registrations and tolerances for dioxathion have been revoked by the EPA (78). The ACGIH TLV for dioxathion is 0.2 mg/m^3 (154). NIOSH has recommended a REL-TWA of 0.2 mg/m^3 with a skin notation. Most other countries have occupational Exposure Limits of 0.2 mg/m^3 with a skin notation for dioxathion (Australia, Belgium, Denmark, France, The Netherlands, Switzerland, United Kingdom).

Organophosphorus Compounds
Jan E. Storm, Ph.D

11.0 Disulfoton
11.0.1 CAS Number:
[*298-04-4*]
11.0.2 Synonyms:
O,*O*-Diethyl-*S*-ethylmercaptoethyl dithiophosphate; phosphorodithioc acid *O*,*O*-diethyl-*S*-(ethylthio) ethyl) ester; Thiodementon; Solvirex; Thiodemeton; Disyton(R); phosphorodithioic acid *O*,*O*-diethyl *S*-[2-(ethylthio)ethyl] ester; *O*,*O*-diethyl-*S*-ethylmercaptoethyl dithiophosphate; dithiodemeton; BAY 19639; Dithiosystox; Di-Syston; Frumin AL; Frumin G; Frumen AL; disulfoton+; *O*,*O*-diethyl *S*-(2-(ethylthio)ethyl) phosphorodithioate; thiometon-ethyl; Root-X; Dot-Son Brand Stand-Aid; Rigo Insyst-D; Terraclor Super-X; Diethyl S-(2-(ethylthio)ethyl) phosphorodithioate; diethyl *S*-(2-ethylmercaptoethyl) dithiophosphate; Dimaz; Disipton; Disystox; Ekatin TD; ethylthiometon; Glebofos
11.0.3 Trade Names:
Di-Syston®; Dithiosystox®
11.0.4 Molecular Weight:
274.38
11.0.5 Molecular Formula:
$C_8H_{19}O_2PS_3$

11.0.6 Molecular Structure:

11.1 Chemical and Physical Properties

Pure disulfoton is a colorless oil that has low volatility and water solubility. The technical product is yellow.

Specific gravity	1.144 at 20°C
Boiling point	108°C at 0.01 mmHg
Vapor pressure	0.00018 torr at 20°C
Solubility	insoluble in most organic solvents; slightly soluble in water (25 mg/L)

11.2 Production and Use

Disulfoton is an organophosphate insecticide effective against aphids, leafhoppers, thrips, spider mites, and coffee leaf miners. It is used on cotton, tobacco, sugar beets, corn, peanuts, wheat, ornamentals, potatoes, and cereal grains. Disulfoton is used to treat seeds and is applied to soils or plants as an emulsifiable concentrate and in granular or pelletized forms.

11.4 Toxic Effects

11.4.1.1 Acute Toxicity Disulfoton is a highly toxic organophosphate that has oral LD_{50}s of 2.3–12.7 mg/kg for rats, mice, and guinea pigs (54, 64a). Dermal LD_{50}s are 3.6–20 mg/kg for rats, demonstrating a relatively high dermal toxicity (64a). Two of two rabbits died after dermal application of 10 mg/kg/day disulfoton that lasted 6 hours, whereas no rabbit similarly treated with 0.4 or 2.0 mg/kg/day for five days died. Treatment of rabbits five days/week for three weeks with 0.4, 0.8, 1.0, 1.6, 3.0, or 6.5 mg/kg resulted in marked cholinergic toxicity following 6.5 mg/kg, cholinergic signs and significant RBC and brain cholinesterase inhibition following 3.0 mg/kg, slight but significant RBC cholinesterase inhibition following 1.0 or 1.6 mg/kg, and, no cholinesterase inhibition following 0.4 or 0.8 mg/kg (171).

One-hour LC_{50}s values for disulfoton aerosol for rats are 290 mg/m^3 and 63 mg/m*3* for males and females, respectively; four-hour LC_{50} values are 60 mg/m^3 and 15 mg/m^3 for males and females, respectively (178). Repeated inhalation exposures are more lethal than single exposures. When female rats were exposed to disulfoton 4 h/day for 5 days, the LC_{50} was between 1.8 and 9.8 mg/m^3 (sic) (178).

Symptoms caused by acutely toxic levels of disulfoton are similar to those caused by other organophosphates and develop beginning about 30 minutes after exposure, depending on dose. Time of death depends on dose; it generally occurs within 48 hours at lethal doses but is sometimes delayed by several days for doses near the LD_{50} (172).

When rats were given single gavage doses of 1.5 and 5.2 mg/kg (males) and 0.76 and 1.5 mg/kg (females) disulfoton, cholinergic toxicity developed within 0–3 days and resolved by day 4 after treatment (178). RBC cholinesterase was inhibited in mid- and high-dose females and in high-dose males. Tolerance to the cholinergic toxicity of disulfoton occurs upon repeated, subtoxic exposures. Male rats given 2.0 or 2.5 mg/kg/day disulfoton for 1–14 days exhibited cholinergic signs whose severity diminished with repeated dosing (173, 174). When rats were given 3.5 mg/kg/day for 3–4 days, clinical cholinergic signs were more severe than those exhibited by rats pretreated with 2.5 mg/kg/day for 6 days and then given 3.5 mg/kg/day for 6 more days (173, 174). Thus, rats pretreated with 2.5 mg/kg/day became tolerant to even higher doses of disulfoton. After 3 days on a diet that provided 1 mg/kg/day disulfoton, rats developed severe cholinergic signs that diminished

markedly during a 62-day period despite the fact that brain and diaphragm cholinesterase activity was depressed at day 6 and remained depressed throughout the study (173).

Inhalation exposure of rats to 0.02 mg/m^3 disulfoton for 6 h/day, 5 days/week for three weeks did not cause any signs of cholinergic toxicity (171). Exposure to 0.1 to 0.5 mg/m^3 resulted in behavioral changes linked to inflammatory changes in the respiratory system, and exposure to 3.1 or 3.7 mg/m^3 caused cholinergic symptoms (muscle tremors, convulsions, increased salivation, dyspnea). Five of ten females exposed to 3.7 mg/m^3 died after three to twelve exposures, and three of twenty females exposed to 3.1 mg/m^3 died after eight to fifteen exposures. No deaths occurred in males at any exposure level. RBC cholinesterase was significantly inhibited at 0.1 mg/m^3 or more, and brain cholinesterase was significantly inhibited at 0.5 mg/m^3 in females and 3.7 mg/m^3 in males. In another 21-day study, rats exposed to 0.006, 0.07, or 0.7 mg/m^3 disulfoton showed no compound-related mortality or clinical signs of toxicity in any group. However, RBC cholinesterase was significantly inhibited at 0.7 mg/m^3. Brain cholinesterase activity was unaffected.

Neuronal degeneration was evident in some hens administered disulfoton (30 mg/kg) twice 22 days apart (95)

11.4.1.2 Chronic and Subchronic Toxicity The mortality rate was 20% in rats given daily intraperitoneal injections of 1.0 mg/kg/day disulfoton and 100% in rats given 1.2 or 1.5 mg/kg/day for 60 days (172). After the first two doses of 1.0 mg/kg, rats displayed cholinergic signs immediately after each dose for up to 7 or 10 days. Then the rats began to recover in spite of daily treatment. Intraperitoneal doses of 0.25, 0.5, and 1.0 mg/kg produced rapid dose-related inhibition of brain and serum cholinesterase that persisted throughout the entire study period, even though cholinergic signs disappeared (175).

Disulfoton caused no cholinergic clinical signs, or adverse effects on mortality, ophthalmology, feed consumption, or body weight gain in rats exposed to 0.018, 0.16, or 1.4 mg/m^3 for 6 h/day, 5 days/week for 13 weeks (178). However, RBC, brain and plasma cholinesterase activities were significantly inhibited in rats exposed to 1.4 mg/m^3.

No adverse effects occurred in rats fed diets that contained 1, 2, 4, 5, 6, 10, or 16 ppm disulfoton (0.1, 0.2, 0.5, or 1.0 mg/kg/day) for 13 or 16 weeks, other than decreased body weight gain at 16 ppm and urine stains in females at 4 ppm (63, 171). However, RBC, brain, plasma, and tissue (submaxillary gland) cholinesterase activity was significantly inhibited in females given 2 ppm or more and in males given 5 ppm or more. In mice fed diets that provided 0.63–0.71 mg/kg/day disulfoton, cholinesterase was inhibited in all tissues, although the tissues were not specified (176). No-effect levels were 0.13–0.14 mg/kg/day.

Dogs fed diets that contained 1, 2, or 10 ppm disulfoton for 12 weeks exhibited no signs of toxicity, although plasma and RBC cholinesterase activity were significantly inhibited in dogs given 2 or 10 ppm (171).

11.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Disulfoton is rapidly absorbed after oral exposure. An average of 80–84%, 6–8%, and 9% of a single oral dose of disulfoton was eliminated by rats in urine, feces, and expired air, respectively, in the 10 days following exposure that accounted for 96–100% of the administered dose (171). The rate of excretion was significantly lower in females—males eliminated one-half the dose in 4–6 hours, whereas females required 30–32 hours. Another experiment showed that 72 hours after an oral dose of disulfoton to rats, about 97% was eliminated in urine, 2% was eliminated in feces, and less than 1% remained in the body (171). Similar results were obtained at 12 hours in rats given 15 consecutive doses of disulfoton. There was no accumulation of disulfoton in the body. Tissue and blood levels of disulfoton peaked at 6 hours

and were highest in liver followed by kidney, plasma, fat, whole blood, skin, muscle, and brain. However, on a percentage of dose basis, female livers contained a much greater amount of disulfoton than males (34% vs. 10% at 6 hours; 3% vs. 9% at 12 hours), possibly indicating slower metabolism and accounting for longer elimination in females.

Dermal absorption of 0.85, 8.5, or 85 mg/cm^2 of a disulfoton formulation ranged from 39–44% of an applied dose applied to the skin (15 cm^2) of rats (178). There was no concentration-dependent effect; the majority of absorption occurred within the first hour, and, the majority of the absorbed dose (66–91%) excreted was found in the urine.

Disulfoton is rapidly metabolized via oxidation to sulfoxides and sulfones, oxidation to oxygen analogs, and/or hydrolysis to produce a corresponding phosphorothionate or phosphate (54). Metabolism is accompanied by inhibition of microsomal enzymes (183).

In humans exposed to disulfoton, sulfones (disulfoton sulfone and demeton *S*-sulfone) were detected in blood (104), and diethyl phosphate (DEP), diethyl thiophosphate (DETP), diethyl dithiophosphate (DEDPT), and diethyl phosphorothiolate were detected in urine (184). Similar metabolic products were detected in the urine of rats and mice administered disulfoton intraperitoneally or orally and in liver homogenates of treated rats (54).

The oxidation reactions are toxification reactions that create metabolic products that bind to cholinesterase. In an oral study of rats, the metabolites, disulfoton sulfoxide, disulfoton sulfone, demeton-*S*-sulfoxide, and demeton *S*-sulfone caused mortality and signs of toxicity at lower doses than disulfoton itself (171a). The hydrolytic reactions create more polar products that are eliminated in the urine and therefore are detoxification reactions.

11.4.1.4 Reproductive and Developmental Two-generation reproductive studies indicates that diets that contained 3 or 9 ppm disulfoton have adverse reproductive effects; diets that contained 0.5–2 ppm do not (242). Adverse outcomes among rats fed 9-ppm diets include decreased body weight gain during pregnancy and lactation; decreased number of implantations; decreased litter size, weights and viability; and decreased brain cholinesterase activity in F1a pups. Adverse outcomes among rats fed 3 ppm disulfoton include decreased litter size, weights, and viability in the F2 generation. Cholinergic signs were evident in rats fed 9 ppm; decreased brain cholinesterase activity occurred in rats fed a 0.5-ppm diet or more. Reproductive effects were also reported in a study in which male and female rats were given 0.5 mg/kg/day disulfoton for 60 days before and/or during mating. Two-fifths of the treated females failed to become pregnant (182).

There was no indication of a teratogenic effect in any rats given 0, 0.1, 0.3, or 1.0 mg/kg/day disulfoton via gavage on gestation days 6–15 (171). Significant depressions of RBC cholinesterase activity occurred in dams given 0.3 and 1.0 mg/kg/day. A significant increase in the incidence of incomplete ossification of the sternebrae was observed in fetuses at 1.0 mg/kg/day which was considered an effect of growth retardation due to maternal toxicity. There was no evidence of teratogenicity or embryo toxicity in rabbits given 0, 0.3, 1.0, or 3.0 mg/kg/day disulfoton (95). The highest dose was lowered to 2.0 and later to 1.5 in some but not all of the high-dose animals due to severe toxic responses and mortality.

11.4.1.5 Carcinogenesis There was no evidence of carcinogenicity or any other adverse effect among rats fed diets that contained 1 or 2 ppm disulfoton for 104 weeks or 0.5 ppm for 80 weeks followed by 5 ppm for 24 weeks (242). Females fed 5 ppm, however, exhibited significantly inhibited plasma and brain cholinesterase. Rats fed diets that contained 10, 25, or 50 ppm disulfoton for 178 days had significantly inhibited brain cholinesterase activities but exhibited no signs of cholinergic toxicity (177). There was no evidence of carcinogenicity in rats given feed that contained 0, 1, 4, or 16 ppm disulfoton, (0.05, 0.2, and 0.1 mg/kg/day) (178). Females given the 16-ppm diet had a 40% mortality rate during the last week of the study compared with a 12% mortality in controls, and both sexes

given the 16-ppm diet exhibited cholinergic signs and increased relative brain weight. There was an increased incidence of optic nerve degeneration in males given the 4-ppm diet and in females given the 4- or 16-ppm diet. Increased incidences of mucosal hyperplasia and chronic inflammation of the forestomach occurred in females given 16 ppm. Cystic degeneration of the Harderian gland occurred in male rats given 16 ppm and in female rats given 4 ppm. Corneal neovascularization was significantly increased in rats given 16 ppm. RBC and brain cholinesterase activity was inhibited in rats given 1 ppm.

There was no evidence of cancer in mice fed diets that contained 0, 1, 4, or 16 ppm disulfoton for 99 weeks (171). Nor was there any adverse effect on behavior, feed consumption, hematology, or organ weights. Significant depression of RBC, plasma, and brain cholinesterase activity occurred in mice fed diets that contained 16 ppm (equivalent to 2–2.5 mg/kg/day).

Dogs did not exhibit cholinergic signs, opthalmoscopic changes, hematological or clinical chemical changes, or any evidence of carcinogenicity when given diets that contained 0.5 or 1.0 ppm disulfoton for two years (equivalent to 0.03 or 0.14 mg/kg/day) (242). Nor was RBC cholinesterase activity inhibited. RBC cholinesterase activity was inhibited in dogs after five months exposure to □0.5 mg/kg/day given by capsule and when they were fed diets that contained disulfoton at a dose of 0.06 mg/kg/day for 40 weeks (242). Moderate inhibition of RBC cholinesterase occurred in dogs given diets that contained 5.0 ppm for 69 weeks (equivalent to about 0.7 mg/kg/day). Brain cholinesterase was not inhibited in dogs given a 0.5- or 1.0-ppm diet for two years but was markedly inhibited in dogs given diets that contained 2.0 ppm or more.

Ocular effects (myopia and astigmatism) associated with degenerative changes in the ciliary muscle cells occurred after 12 months in dogs given □0.63 mg/kg/day disulfoton for two years (128, 179). The myopia became progressively worse until dosing ceased. Necrosis and atrophy of the optic nerve and retina was observed in dogs given disulfoton (0.5–1.5 mg/kg/day) for 2 years (180). However, no ophthalmological effects occurred in dogs given diets that contained 0.5, 4, or 12 ppm disulfoton (0.015, 0.1, or 0.3 mg/kg/day) for 1 year (181). Dogs given the 4-ppm diets “demonstrated intermediate toxicity” (*sic*), and those given the 12-ppm diet “demonstrated systemic toxicity near the Maximum Tolerated Dose” (*sic*). RBC cholinesterase was significantly inhibited in females given 4 and 12 ppm, corneal cholinesterase was significantly depressed at 4 and 12 ppm in both sexes, retinal cholinesterase was significantly inhibited at 4 ppm in females in 12 ppm in males, and ciliary body cholinesterase was significantly inhibited at 12 ppm in both sexes.

11.4.1.6 Genetic and Related Cellular Effects Studies The genotoxicity of disulfoton in *in vitro* assays has been reviewed and was mainly negative (54). Positive results for reverse mutation occurred in single assays with LT-2 or TA1535 stains of *S. typhimurium* without activation but not in several other assays with or without activation (54). Similarly, both positive and negative results for reverse mutation have been reported in *E. coli* and *S. cerevisiae* (54). Disulfoton was negative of gene conversion, mitotic crossing over and recombinants, and for DNA damage in *S. cerevisiae* with or without activation but was positive in an assay for chiasmatic frequency (genetic recombinants), mitotic index, chromosomal aberrations, and pollen fertility in barley (54).

Disulfoton was positive or weakly positive for sister chromatid exchange in Chinese hamster ovary cells in some studies, but negative in others; negative for HGPRT mutations in Chinese hamster ovary cells with or without activation; positive for forward mutations in mouse lymphoma cells for unscheduled DNA synthesis in human lung fibroblasts, and for growth inhibition and increased protein synthesis in human HeLa cells; and negative for chromosomal aberrations in human hematopoietic cell lines and for alterations of DNA or RBA synthesis in human HeLa cells (54).

11.3.5 Biomonitoring/Biomarkers The presence of disulfoton and/or its metabolites in urine is a reliable biomarker for disulfoton exposure. At 2–10 days post exposure, 30–84% of an oral dose can be accoun-ted for in the urine of animals. Although precise relationships between disulfoton exposure and urinary DEP have not been established, DEP is considered a relatively sensitive

biomarker for exposure to disulfoton and other diethyl organophosphate esters (54).

11.4.2 Human Experience 11.4.2.2 Clinical Cases A 30-year-old man was found dead after consuming an unknown amount of disulfoton, as evidenced by the presence of disulfoton in urine and blood (186). A 75-year-old woman who ingested an unknown quantity of disulfoton as Di-Syston (5%, granular) experienced severe organophosphate poisoning from 3.5 hours to 11 days, characterized first by vomiting and diarrhea, followed by nausea, fasciculations, and then confusion, miosis, and cardiac arrhythmias. She recovered after 28 days (186a). A farmer who had worn disulfoton-contaminated gloves for several days developed signs of disulfoton toxicity (weakness, fatigue, and cyanosis) and had to be hospitalized (187).

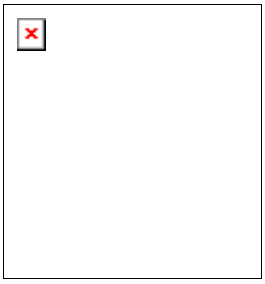
The inhalation exposure potential of wet and dry mix procedures used to prepare disulfoton fertilizer mixtures were compared by measuring disulfoton on special filter pads used in place of the usual outer absorbent filter pads that cover the filter cartridges of respirators worn by workers (31). Dermal exposure was measured by attaching layered gauze absorbent pads to various parts of the body or clothing and allowing workers to be exposed for a timed period of work. Air exposures during dry mix operations averaged 0.633 mg/m^3 1–5 meters from the work station and, during wet mix operations, averaged 0.06 mg/m^3 1–5 meters from the work station. Dermal exposures averaged 2.0 mg/h and 0.09 mg/h during dry and wet mix operations, respectively. RBC cholinesterase values for dry mix workers were reportedly depressed by about 23% after 9 weeks of work, but it was not clear whether these measurements were from workers wearing respirator or not—which would have decreased the anticholinesterase effect.
11.5 Standards, Regulations, or Guidelines of Exposure
Disulfoton is undergoing reregistration by the EPA (178). The ACGIH TLV for disulfoton is 0.1 mg/m^3 with a skin notation (154). NIOSH has recommended a REL-TWA of 0.1 mg/m^3 with a skin notation. Most other countries also have Occupational Exposure Limits of 0.1 mg/m^3 (Australia, Belgium, Denmark, France, The Netherlands, Switzerland, and the United Kingdom).

Organophosphorus Compounds
Jan E. Storm, Ph.D

12.0 EPN
12.0.1 CAS Number:
[*2104-64-5*]
12.0.2 Synonyms:
O-ethyl *O*-*p*-nitrophenyl phenylphosphonothioate; PIN; EPN; phenylphosphonothoic acid, *O*-ethyl *O*-*o*-nitrophenyl ester; *O*-ethyl *O*-*p*-nitrophenylbenzenethionophosphonate; *O*-ethyl *O*-*p*-nitrophenyl benzenephosphonothioate; phenylphosphonothioic acid *O*-ethyl *O*-(4-nitropheny) ester; ethyl *p*-nitrophenyl benzenethiophosphonate; *O*-ethyl *O*-(4-nitrophenyl) phenylphosphonothioate; ethoxy-((4-nitrophenoxy) (phenyl) phosphine) sulfide; ethyl (*p*-nitrophenyl) phenylphosphonothioate; ethyl (*p*-nitrophenyl) benzenethionophosphonate; ethyl *O*-(4-nitrophenyl) benzenethionophosphonate; ethyl *O*-(*p*-nitrophenyl) benzenethionphosphonate; Ethyl *O*-(*p*-nitrophenyl) phenylphosphonothioate; ethyl p-nitrophenyl thiobenzene phosphonate; ethyl phenyl (*p*-nitrophenyl) thiophosphonate; ethyl phenylphosphonothioic acid *O*-(4-nitrophenyl) ester; phenol, *p*-nitro-, *O*-ester with *O*-ethyl phenyl phosphonothioate; Santox; *O*-ethyl O-*p*-nitrophenyl phenylthiophosphonate; ethyl *p*-nitrophenyl Benzenethiophosphate
12.0.3 Trade Names:
Santox
12.0.4 Molecular Weight:
323.31
12.0.5 Molecular Formula:

$C_{14}H_{14}NO_4PS$

12.0.6 Molecular Structure:



12.1 Chemical and Physical Properties

EPN is a noncombustible, light yellow solid or brown crystalline substance. Contact of EPN with strong oxidizers may cause fires and explosions. Toxic gases and vapors (e.g., oxides of sulfur and nitrogen, phosphoric acid mist, and carbon monoxide) may be released when EPN decomposes.

Specific gravity	1.268 at 25°C
Melting point	36°C
Boiling point	215 at 5 mmHg
Vapor pressure	0.0003 torr at 100°C
Solubility	soluble in acetone, alcohols, ether, toluene; slightly soluble in water

12.2 Production and Use

EPN was introduced in 1949 for use as a nonsystemic insecticide and acaricide. It was used primarily on cotton to control the boll weevil and lepidopterous pests and was available as a 45% emulsifiable concentrate, as granules, and in combination with other insecticides (188). EPN is no longer registered for use in the United States (45).

12.4 Toxic Effects

12.4.1.1 Acute Toxicity EPN is an organophosphate compound that has high oral toxicity and oral LD_{50}s of 14.5–91 mg/kg for rats (64a). Oral doses of 2–75 and 2–50 mg/kg technical EPN were fatal to female and male dogs, respectively (277). Oral and intraperitoneal LD_{50}s for the mouse were 12.2 and 8.4 mg/kg, respectively, and an oral LD_{50} for the dog was 20 mg/kg (545). EPN was about five times more potent in young rats compared to adult rats; the intraperitoneal LD_{50} in 23-day-old rats was 8 mg/kg, whereas it was 33 mg/kg in adults (189). Dermal LD_{50}s were 25–230 mg/kg in rats (64a). A dermal LD_{50} for the rabbit was 30 mg/kg (529), and the lethal range for dermal exposure to EPN for rabbits was 30–150 mg/kg (277). The only acute inhalation toxicity value available for EPN is a 1-hour LC_{50} of 160 mg/m^3 that was reported for rats (545).

The magnitude of brain, plasma, and RBC cholinesterase activity inhibition and its rate of recovery in rats was determined following a sublethal dose of 25 mg/kg EPN (38). Maximum brain cholinesterase inhibition occurred 4–24 hours after exposure and recovered to normal by 2 weeks, maximum plasma cholinesterase inhibition occurred at 4 hours and recovered by 72 hours, and maximum RBC inhibition occurred at 24 hours and recovered by 4 weeks (the same rate at which new rat RBCs are formed) (38).

Adult, atropinized hens treated subcutaneously with doses of EPN equivalent to the hen subcutaneous LD_{50} (60 mg/kg) developed leg weakness immediately after dosing that persisted for more than 48 hours and occurred in addition to cholinergic symptoms (140). Only 3 of 21 animals that exhibited leg weakness survived. In another study, EPN produced neurotoxicity when administered subcutaneously to atropinized hens at doses of 40 mg/kg or more, but not at doses of

20 mg/kg. Although this effect was prompt in onset and lasted as little as 6 days in some hens, it persisted for more than 330 days in others (64a). High, lethal, single oral exposures (65–100 mg/kg) also caused delayed neuropathy in atropinized hens (191). Delayed neurotoxic ataxia was also observed in mice following oral dosing. A sublethal oral dose (20 mg/kg) produced an irreversible neurotoxic ataxia in mice after 29 days (192).

EPN potentiates malathion toxicity and is itself potentiated by malathion. Oral LD_{50}s for EPN and malathion given by gavage to rats were 65 and 1400 mg/kg, respectively. When given together at approximately equitoxic doses (about a 25:1 malathion: EPN ratio), a tenfold potentiation was observed. The LD_{50} for malathion was 167 mg/kg and for EPN was about 6.6 mg/kg (193, 194). Similarly, when single doses of EPN were administered to dogs, 200 mg/kg was fatal, and 50–100 mg/kg caused moderate to severe symptoms; however, when EPN was administered simultaneously with as little as 100 mg/kg malathion (<10% of the malathion LD_{50}), 2 mg/kg EPN caused 100% mortality.

Potentiation, it is believed, results from inhibition of the hydrolytic detoxification of malathion by EPN (194a, 195). The rate of malaoxon detoxification in liver was 10 to 80% inhibited in rats given single injections of 0.5 to 1.5 mg/kg EPN and was 29 to 95% inhibited in rats fed diets containing 5 to 100 ppm EPN for 2 weeks compared to controls. In this study, the LD_{50} of malathion was 550 mg/kg 1 hour after an intraperitoneal injection of 1.5 mg/kg EPN, compared to 1100 mg/kg in untreated controls.

Neither brain, plasma, or RBC cholinesterase inhibition occurred in rats maintained on a dietary level of 5 or 25 ppm EPN (about 0.25 and 1.25 mg/kg/day) for 8 or 2 weeks, respectively (38). When rats were given diets that contained 0, 100, 300, or 600 ppm (males) (equivalent to 5, 15, or 30 mg/kg/day) or 0, 35, 100, or 300 ppm (females) (equivalent to 2, 5, or 15 mg/kg/day) EPN for 30 days (279), “transitory nervous manifestations” (*sic*) (excitability, tremors) were noted and mortality occurred in the 600- (males) and 300-ppm (females) groups. Body weight gain decreased in the 300- (males) and 100-ppm (females) groups. The authors noted that comparable studies of rats fed the commerical 35% formulation gave consistent results.

12.4.1.2 Chronic and Subchronic Toxicity In rats fed ground chow contaminated with EPN for 90 days and then observed until death, a calculated 90-dose LD_{50} was 12 mg/kg/day (196). Using the 90-dose LD_{50} and the single dose LD_{50} of 7.7 mg/kg previously obtained, a “chronicity factor” (single dose $LD_{50/90}$-dose LD_{50}) of 0.64 mg/kg was calculated, indicating that EPN does not exhibit a cumulative toxic effect.

Cholinesterase activity declined in all organs and tissues in rats after being fed diets that contained 75 ppm EPN for 1 month (154). When rats were fed diets that contained 0.2, 1, 5, or 25 ppm EPN (0.01, 0.05, 0.25, or 1.25 mg/kg/day) for 1, 3, 6, or 13 weeks, cholinesterase activity in the brain was unaffected, although there was a dose-related inhibition of aliesterase activity in both liver and serum at dietary level of 1 ppm and above (197, 285). When rats were given diets, that contained up to at least 125 ppm, the effects noted at 125 ppm (6.25 mg/kg/day) included decreased plasma and brain cholinesterase activity, decreased female growth and decreased RBC, hemoglobin, and hematocrit in both sexes (95). At 25 ppm (1.25 mg/kg/day), RBC cholinesterase was significantly inhibited. At 5 ppm (0.25 mg/kg/day), no adverse effects were noted (95).

When dogs were treated orally with repeated doses of up to 3.0 mg/kg/day EPN, decreased RBC and brain cholinesterase activity; decreased red blood cells, hemoglobin, and hematocrit in both sexes; and pancreatic acinar cell atrophy in two males were recorded (95). Administration of 1.0 mg/kg/day had no adverse effect. No other details were provided in the study summary (95).

Potentiation of cholinesterase inhibition occurs when subchronic exposure is to EPN and malathion simultaneously (194). When rats were fed diets that contained 25 ppm EPN for 8 weeks, a small but significant inhibition of RBC cholinesterase was observed, whereas when 25 ppm EPN was fed simultaneously with 500 ppm malathion, RBC cholinesterase inhibition was marked. (500 ppm malathion alone had no effect on RBC acetylcholinesterase activity.) Similarly, when dogs were fed diets that contained 20 or 50 ppm EPN for 12 weeks, RBC cholinesterase activity marginally decreased (5 ppm had no effect), whereas diets that contained 3, 20, or 50 ppm EPN combined with 8, 100, or 250 ppm malathion (levels which did not inhibit RBC cholinesterase), respectively, markedly inhibited RBC cholinesterase (193).

12.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms EPN is readily absorbed following either oral or dermal exposure. In rats, following a single oral dose of 1.5 mg/kg EPN, about 61–68% of the dose was excreted in urine and 7–21% of the dose was excreted in the feces (279). Metabolism was essentially complete because urinary excretion of metabolites totaled 60–68% of the total dose; the corresponding fecal values were 6.7–17.2% (279). The plasma half-life was approximately 33.6 hours in males and 38.6 hours in females. In rats given 0.72 or 0.072 mg/kg EPN three times at 24-hour intervals, 14 and 26% of the dose was excreted as *p*-nitrophenol in urine (280). EPN was not detectable in blood at any time after the final dose but was detectable in adipose tissue (0.06 ppm) only on day 3.

It has been argued that the toxicokinetics and metabolism of EPN plays a major role in the development and expression of neuropathy. When a rat was preconditioned for 21 days on a diet that contained 450 ppm EPN, only traces of the dose remained in body tissues after 72 hours (280). Thus, EPN was practically completely metabolized and eliminated in rats. Two EPN-conditioned hens that received 2.5 mg/kg EPN for 21 days and two unconditioned hens excreted 94–100% of a single oral, nonneurotoxic 4-mg/kg dose within 72 hours of administration. No significant difference was apparent in the dose excreted from conditioned or unconditioned chickens. Small amounts of EPN remained in body tissues; only trace amounts were found in the brain and spinal cord. By contrast, a single oral neurotoxic dose of 50 mg/kg EPN was slowly metabolized and excreted by chickens. Only 65% of the dose was eliminated during the 72 hour test. Excreta extract contained the same five metabolites found in the rat. Thus, the 50-mg/kg dose may have exceeded the metabolic capacity of the liver to detoxify EPN (280). Based on these data, half-lives for EPN were 1.1 days for a single oral 17.3-mg/kg dose in male rats, 1.8 days for a single oral 4-mg/kg dose in chickens, and 3.5 days for a single oral dose of 5 mg/kg in chickens (280).

In cats, EPN was readily absorbed when a single dose of 20 mg/kg was dermally applied as reflected by disappearance of EPN from the application site (281). Most of the absorbed dose was excreted in urine (29.9%); 3.2% was recovered in the feces. In cats given daily dermal doses of 0.5 mg/kg EPN for 10 days, 62% of the total dose was eliminated in the urine. Thus, the metabolism and toxicokinetics of EPN in the cat are intermediate between those in the rat and in the chicken. Similarly to the rat, EPN is excreted as polar metabolite, mostly in the urine. As in the chicken, however, EPN is persistent in cat tissues, especially in nervous tissues. The finding that the cat is ten times less sensitive than the chicken to subchronic dermal exposure to EPN may be explained by the relatively rapid metabolism and elimination of EPN in the cat. (The extensive metabolism of EPN in the rat compared to (the chicken or) the cat might be explained by the presence of a higher level of cytochrome P-450 in rat liver microsomes than in the chicken or in the cat.)

EPN undergoes oxidative toxication through desulfuration that is catalyzed by microsomal oxidases (282) and detoxication through hydrolytic removal of *p*-nitrophenol (280, 283). Moreover, has been shown that the rate of hydrolytic detoxication of EPN more closely correlates with sex and age differences in EPN toxicity than the rate of toxication (20). The nitro group can be further reduced to an amino group by enzymes in the livers of mammals, birds, and fish and in the kidneys, spleens, hearts, lungs, and RBCs of mammals. The resulting amine is a weak inhibitor of cholinesterase but the importance of this reduction for detoxication *in vivo* is unknown 283. Activation and degradation of EPN is not restricted to the liver. *In vitro* studies have shown that rat brain also possesses

activation and degradation capability (284).

Overall, metabolism evidently reduces the toxicity of EPN, maybe even to a greater extent than for parathion or methyl parathion. The intraperitoneal LD_{50} was 7.3 mg/kg in untreated rats and 75 mg/kg in phenobarbital-treated rats, whereas for parathion and methyl parathion, these values were 2.5 and 7.3 mg/kg and 7.0 and 8.0 mg/kg, respectively (197).

12.4.1.4 Reproductive and Developmental EPN was administered via gavage once daily to mice (1, 3, 6, or 12 mg/kg) on days 6 through 16 of gestation (278). EPN, at dose levels up to those that were maternally lethal (12 mg/kg), did not produce fetotoxicity, fetal lethality, or teratogenicity (591).

12.4.1.5 Carcinogenesis No evidence of carcinogenicity occurred in rats fed EPN at levels of 50, 150, or 450 ppm (males) or 0, 25, 75, or 255 ppm (females) for two years (277). Dietary levels of 450 ppm (males) and 225 ppm (females) caused intermittent tremors and slight retardation of growth. Rats given the highest dietary level had depressed growth from the start of EPN feeding. Other groups of rats tolerated oral dosages up to 10 mg/kg/day. There was no indication of increasing mortality with increasing doses of EPN, although the mortality by the end of the two year study was high (86–98%).

12.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Delayed neurotoxicity was produced in hens given daily oral doses of 0.01, 0.1, 0.5, 1.0, 0.5, 5.0, or 10.0 mg/kg EPN for 90 days and observed for 30 days (274). Hens treated with 5 mg/kg or more were atropinized to protect them from acute cholinergic toxicity. The clinical condition of most ataxic hens deteriorated during the 30-day observation period following the end of dosing, and the severity of effects dependend on the size of the daily ingested dose. Hens given small doses showed only ataxia, but those treated with large doses progressed to paralysis and died. Hens treated daily with 0.01 mg/kg EPN showed no abnormality in gait or behavior. In a study summarized by EPA, when adult hens were dosed orally at 0.01, 0.1, 0.5, 1.0, 2.5, or 5.0 mg/kg/day for 90 days, organophosphate type delayed neurotoxicity (ataxia) was seen at doses of 2.5 and 5.0 mg/kg/day but not at lower doses (95). Histopathologically observed damages to the nervous system was seen at doses of 0.1 mg/kg, but not at 0.01 mg/kg/day.

When EPN was applied dermally at doses of 0.01 to 10 mg/kg to the necks of hens for 90 days, all hens given 2.5 to 10 mg/kg EPN developed signs of cholinergic poisoning despite treatment with atropine (269). All hens given EPN, except those that received the 0.01 mg/kg dose, developed signs of delayed neurotoxicity, such as ataxia, paralysis, and death. All doses of EPN, except for the 0.01 mg/kg/day dose, caused degeneration of axons and myelin in the spinal cord.

Delayed neurotoxicity was produced in cats following the administration of a single dermal dose of 22.5, 45, 112.5, or 225 mg/kg (0.2 to 5.0 times the dermal LD_{50} of 45 mg/kg) or repeated daily doses of 0.5, 1.0, or 2.0 mg/kg EPN (269). Single dermal doses of 9.0 mg/kg and repeated dermal doses of 0.1 mg/kg were without effect. Therefore, the cat is about ten times less sensitive than the hen to EPN-induced delayed neurotoxicity.

When dogs were given 2.8 to 5.0 mg/kg EPN orally for up to a year, the first symptoms were vomiting and diarrhea, followed by gait disturbances and weight loss; histopathological changes in the nervous system were noted (275). Male sheep treated orally with 1 mg/kg/day EPN for 180 days showed no clinical signs of neurotoxicity, no histological changes in tissues, and no remarkable neurotoxic esterase (NTE) measurements (214).

12.4.2 Human Experience 12.4.2.2 Clinical Cases In one case, ingestion of an estimated 200 mL of 50% EPN resulted in coma, miosis, sweating, bloody stools, pulmonary edema, and death despite treatment with pralidoxime and atropine (286). In another case, a 500 mL suspension that contained EPN was obtained from the gastrointestinal tract of a 46-year-old farmer who died following generalized convulsions and cardiorespiratory arrest (287). Signs and symptoms of EPN poisoning

may persist for years after acute or chronic exposure due to permanent nerve damage; symptoms of nerve damage being and may be irreversible at the time of severe acute exposure (294).

Applicator personnel were monitored during aerial and ground applications of EPN to cotton in Mississippi and Arizona. Respiratory exposures based on an 8-hour work day averaged 11 mg for pilots, 15 mg for loaders, and 39 mg for ground applicators. Respiratory exposure of flagmen, monitored during a complete application cycle, averaged 317 mg/8 hours. Mean 8-hour dermal exposures were 2.1 mg for pilots, 6.3 mg for loaders, 117.7 mg for flagmen, and 7.5 mg for ground applicators (185).

Neither plasma nor RBC cholinesterase activity was affected among five volunteers given 3 mg EPN/day by capsule (about 0.04 mg/kg/day) for 32 days, nor were any clinical effects observed or reported (294). No significant effect on plasma or RBC cholinesterase activity occurred when the dose was increased to 6 mg EPN/day (0.0857 mg/kg/day) for 47 days, nor were any clinical effects observed or reported (294). When the dose was further increased to 9 mg EPN/day (about 0.13 mg/kg/day) for 56 days, plasma cholinesterase activity that began 2 weeks after first administration of EPN was depressed and continued to be depressed at 3 weeks after dosing stopped. RBC cholinesterase activity inhibition was similar to that of plasma but did not occur as soon. However, in a later study, when five other volunteers were given 6 mg EPN/day (0.086 mg/kg/day) plus 16 mg malathion/day for 44 days, both RBC and plasma cholinesterase were significantly depressed (288).

12.5 Standards, Regulations, or Guidelines of Exposure

EPN is not registered for use in the United States. The ACGIH TLV for EPN is 0.1 mg/m^3 with a skin notation (154). The OSHA PEL-TWA is 0.5 mg/m^3 with a skin notation. The NIOSH REL-TWA is 0.5 mg/m^3 with a skin notation.

Organophosphorus Compounds
Jan E. Storm, Ph.D

13.0 Ethion

13.0.1 CAS Number:

[*563-12-2*]

13.0.2 Synonyms:

O,O,O′,O′-Tetraethyl-*S,S′*-methylene di(phosphorodithioate; *O,O,O′,O′*-tetraethyl *S,S′*-methylene bis phosphorodithioate; Diethion; Ethanox; Ethiol; FMC 1240; Hylemox; Niagra 1240; Rhodiacide; Rhodocide; RP-Thion; *O,O,O,O*-tetraethyl *S,S*-methylene bisphosphorodithioate; Nialaten; Nialate (R); ethyl methylene phosphorodithioate; *O,O,O′,O′*-tetraethyl *S,S′*-methylenediphosphorodithioate; bis[S-(diethoxyphosphinothioyl)mercapto]methane; *S,S*-methylene *O,O,O′,O′*-tetraethyl phosphorodithioate; Ethion 8; phosphorodithioic acid, *S,S′*-methylene *O,O,O′O′*-tetraethyl ester; Bis (diethoxyphosphinothioylthio)methane; Embathion; Ethodan; Ethopaz; Fosfatox E; Fosfono 50; Itopaz; KWIT; methanedithiol, *S,S*-diester with *O,O*-diethyl phosphorodithioate; methylene *O,O,O′,O′*-tetraethyl phosphorodithioate; tetraethyl *S,S′*-methylene bis(phosphorodithioate)

13.0.3 Trade Names:

Nialate®; Bladan; Embathion, Ethanox Ethodan, Fosfatox E; Fosfono 50; Hylemax; Hylemox Itopax, Niagara 1240; Soprathion

13.0.4 Molecular Weight:

384.48

13.0.5 Molecular Formula:

$C_9H_{22}O_4P_2S_4$

13.0.6 Molecular Structure:

13.1 Chemical and Physical Properties

Pure ethion is a colorless liquid. Ethion emits toxic fumes of oxides of sulfur and phosphorous when heated to decomposition. It is subject to acid and base hydrolysis, and undergoes oxidation in air slowly

Specific gravity	1.220 at 20°C
Melting point	–12° to –13°C
Boiling point	decomposes above 150°C
Vapor pressure	1.5×10^{-6} mm Hg at 25°C
Solubility	slightly soluble in water; readily soluable in most organic solvents, including acetone, xylene, chloroform, and methylated naphthalene

13.1.2 Odor and Warning Properties The technical material has a very disagreeable odor.

13.2 Production and Use

Ethion is a preharvest, topical insecticide used primarily on citrus fruits, deciduous fruits, nuts, and cotton. End-use product formulations for citrus consist of emulsifiable concentrates (EC) that contained 9–82% active ingredient. Applications are made using ground boom or air blast equipment. High-pressure and low-pressure hand wands along with backpack sprayers are used for spot treatment. It is also used as a cattle dip for ticks and as a treatment for buffalo flies. Ethion is marketed as a 25% wettable powder; 2%, 3%, and 4% dusts; 5% granules; and various oil solutions and combinations with other materials (296).

13.4 Toxic Effects

13.4.1.1 Acute Toxicity Ethion is an organophosphate that has relatively high oral toxicity and oral LD_{50}s for rats of 21 to 191 mg/kg (64). Dermal LD_{50}s for rats are 62 to 838 mg/kg (Gaines 1969; 242). For rabbits, the dermal LD_{50} was 915 mg/kg (IPCS 1986). A 4-hour LC_{50} of 864 mg/m^3 for ethion in rats has been reported and in studies submitted to EPA, 4-hour LC_{50}s of 2310 mg/m^3 and 450 mg/m^3 were obtained for male and female rats, respectively (155, 296).

When goats were given single intravenous injections of 2, 5, or 10 mg/kg ethion, only those given 5 or 10 mg/kg displayed cholinergic toxicity (291). All doses decreased RBC cholinesterase activity that lasted for about 4 days and recovered by 8–10 days.

Ethion was slightly irritating to rabbit eye and skin but did not cause dermal sensitization in guinea pigs (296). In a study submitted to EPA, ethion was negative in an acute neurotoxicity test using hens (296).

13.4.1.2 Chronic and Subchronic Toxicity When dogs were given diets that contained 0.5, 2.5, 25, or 300 ppm ethion for 90 days, cholinergic toxicity and body weight gain and food consumption decreased among dogs given 300 ppm (equivalent to about 6.9 or 8.25 mg/kg/day) but not 25 ppm (about 0.71 mg/kg/day). Brain and RBC cholinesterases were inhibited at 25 and 300 ppm, respectively (296).

When rabbits were treated dermally for 21 days with 0, 1.0, 3.0, 25, or 250 mg/kg/day ethion, RBC and brain cholinesterase activity were inhibited at all doses (296). Cholinergic signs were not noted.

Erythema and desquamation at the application sites occurred at 25 and 250 mg/kg. Inhibition of brain cholinesterase was again observed when rabbits were treated dermally for 21 days with 0, 0.1, 0.25, 0.8, 1.0, 3.0, or 25 mg/kg/day (296).

13.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms About 80% of an oral dose to goats was excreted (in urine (64%), feces (14%), and milk (2%)) within 14 days and about 55% was excreted within the first 96 hours (291). Less than 5% of the dose was absorbed unchanged, consistent with the hydrolysis of organophosphate due to ruminal microflora. About 20% of a dermal dose of ethion (100 mg/kg) applied to goats was absorbed during 14 days. Following intravenous treatment of goats with 2 mg/kg ethion, unchanged ethion was rapidly eliminated (effective half-life of 2 hours) demonstrating the large role of ruminal microflor metabolism. Metabolized, ethion was distributed primarily to liver, kidney and fat. Tissue elimination was relatively fast the first 3 days but slow during the third and fourth weeks after dosing. The half life was about 2 weeks. Seventy-seven percent of the dose was recovered after 2 weeks in urine (55%) and feces (22%). At least five major metabolites were identified in the urine. Regardless of route of exposure, ethion was extensively bound to plasma proteins.

In humans given an intravenous dose of ethion, 38.4% of the dose was excreted in the urine by 5 days (66). About 15% of the administered dose was excreted in the first 12 hours, 9.5% in the second 12 hours, and 7.6% over the next 24 hour period. The elimination half-life was estimated at 14 hours. After topical administration of 4 mg/cm^2 to the forearm, about 3.3% of the applied dose was excreted by 5 days.

13.4.1.4 Reproductive and Developmental In a three-generation study in which rats were given diets that contained 2, 4, or 25 ppm ethion, no adverse effects on reproduction occurred at any dose (296). In rats given 2.0, 0.6, or 2.5 mg/kg/day ethion by gavage on gestation days 6–15, maternal toxicity (hyperactivity) and developmental toxicity (delayed ossification of pubes) occurred only at 2.5 mg/kg/day (242). In rabbits given 0, 0.6, 2.4, or 9.6 mg/kg/day ethion by gavage on gestation days 6–18, maternal toxicity (weight loss, reduced food consumption, and orange colored urine) occurred at 9.6 mg/kg/day; developmental toxicity was not observed (296).

13.4.1.5 Carcinogenesis When dogs were given diets containing 0.5, 1, 2, 20, or 100 ppm ethion (about 0.01, 0.03, 0.05, 0.5, or 2.5 mg/kg/day) for one year, cholinergic signs were not noted in any group (296). At 20 ppm, RBC cholinesterase was inhibited in females, and, at 100 ppm, both brain and RBC cholinesterase activities were (296). When rats were fed diets containing 0, 2, 4, or 40 ppm ethion (about 0.1, 0.2, and 2.0 mg/kg/day) for 24 months, the only effect was reduction in serum cholinesterase activity at 40 ppm (178). No evidence of carcinogenicity was observed. No evidence of carcinogenicity or other adverse effects occurred in mice fed diets containing 0, 0.75, 1.5, or 8.0 ppm (about 0.11, 0.22, or 1.2 mg/kg/day) ethion for 2 years (296).

13.4.1.6 Genetic and Related Cellular Effects Studies Ethion is not mutagenic. Ethion did not cause mutations in the Ames test with or without metabolic activation, did not cause chromosomal aberrations in an *in vivo* cytogenetic test in rats, did not increase unscheduled DNA synthesis in an *in vitro* test with rat hepatocytes, and did not cause mutation in a recombinant/conversion assay using *S. cerevsiae* (296). However, there is also a report that ethion was mutagenic in an *in vivo* (mouse bone marrow) and *in vitro* (Chinese hamster lung cells) micronucleus test (289) and a report that ethion induces chromosomal aberrations when administered to chicks (290).

13.4.2 Human Experience Six male adult human volunteers were given ethion via capsule according to the following sequential dosing regime: (1) 0.05 mg/kg/day for 21 days, (2) 0.075 mg/kg/day for 21 days, (3) 0.10 mg/kg/day for 21 days, (4) 0.15 mg/kg/day for 3 days, and (5) recovery for 19 days (296). RBC cholinesterase activity, averaged across subjects, was not inhibited at any dose level. Signs of overt cholinergic toxicity occurred in one subject on days 19–21 of 0.05 mg/kg/day dosing (headache, blurred vision, lightheadedness, and dizziness) and on day 1 of 0.075 mg/kg/day dosing.

Signs of overt cholinergic toxicity (partial blindness, lightheadedness) also occurred in another subject on the first day of receiving 0.075 mg/kg/day for 0.15 mg/kg/day. EPA concluded that these results suggested a cumulative effect of ethion when administered at a dose of 0.05 mg/kg/day or higher.

13.5 Standards, Regulations, or Guidelines of Exposure

Ethion has been reregistered for use by the EPA. The ACGIH TLV for ethion is 0.4 mg/m^3 with a skin notation (154). There is no OSHA PEL-TWA. The NIOSH REL-TWA is 0.4 mg/m^3 with a skin notation. Other countries generally have the same standard (Australia, Belgium, France, The Netherlands, and Switzerland).

Organophosphorus Compounds
Jan E. Storm, Ph.D

14.0 Fenamiphos

14.0.1 CAS Number:

[*22224-92-6*]

14.0.2 Synonyms:

Bay SRA 3886; Nemacur; ethyl 4-(methylthio)-*m*-tolyl isopropylphosphoramidate; Nemacur(R); (1-methylethyl)phosphoramidic acid ethyl 3-methyl-4-(methylthio)phenyl ester; isopropylphosphoramidic acid, 4-(methylthio)-m-tolyl ethyl ester; ethyl 3-methyl-4-(methylthio) phenyl (1-methylethyl)phosphoramidate; isopropylamino-*O*-ethyl-(4-methylmercapto-3-methylphenyl)phosphate; 1-(methylethyl)-*O*-ethyl-*O*-(3-methyl-4-(methylthio) phenylphosphoramidate; nemacur p; phosphoroamidic acid, isopropyl-, 4-(methylthio)-*m*-tolyl ethyl ester

14.0.3 Trade Names:

Bay SRA 3886; Nemacur®

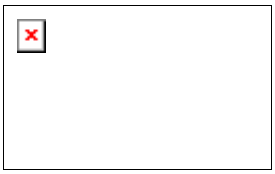
14.0.4 Molecular Weight:

303.4

14.0.5 Molecular Formula:

$C_{13}H_{22}NO_3PS$

14.0.6 Molecular Structure:



14.1 Chemical and Physical Properties

Pure fenamiphos is a colorless crystal; technical fenamiphos is an off-white to tan, waxy solid. Fenamiphos is stable under most normal use conditions but is subject to hydrolysis under alkaline conditions

Melting point	49.2°C (pure); 40°C (technical)
Density	1.15 g/cm^3 at 20°C
Vapor pressure	7.5×10^{-7} mmHg at 30°C; 4.7×10^{-5} mmHg at 20°C
Concentration in saturated air	0.001 ppm (0.01 mg/m^3) at 30°C
Solubility	soluble in most organic solvents; soluble in water (approximately

400 mg/L)

14.2 Production and Use

Fenamiphos is used as a selective nematocide and insecticide to control nematodes, thrips, beetles, aphids, and root borers on terrestrial food crops and nonfood sites (297). It is applied by a variety of methods including broadcast, row, drench, and irrigation before or at planting time or to established plantings.

14.4 Toxic Effects

14.4.1.1 Acute Toxicity Fenamiphos is a highly toxic organophosphate that has oral LD_{50}s of 2–100 mg/kg for rats, mice, rabbits, dogs, and guinea pigs (61 292–294). Analytical preparations of fenamiphos are slightly more toxic than technical preparations (295). Intraperitoneal LD_{50}s are equivalent to oral LD_{50}s indicating high oral absorption (61, 292). Dermal LD_{50}s were 72–225 mg/kg for rats and rabbits (292, 296). Rabbits dermally treated with 0, 0.5, 2.5 or 10 mg/kg/d fenamiphos for 6 h/day for 21 consecutive days showed slight erythema of abraded skin that lasted 3–6 days, and inhibition of RBC and brain cholinesterase occurred at doses of 2.5 and 10 mg/kg/day. Cholinergic effects were not reported at any dose (297).

One- and 4-hour LC_{50}s and 110–175 mg/m^3 and 91–100 mg/m^3, respectively, were reported (298). When 4-hour exposures were repeated for 5 days, the LC_{50} was >28 mg/m^3 but <100 mg/m^3, indicating a cumulative effect (299). No-effect levels for RBC cholinesterase inhibition were 28 mg/m^3 (males) and 4 mg/m^3 (females) for RBCs. Male and female rats exposed to 0.03, 0.25, or 3.5 mg/m^3 fenamiphos aerosols 6 hours/day for 5 days/week for 3 weeks showed no overt cholinergic symptoms or changes in physical appearance, behavioral patterns, body weights, hematology, clinical chemistry, urinalysis, gross pathology, or organ weights (299). RBC and brain cholinesterase were unaffected at any level.

When rats were given single oral doses of 0.4, 1.6, or 2.4 mg/kg fenamiphos, four males and one female that were given 2.4 mg/kg died within 30 minutes of dosing (300). Cholinergic effects occurred among rats given 1.6 or 2.4 mg/kg, were maximum about 25 minutes after dosing, and were relatively quickly reversed. All treatment-related effects had completely resolved by 7 days after dosing. RBC cholinesterase activities were inhibited among rats given 1.6 or 2.4 mg/kg, and brain cholinesterase was not affected in any group.

There was no evidence of delayed neurotoxicity in atropinized hens that were treated with single doses of 12.5 mg/kg fenamiphos, in atropinized hens treated with 25 mg/kg twice at an interval of 3 weeks, or, in unprotected hens treated with up to 50.0 mg/kg and observed for 21 days (301).

Fenamiphos was only slightly irritating (caused mild erythema) when applied to skin of rabbits and was mildly irritating to the eye of rabbits (297). Fenamiphos did not cause either contact dermatitis or “tuberculin type allergy” in a guinea pig sensitization study (302).

14.4.1.2 Chronic and Subchronic Toxicity Repeated intraperitoneal injections of 1 mg/kg/day fenamiphos for 60 days caused no mortality in rats, although brain and tissue cholinesterase activity was inhibited (198). Administration of 2 mg/kg/day fenamiphos for 60 days resulted in 40% and 100% mortality by 30 and 60 days, respectively, as well as significant brain and tissue cholinesterase inhibition.

No cholinergic signs or decreases in brain or RBC cholinesterase activity occurred in rats given diets that contained fenamiphos at 0, 0.36, 0.60, or 1.0 ppm for 14 weeks (approximately 0.02, 0.03, or 0.05 mg/kg/day) (297). When rats were given fenamiphos via diets that contained 0, 4, 8, 16, or 32 ppm (about 0.2, 0.4, 0.8, and 1.6 mg/kg/day) for 90 days, cholinergic signs occurred in rats given only the 32-ppm diet (297). RBC cholinesterase was inhibited in rats given 8 ppm or more. When rats were fed diets that contained 0, 1, 10, or 50 ppm fenamiphos (equivalent to about 0, 0.1, 0.7,

3.3–4.0 mg/kg/day) for 13–14 weeks, treatment-related cholinergic signs (muscle fasciculations) occurred only in high-dose females during weeks 1–3; no cholinergic signs occurred in males (303). There were no adverse ophthalmic findings. Decreases in RBC cholinesterase activity occurred in the 10- and 50-ppm group in males and in all treated groups in females, were evident at 4 weeks, and, remained at about the same level for 13 weeks. A no-observed-effect level for RBC cholinesterase inhibition extrapolated from the data was 0.4 ppm for females (approximately 0.032 mg/kg/day). No effect on brain cholinesterase was observed.

When dogs were given diets that contained 18 ppm or more for 3 months, overt cholinergic toxicity occurred (303a). No adverse effects were observed at dietary levels of 16 ppm or less (equal to about 0.45 mg/kg/day). RBC cholinesterase was inhibited in dogs fed diets that contained 2 (females only), 5 (females only), 6, 10, or 18 ppm. No adverse effects of any kind and no inhibition of RBC cholinesterase occurred in dogs given diets that contained 0 or 0.5 ppm fenamiphos for six months (equivalent to 0 and 0.01–0.02 mg/kg/day) or in dogs given diets that contained up to 1.7 ppm fenamiphos (equivalent to 0.04 mg/kg/day) for 100 days (304, 305).

14.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms About 93–95% of an oral dose of fenamiphos was absorbed by rats and excreted by 12–15 hours after treatment (309). Forty-eight hours later, residues in tissues were greatest in liver and kidney; less in fat, gastrointestinal tract, and heart; and minimal in brain and muscle. Similar results were obtained in a whole body autoradiographic study of rats treated orally with fenamiphos which showed that oral absorption was virtually complete, distribution volume was low, and excretion was rapid and nearly complete by 8 hours after dosing (310). Pretreatment of rats for 14 days before treatment with fenamiphos did not alter absorption, distribution, or elimination patterns. Distribution following oral doses was rapid in brain, and plasma and concentrations in brain exceeded concentrations in plasma by about 1.3-fold to twofold (311). Concentrations in brain and plasma were highest 0.5 hours after dosing and declined; a and b half-lives in the brain were 2 and 100 hours, respectively, and a and b half-lives in plasma were 17.5 and 212 hours, respectively. Oral absorption of fenamiphos sulfoxide was equally rapid in pigs and reached maximum blood concentrations 2 hours after a 0.9-mg/kg dose (312). Fifty-seven percent of the administered dose was excreted within 5 hours and 90% was recovered after 48 hours. Tissue residues were minimal; only liver and kidney contained residues >0.1 ppm.

In vitro dermal absorption of fenamiphos by human and rat skin accounted for 0.42–9.95% of the applied dose and was 2.07 ± 0.33 mg/cm^2/h (human) and 3.15 ± 0.40 mg/cm^2/h (rat) (313). Dermal absorption of a granular formulation was considerably less (0.01–0.03 mg/cm^2/h) and dermal absorption of a liquid formulation was considerably more (13.0 ± 1.87 mg/cm^2/h (human) and 49.0 ± 2.69 mg/cm^2/h (rat) during 24 hours.

The major metabolic pathway for fenamiphos is oxidation and formation of the sulfoxide and sulfone analogs. Loss of the isopropyl and probably the isopropyl amine moieties are also likely. Subsequent hydrolysis, conjugation, and excretion in urine gives nonorganosoluble compounds whose molecular weights are 400–800. Rats treated intravenously or orally with fenamiphos excreted fenamiphos phenols in different stages of oxidation at the sulfur atom and their respective sulfuric acid conjugates (276).

In pigs given fenamiphos sulfoxide orally, excreted metabolites were primarily conjugated phenols of the sulfoxide and sulfone. The metabolic pathway was hydrolysis and/or oxidation followed by conjugation.

14.4.1.4 Reproductive and Developmental No treatment-related endocrine effects, reproductive effects, or clinical signs occurred in adults or pups given diets that contained 0, 2.5, 10, and 40 ppm fenamiphos (about 0, 0.2, 0.6–0.7, and 2.8–3.2 mg/kg/day) for two generations. Among rats fed the 40-ppm diet, F1 pups experienced decreased body weight gain during lactation, F0 and F1 females had lower body weights during lactation, terminal body weights significantly decreased in adult rats,

and absolute and relative ovary weights significantly decreased. RBC cholinesterase was significantly inhibited in adult rats fed the 10-ppm diet and in 4 day old pups fed the 10-ppm diet. Brain cholinesterase was significantly inhibited in adult rats fed the 40-ppm diet but was not inhibited in 4- or 21-day-old pups fed any dietary concentration. No adverse reproductive outcomes occurred in rats given diets that contained 0, 3, 10, or 30 ppm fenamiphos (equivalent to about 0, 0.15, 1.0, and 1.5 mg/kg/day) (276). Reduced body weight gain occurred only in the F2b generation males of the 30-ppm group.

No adverse developmental outcomes occurred among offspring of rats given fenamiphos at dose levels of 0, 0.3, 1.0, and 3.0 mg/kg by gavage on gestation days 6 through 15 (276). Dams in the 3-mg/kg group exhibited cholinergic signs of toxicity within 30 minutes after dosing, and two dams in this group died. No treatment-related maternal effect were seen at lower doses.

Fenamiphos was not fetotoxic or embryotoxic at any dose in rabbits treated orally on gestation day 6–18 with 0.1, 0.3 or 1.0 mg/kg/day fenamiphos (242). However, chain fusion of sternebra was found in five fetuses in the 1.0-mg/kg/day group and was higher than controls. The authors concluded that this may have been a treatment-related abnormality. When rabbits were given 0, 0.1, 0.5, and 2.5 mg/kg/day fenamiphos by gavage on gestation days 6–18, neither visible nor measurable treatment-induced effects were observed in dams given 0.1 or 0.5 mg/kg day (276). However, 2.5 mg/kg/day produced frank maternal toxicity, evidenced by four treatment-induced deaths, decreased body weight gains, and decreased food consumption. There were no treatment-related effects in mean numbers of corpora lutea; in numbers of live or dead fetuses, litter size, or sex ratio, or in the numbers of live or resorbed fetuses. However, preimplantation loss was elevated in the 2.5-mg/kg/day group, and, in addition, the mean live pup weight was slightly reduced. Except for one malformation observed in the high-dose group, no other fetal visceral anomalies were observed.

14.4.1.5 Carcinogenesis There was no evidence of carcinogenicity or adverse effects of any kind in dogs given a diet that contained 0.5, 1, 2, 5, and 10 ppm fenamiphos for 2 years (about 0.01, 0.025, 0.05, 0.125, or 0.250 mg/kg/day), although RBC cholinesterase activities were inhibited at 2 ppm (312a). When dogs were fed diets that contained 1, 3, or 12 ppm fenamiphos (about 0, 0.030, 0.08, and 0.3 mg/kg/day), no adverse effects of any kind occurred, except for mild anemia (decreased RBC counts, hemoglobin, hematocrit) among dogs given the 12-ppm diet (304). RBC cholinesterase activity was inhibited in dogs given 3- or 12-ppm diets, and brain cholinesterase activity was inhibited in dogs given 12-ppm diets.

There was no evidence of carcinogenic effect in rats maintained on a diet that contained 3, 10, or 30 ppm fenamiphos for two years (about 0.2, 0.67, and 2.0 mg/kg/day) (306). In the 30-ppm group, mild symptoms that reflected cholinergic toxicity were observed temporarily, and mortality in female rats increased slightly. The 3-and 10-ppm diets did not cause evident adverse effects of any kind. There was no evidence of carcinogenicity or ophthalmologic effects in rats fed diets that contained 0, 2, 10, or 50 ppm fenamiphos for 2 years (equivalent to about 0, 0.1, 0.5–0.6, or 2.4–3.4 mg/kg/day) (307). RBC cholinesterase was significantly inhibited in the 10- and 50-ppm groups. Brain cholinesterase was marginally inhibited in the 50-ppm group. Females that consumed the 50-ppm diet exhibited an increase of rough coats and alopecia “associated with stress due to severe cholinesterase inhibition” (*sic*). No other compound-related effect occurred.

There was no evidence of carcinogenicity or other adverse effect in mice given diets that contained 0, 2, 10, or 50 ppm fenamiphos for 20 months (equivalent to doses of about 0, 0.2, 1.0, and 5.0 mg/kg/day), except that mice that received 50 ppm had reduced body and organ weights, and absolute brain weights decreased at 2 ppm or more (147).

14.4.1.6 Genetic and Related Cellular Effects Studies Fenamiphos was negative in Ames tests using *S. typhimurium* with and without metabolic activation, and negative in a preincubation reverse mutation test with a tryptophan mutant strain of *E. coli* with and without mammalian metabolic activation (276). In a forward mutation assay using Chinese hamster cells (CHO), fenamiphos

induced an increase in the mutant frequency in an initial test conducted without metabolic activation. However, the response was not dose-dependent and could not be reproduced in two subsequent repeat assays. Therefore, the authors concluded that fenamiphos is not mutagenic in the CHO/HGRPT forward mutation assay. Fenamiphos did not induce an increase of sister chromatid exchange in Chinese hamster V-79 cells (308).

In a micronucleus test, there was no evidence of any mutagenic effect of fenamiphos. Nor was there any deleterious influence on erythrocyte formation as measured by the ratio of polychromatic to normochromatic erythrocytes. Fenamiphos did not have a mutagenic effect in a dominant lethal test using mice (276).

Increased chromosomal aberration rate was observed in cultures of human lymphocytes, but only in the cytotoxic range. Therefore, this evidence of mutagenicity is considered equivocal (276).

14.4.2 Human Experience No published reports of human poisonings as a result of fenamiphos exposure were identified. However, the EPA noted that "fenamiphos has been implicated in a handler poisoning incident which resulted in hospitalizing the worker" (276).

Potential inhalation and dermal exposures to fenamiphos were estimated over 2 to 4-hour periods for six mixer-loaders or applicators involved in treating agricultural soil (1 lb a.i./acre). Inhalation exposures (measured using personal air pumps attached to the collar) were less than the detectable level of 0.001 mg/h; dermal exposures (measured using cloth patches and by collecting hand wash water) were substantially higher and ranged from about 93 to 667 mg/h (314).

14.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV for fenamiphos is 0.1 mg/m^3 with a skin notation (154). There is no OSHA PEL-TWA for fenamiphos. The NIOSH REL-TWA is 0.1 mg/m^3 with a skin notation. Most other countries also have an Occupational Exposure Limit of 0.1 mg/m^3 with a skin notation (Australia, Belgium, Denmark, France, The Netherlands, and Switzerland).

Organophosphorus Compounds
Jan E. Storm, Ph.D

15.0 Fensulfothion
15.0.1 CAS Number:
[*115-90-2*]
15.0.2 Synonyms:
(*O*,*O*-Diethyl-*O*-4(methylsulfinyl)phenyl)-phosphorothioate Dasanit; Bay 25141; S767; phosphorothioic acid *O*,*O*-diethyl *O*-[methylsulfinyl)phenyl] ester; Dansanit; Fonsulfothion; Terracur P; Daconit; Agricur; Chemagro 25141; diethyl *O*-(4-(methylsulfinyl)phenyl) phosphorothioate; DMSP; phenol, p-(methylsulfinyl)-, *O*-ester with *O*,*O*-diethyl phosphorothioate
15.0.3 Trade Names:
Dasanit®; Terracur R®
15.0.4 Molecular Weight:
308.35
15.0.5 Molecular Formula:
$C_{11}H_{17}O_4PS_2$
15.0.6 Molecular Structure:

15.1 Chemical and Physical Properties

Fensulfothion is a yellow, oily liquid. Fensulfothion is oxidized readily to the sulfone and apparently isomerizes readily to the *S*-ethyl isomer

Specific gravity	1.202 at 20°C
Boiling point	138–141°C at 0.01 mmHg
Solubility	soluble in most organic solvents except aliphatics; slightly soluble in water (approximately 160 mg/100 mL)

15.2 Production and Use

Fensulfothion was introduced in 1957 as a systemic and contact insecticide and nematicide for use against free living and root knot nematodes. Until 1990 when its manufacture and use was discontinued, it was available as an emulsifiable concentrate, a wettable powder, a dust, and as granules (1, 155).

15.4 Toxic Effects

15.4.1.1 Acute Toxicity Fensulfothion is an organophosphate compound that has high oral toxicity and oral LD_{50}s are 1.8–10.2 mg/kg for rats (64a, 315). Intraperitoneal LD_{50}s are 1.5–5.5 mg/kg, indicating that fensulfothion is well absorbed from the gastrointestinal tract. Dermal LD_{50}s are 3.5–30.0 mg/kg (64a, 315). A 1-hour LC_{50} of 113 mg/m^3 and a 4-hour LC_{50} of 29.5 mg/m^3 were reported for rats (123). Following either oral or intraperitoneal doses, the onset of poisoning is rapid, and symptoms appear within 15 minutes, although death may be delayed. When lethal doses were given, death usually occurred within 2 hours, but after sublethal doses, the symptoms often persisted for 3 or 4 days (315).

Fensulfothion may have potentiating characteristics. An ordinarily harmless dose (550 mg/kg) of the anesthetic tricaine caused loss of righting ability in all rats and 20% mortality when it was given 1 hour after administering 2.5 mg/kg fensulfothion, a dose that inhibited carboxylesterase(s) but had no overt toxic effect (316a).

Fensulfothion did not produce neurotoxicity when given orally or intraperitoneally at doses up to 50 mg/kg to chickens protected by atropine and 2-PAM (1).

15.4.1.2 Chronic and Subchronic Toxicity When rats were given 0.25, 0.5, or 0.75 mg/kg/day fensulfothion via intraperitoneal injection for up to 60 days, all rats given 0.75 mg/kg died within 5 days, 1 of 5 rats given 0.5 mg/kg died by day 60, and no rats given 0.25 mg/kg died within 60 days (315).

15.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Fensulfothion is well absorbed orally as reflected by the similarity of oral and intraperitoneal LD_{50}s.

Based on findings for other phosphorothioates, it can be concluded that fensulfothion undergoes desulfuration to the corresponding oxygen analog to exert an anticholinesterase action (315). Indeed, the intraperitoneal LD_{50} of the oxygen analog in female rats was 1.2 mg/kg, equivalent to the 1.5 mg/kg observed for the parent compound. The thioether linkage of fensulfothion may also undergo oxidation to the sulfone derivative. The intraperitoneal LD_{50} of the oxygen analog sulfone was 0.9 mg/kg in female rats.

15.4.1.4 Reproductive and Developmental Some female mice given a diet that contained 5 ppm fensulfothion died before mating (316). There was no effect on reproduction, gestation, or the lactation index of the survivors, except a slight reduction in the lactation index of third-generation pups. A level of 1 ppm had no effect. A slight nonsignificant increase of minor skeletal abnormalities occurred in rabbits that received fensulfothion during pregnancy at 0.10 mg/kg/day; no effect occurred on 0.05 mg/kg/day (316).

15.4.1.5 Carcinogenesis When rats were provided diets that contained 1, 5, or 20 ppm fensulfothion, mortality increased in male rats given the 5- and 20-ppm diets, and body weight gain was depressed in both sexes given the 20-ppm diet (316). Plasma, RBC, and brain cholinesterase activities in females were “detectably” (*sic*) inhibited in rats given the 1-ppm diet (about 0.053 mg/kg/day).

When dogs were provided diets that contained 1, 2, or 5 ppm fensulfothion for 2 years, reduced food consumption, severe weight loss, and signs of cholinergic poisoning were initially evident in dogs given the 5-ppm diet, although food consumption increased and lost body weight was regained after the second month (316). Slight, temporary cholinergic effects and a slight reduction of cholinesterase (*sic*) occurred in dogs provided the 2-ppm diet, but not the 1-ppm diet (316).

15.4.1.6 Genetic and Related Cellular Effects Studies Fensulfothion did not increase the incidence of sister chromatid exchanges in V79 cells, nor did it induce cell cycle delay (308).

15.4.2 Human Experience 15.4.2.2 Clinical Cases Fensulfothion caused death by the following morning of a 34-year-old farmer who had applied fensulfothion to potato plants during the day. Autopsy indicated that death was due to pulmonary edema and blood cholinesterase activity which was far below normal (1). Death also occurred to a 5-year-old child who resided in a home 6 days after about 12,000 mg of fensulfothion was applied to about 10 m^2 of surface in two rooms (1). Other members of the family suffered nausea, vomiting, disorientation, diarrhea, and abdominal pain. Combined dermal and oral exposure led to severe poisoning characterized first by vomiting and weakness and by coma the next morning for a 7-year-old girl who had been playing with an empty fensulfothion container (1).

Fensulfothion poisoning from its accidental ingestion was recently reported in a family of four (317). Fensulfothion was misidentified as pepper and applied to the family's fish dinner. Shortly after the meal family members experienced nausea, vomiting, abdominal pain, and weakness. Two members had bradycardia, hypotension, and seizures. They were treated with atropine, artificially ventilated, and eventually recovered.

15.5 Standards, Regulations, or Guidelines of Exposure

Fensulfothion is not registered for use in the U.S. (145). The ACGIH TLV for fensulfothion is 0.1 mg/m^3 (154). There is no OSHA PEL-TWA. The NIOSH REL-TWA for fensulfothion is 0.1 mg/m^3. Most other countries also have an OEL of 0.1 mg/m^3 with a skin notation for fensulfothion (Australia, Belgium, France, The Netherlands, and Switzerland).

Organophosphorus Compounds
Jan E. Storm, Ph.D

16.0 Fenthion
16.0.1 CAS Number:
[*55-38-9*]
16.0.2 Synonyms:
O,*O*-dimethyl *O*-4-(methylmercapto)-3-methylthio)-*O*-ester with *O*,*O*-dimethyl phosphorothiate, phosphorothioic acid *O*,*O*-dimethyl *O*-(3-methyl-4(methylthio)phenyl)ester; Baycid; Baytex; Entex;

Lebayeid; Queletox; Spotten; Talodex; Tiguvon; Lebaycid; *O*,*O*-dimethyl-*O*-[4-(methylthio)-*m*-tolyl] phosphorothioate; *O*,*O*-dimethyl *O*-(4-methylmercapto-3-methylphenyl) thionophosphate; *O*,*O*-dimethyl *O*-(3-methyl-4-methylthiophenyl) thiophosphate; *O*,*O*-dimethyl O-(4-methylthio-3-methylphenyl) thiophosphate; phosphotothioic acid *O*,*O*-dimethyl *O*[3-methyl-4-(methylthio)phenyl] ester; phosphorothioic acid *O*,*O*-dimethyl *O*-(4-methylthio)-*m*-tolyl ester; b 29493; bay 29493; bayer 9007; bayer 29493; bayer s-1752; *m*-cresol, 4-(methylthio)-, *O*-ester with *O*,*O*-dimethyl phosphorothioate; *O*,*O*-dimethyl *O*-4-(methylmercapto)-3-methylphenyl phosphorothioate; *O*,*O*-dimethyl *O*-3-methyl-4-methylthiophenyl phosphorothioate; DMTP; MPP; OMS 2; S 1752; spotton; Mosquitocide 700; Rid-a-Bird; BX-1; BX-2; cresol, 4-(methylthio)-, *O*-ester with *O*,*O*-dimethyl phosphorothioate; dimethyl (3-methyl-4-(methylthio) phenyl) phosphorothionate; dimethyl methylthiotolyl phosphorothioate; dimethyl *O*-((4-methylmercapto)-3-methylphenyl) thionophosphate; dimethyl *O*-(3-methyl-4-(methylthio)phenyl) thiophosphate; dimethyl *O*-(4-(methylthio)-*m*-tolyl) phosphorothioate; Mercaptofos; Thiophos; 4-methylmercapto-3-methylphenyl dimethyl thiophosphate

16.0.3 Trade Names:

Baycid; Baytex® Entex® Lebaycid; Tiguvon

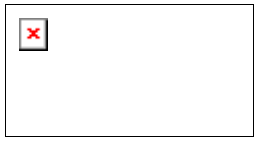
16.0.4 Molecular Weight:

278.34

16.0.5 Molecular Formula:

$C_{10}H_{15}O_3PS_2$

16.0.6 Molecular Structure:



16.1 Chemical and Physical Properties

Fenthion is a yellow to tan, oily liquid

Specific gravity	1.250 at 20°C
Melting point	7.5°C
Bioling point	87°C at 0.01 mmHg (pure); 105°C at 0.01 mmHg (commercial grade)
Vapor pressure	3×10^{-5} torr at 20°C; (technical) 2.1×10^{-6} mmHg at 20°C)
Solubility	soluble in organic solvents; nearly insoluble in water (56 mg/L)

16.1.2 Odor and Warning Properties Fenthion has a slight garlic odor.

16.2 Production and Use

Fenthion is used primarily for livestock dermal treatments and mosquito control in residential areas. Direct dermal treatments to livestock are by spot treatment and pour-on treatment; ear tags are used for dairy and beef cattle. Mosquito control (adulticide) applications are to residential areas in Florida by ultra low volume spray (aerial and ground application) and by thermal fog (ground application) (317a).

16.4 Toxic Effects

16.4.1.1 Acute Toxicity Fenthion is an organophosphate compound that has moderate oral toxicity and oral LD_{50}s of 215 to 615 mg/kg for rats, mice, and rabbits (64a, 317a). Deaths occurred 1–4 days postdosing (315, 318). Dermal LD_{50}s are 330–963 mg/kg for rats and rabbits (45, 64, 318, 319). Deaths occurred 2–5 days postdosing. The signs of poisoning following oral or dermal exposure develop over a period of hours but then persist for several days (318, 320).

One-hour exposure to 243 mg/m^3 fenthion caused no mortality in mice, but 20 and 40% mortality in

female and male rats, respectively. One-hour LC_{50}s for rats range from, >1125 to 2400 mg/m^3, and, 4-hour LC_{50}s range from 454–2400 mg/m^3 (123, 321). When 4-hour exposures were repeated for 5 days, the LC_{50} was reduced to approximately 212 mg/m^3 for males and to between 55 and 212 mg/m^3 for females (321). Acute exposures of 209 mg/m^3 resulted in deaths in 2/20 female rats and ataxia and tremors in both sexes (322, 323).

Lethal doses of fenthion, when given in fractions on successive days, are lower than they are when given as a single dose, indicating cumulative toxicity. There was 75% mortality in female rats given 50 mg/kg via gavage for 5 days (about one tenth the LD_{50}) and 100% mortality in female rats given 100 mg/kg for 5 days (about one sixth the LD_{50}) (318). The dermal LD_{50} for a dose applied on 5 consecutive days was 73 mg/kg/day, whereas the single-dose dermal LD_{50} was 500 mg/kg. Daily intraperitoneal doses of 10 mg/kg for 60 days caused no mortality, but doses of 20 mg/kg caused 80% mortality by 30 days, doses of 40 or 50 mg/kg caused 100% mortality by 10 days, and, a dose of 100 mg/kg caused 100% mortality by 5 days (315).

When rats were given single oral doses of 0, 20, 75, or 150 mg/kg fenthion, cholinergic signs occurred in all groups that peaked at 1.5 hours and persisted for at least 24 hours (324). When rats were given single oral dose of 0, 1, 50, or 125 mg/kg (males) and 0, 1, 75, and 225 mg/kg (females) fenthion, clinical signs of acute cholinergic toxicity occurred in mid- and high-dose rats of both sexes (325). RBC and brain cholinesterase activities were inhibited in the mid- and high-dose males and in the low-, mid- and high-dose females. A no-effect level for RBC cholinesterase of 0.7 mg/kg was derived from these data.

Dogs given a single oral dose of 220 mg/kg fenthion exhibited cholinergic signs, that disappeared by 5 days after dosing (326). RBC cholinesterase was inhibited 20 minutes after exposure, increased to pre-exposure levels by 3–12 hours after exposure, but then decreased again below control levels from 24 hours to 30 days after dosing.

One of the relatively unique toxic effects associated with fenthion is acute ocular toxicity (327). Four days after single intramuscular doses of 0.005, 0.05, 0.5, or 5.0 mg/kg fenthion, electroretinograms (ERG) in rats were supernormal (*sic*) 4 days after a dose of 25 mg/kg, the ERG was normal; and 4 days after a 100-mg/kg dose, the ERG was subnormal (327–329). Retinal acetylcholinesterase was unaffected 4 days after 0.005- or 0.05-mg/kg doses but decreased after doses of 0.5–100 mg/kg (327–329). Further study indicated that supernormal ERG changes associated with 5 mg/kg peaked at 10 days and returned to normal by two months, supernormal ERG changes associated with 25 mg/kg peaked at four days then became subnormal and recovered by two months, and ERGs associated with 50 mg/kg remained subnormal for at least 66 days (327). Single acute intraperitoneal doses of 100 mg/kg fenthion were associated with retinotoxicity and characterized by inhibition of retinal cholinesterase and temporary down-regulation of muscarinic receptors in the retina (330).

Fenthion is not considered as an eye or dermal irritant and does not cause dermal sensitization (317a).

16.4.1.2 Chronic and Subchronic Toxicity Rats fed a daily diet that contained 300 ppm fenthion for approximately 30 days showed symptoms of organophosphate intoxication (331). When rats were given diets that contained 5, 10, 20, or 250 ppm fenthion (equivalent to daily doses of about 3, 5–6, 11–12, and 100–138 mg/kg/day) for 4 weeks, symptoms of cholinergic poisoning were mild and transient and occurred only in the 250-ppm group (318). Brain cholinesterase activities in rats from all groups were significantly inhibited. Among rats fed 0.25, 0.5, 2.5, or 5.0 mg/kg/day fenthion for 12 weeks, cholinergic signs occurred in those fed 2.5 or 5 mg/kg (331a). RBC cholinesterase activity was significantly inhibited in rats fed 0.5 mg/kg or more, and tissue cholinesterase (heart, liver) was significantly inhibited in female rats fed 0.25 mg/kg/day or more and male rats fed 0.50 mg/kg/day

or more. when rats were fed diets that contained 0, 2, 25, or 125 ppm fenthion for 13 weeks (equivalent to 0, 0.13–0.17, 1.6–2.2, and 8.5–12.6 mg/kg/day, clinical cholinergic signs and a dose-related decrease in RBC and brain cholinesterase activities occurred in rats given the 25- or 125-ppm diet (317a). There were no treatment-related opthalmologic findings. When mice were fed diets that contained 0, 50, and 100 ppm fenthion for approximately (*sic*) 5 weeks, no cholinergic signs were observed in any group, but marked RBC and brain cholinesterase inhibition occurred in mice at all treatment levels (333).

When rats were exposed to 0, 1, 3, or 16 mg/m^3 fenthion aerosol for 6 h/day, 5 days/week for 3 weeks, females in the two higher group exhibited behavioral disturbances (*sic*) (334). Male rats tolerated these exposures without clinical symptoms. RBC and brain cholinesterase activity were inhibited in both sexes at 3 mg/m^3.

When rabbits were dermally treated with 5, 50, or 100 mg/kg fenthion for 6 h/day, 5 days/week for 3 weeks, no cholinergic effects occurred (317a). Inhibition of RBC cholinesterase in males and inhibition of brain cholinesterase in females occurred only at the highest dose. Dermal treatment of rabbits with 150 mg/kg according to the same paradigm caused cholinergic signs and significant RBC and brain cholinesterase inhibition (317a). When shaved (one-half abraded) rabbits were dermally treated with 5 or 25 mg/kg fenthion applied as a dilute solution in Cremophor for 21 days, RBC and brain acetylcholinesterase were inhibited at 5 mg/kg/day (317a).

16.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Fenthion is quickly absorbed in the digestive tract, and lung, and skin and is hydrolyzed either unchanged or after enzymatic oxidation. Elimination occurs via urine and feces within 3 days. In lactating cows, fenthion was readily distributed to and eliminated in milk (350).

Peak concentrations of fenthion in milk occurred 18 or 8 hours after dermal or intramuscular exposure, respectively, and by 14–20 days after treatment accounted for 1.1% and 2.2% of the dermal or intramuscular dose, respectively. Fenthion was rapidly degraded and eliminated primarily in the urine. Following topical administration of fenthion of lactating cows, 45–55% was excreted in urine, 2–2.5% was eliminated in feces, and 1.5–2% was eliminated in milk during a period of 4 weeks (350). EPA estimated that dermal absorption would be about 20% of an applied dose (317a) based on a comparison between cholinesterase inhibition no-effect levels in rabbits treated dermally or orally which were 1 mg/kg/day and 5 mg/kg/day, respectively.

The delayed and prolonged effect from a single dose of fenthion suggests that a large portion of a dose is stored and then slowly released to be metabolized (318). Fenthion (and/or fenthion metabolites) is lipid-soluble, and there is evidence that it readily accumulates in the body. In a postmortem analysis following ingestion of fenthion, greater concentrations of fenthion were detected in human organs and fat than in blood (351).

It has been proposed that the sulfoxide and sulfone of the thioether of *fenthion* are produced before P□S to P□O oxidation takes place (352, 353). Both of these compounds given orally to rats are more toxic than fenthion itself, and their effects occur more rapidly than after fenthion. However, neither compound actively inhibits acetylcholinesterase, so presumably these compounds are oxygenated to forms that readily inhibit acetylcholinesterase (318).

16.4.1.4 Reproductive and Developmental Decreased epididymal weight, decreased fertility, increased maternal weight gain during premating, decreased weight gain during gestation, decreased pup weight gain during lactation, and inhibition of brain acetylcholinesterase occurred in rats given a diet containing 100 ppm fenthion (about 5 mg/kg/day) for two generations (317a). Cytoplasmic vacuolation of the epithelial ductal cells of the epididymis and inhibition of RBC acetylcholinesterase occurred in parents and offspring fed 14 ppm (about 0.7 mg/kg/day). Diets that contained 1 or 2 ppm fenthion had no adverse reproductive effect. When mice were given water that

contained 60 ppm fenthion (delivering doses of between 9.5–10.5 mg/kg) for five generations, there was no consistent effect on mating success, although treated mice exhibited longer periods to produce first litters in the first three generations and pup survival and growth decreased in the second, third, and fourth generations (254).

A slightly higher rate of resorptions occurred among rats given 18 mg/kg/day fenthion by gavage on gestation days 6–16 (317a). Adverse developmental effects did not occur in rats given 1 or 4.2 mg/kg/day. Cholinergic signs and decreases in body weight gain also occurred in the 18-mg/kg/day dosed pregnant rats. RBC and brain acetylcholinesterase were inhibited at 1 mg/kg/day and higher. Fetal brain acetylcholinesterase was also inhibited in the high-dose group at day 20. In rabbits given 0, 1, 2.75, or 7.5 mg/kg/day fenthion by gavage on gestation days 6 through 18, a slight increase in resorptions occurred in the 2.75- and 7.5-mg/kg/group, and increases in unossified metacarpals occurred in the 7.5-mg/kg/day group. Dams exhibited "soft stools" at 2.75 mg/kg/day, a weight gain decrease at 7.5 mg/kg/day, and inhibition of brain and RBC acetylcholinesterase at both 2.75 and 7.5 mg/kg/day (317a).

16.4.1.5 Carcinogenesis There was no cholinergic toxicity, lens opacification, clinical chemistry effects, or hematotoxicity among rhesus monkeys that received a daily oral dose of 0.02, 0.07, or 0.2 mg/kg via corn oil gavage for 2 years (317a). However, RBC acetylcholinesterase had a threshold for inhibition at 0.07 mg/kg/day (frequent inhibition at this level up to 39% for the first 3 months of the study). More consistent inhibition was noted at 0.20 mg/kg/day.

When dogs were fed diets containing 0, 2, 5, or 50 ppm fenthion (equivalent to about 0.06, 0.3, and 1.2 mg/kg/day) for 1 year, no signs of cholinergic toxicity occurred at any dose, although the 50-ppm dose caused marked inhibition of RBC and brain cholinesterase (335). No carcinogenicity or other toxicity occurred among dogs given diets containing 0, 3, or 10 ppm fenthion for 104 weeks or among dogs given diets that contained 30 ppm from week 1 to week 64, 60 ppm from week 65 to week 67, and 60 ppm from week 68 to week 104 (317a). However, RBC cholinesterase was inhibited at 10 ppm and higher in males and at 30 ppm and higher in females; brain cholinesterase was inhibited at 30 and 60 ppm. No cholinergic signs, tumors, or other toxicity occurred in dogs given diets that contained 0, 2, 10, or 50 ppm fenthion for 1 year (336). RBC cholinesterase activity was inhibited at 10 or 50 ppm, and brain cholinesterase was inhibited at 50 ppm.

When rats were fed diets that contained 0, 2, 3, 5, 25, or 100 ppm for 1 year, the 100-ppm diet caused decreases in body weight gain, increased mortality and inhibition of RBC, brain and submaxillary gland cholinesterase; the 25-ppm diet increased mortality in female rats and inhibition of RBC, brain, and submaxillary gland cholinesterase; the 5-ppm diet inhibited RBC cholinesterase; and the 3-ppm diet had no effect (335). No gross or microscopic lesions were observed in any group hemosiderosis in the spleen of rats fed 100 ppm. No carcinogenicity, cholinergic toxicity, hematoxicity, or alterations in clinical chemistry occurred in rats given diets that contained 3, 15, or 75 ppm fenthion (about 0.2, 1.0, or 5.0 mg/kg/day) for 24 months (586). However, the 75-ppm diet decreased body weight gain in males and slightly increased mortality in both sexes, and the 15-and 75-ppm diets significantly inhibited RBC cholinesterase in both sexes. There was no evidence of carcinogenicity in rats fed diets that contained 5, 20, or 100 ppm fenthion (about 0, 0.02–0.03, 0.8–1.3, and 5.2–7.3 mg/kg/day) for 2 years (336). However, clinical cholinergic signs, retinal degeneration, and posterior subcapsular cataract formation were observed in the 100-ppm groups; and electroretinograms were flat or suppressed in females given the 20- or 100-ppm diet. Significant RBC and brain acetylcholinesterase inhibition occurred at 5 ppm.

Subnormal ERGs occurred by 3 months and disappeared completely by 1 year among rats injected subcutaneously with 50 mg/kg fenthion once every 4 days for 1 year. Significant histopathology was evident in the retina that included disappearance of the retinal pigmentary epithelial layer, the outer nodes, inner nodes and outer granular layer, and photoreceptor cells (327, 328, 329, 337). ERGs were also extinguished and retinal degeneration was extensive in rats treated subcutaneously with 50 mg/kg twice a week for 1 year (327).

There was no evidence of carcinogenicity in rats or in female mice given fenthion in the diet at 10 or 20 ppm for 103 weeks and then observed for 0–2 additional weeks (338). Doses were 0.49 and 0.98 mg/kg/day for rats and 1.3 and 2.6 mg/kg/day for mice. Some cholinergic signs were noted at both doses in rats and mice. No evidence of carcinogenicity, cholinergic toxicity, hematotoxicity, or other toxicity was seen in mice given diets that contained 0, 0.09, 0.9, 4.6, or 25 ppm fenthion (equivalent to 0, 0.03, 0.4–0.5, 1.95–2.25, and 9.42–10.23 mg/kg/day) for 102 weeks (317a). RBC and brain cholinesterase inhibition was significant at a dietary level of 25 ppm.

16.4.1.6 Genetic and Related Cellular Effects Studies *In vitro* tests of fenthion (339–342) and *in vivo* tests in mice (343, 344) showed no mutagenic effect of fenthion. Fenthion was negative in the dominant lethal mutation assay in male mice (345, 346) and negative or weakly clastogenic at acutely toxic doses in the mouse micronucleus test (347). Among rats treated with two oral doses of 54 mg/kg fenthion (one-fourth LD_{50}) 21 hours apart, there was a fivefold increase in hepatic and brain lipid peroxidation and a 3.5-fold increase in hepatic single-strand DNA breaks (348). Increased numbers of single chromatid gaps and breaks were detected in human lymphocytes incubated in variable concentrations of 98% technical grade fenthion (349).

16.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization Fenthion caused neurotoxicity that lasted from 3 to 10 days when given subcutaneously at a dose of 25 mg/kg to atropinized chickens (64). The lowest lethal dose was 40 mg/kg, indicating that neurotoxicity occurred at a sublethal dose. Atropinized hens treated with 40 mg/kg (orally) or 200 mg/kg (dermally) two times 21 days apart and observed for a total of 42 days showed no behavioral or histopathological signs of delayed type neuropathy (317a). Additionally, no evidence of pathological changes in the structure of brain or peripheral nerve indicative of delayed type neuropathy were observed in hens treated orally by gavage with 0, 084, 1.7, or 3.2 mg/kg/day for 90 days (317a).

16.4.2 Human Experience 16.4.2.2 Clinical Cases A 26-month-old male experienced abdominal pain and vomiting for 8–18 hours after dermal (and possibly oral) exposure of a flea killer that contained fenthion. About 42 hours after exposure, he experienced respiratory arrest accompanied by miosis, hyperactive bowel sounds, pulmonary edema, and diminished muscle tone and reflexes. Therapy with atropine, 2-PAM, and ventilation saved his life, and he recovered about 32 days after exposure (1). A 71-year-old farmer who was estimated to have ingested about 83 mg/kg fenthion suffered nausea, was hospitalized unconscious after 13 hours, and died 4 days later. A 40-year old individual who drank as estimated 25 mg/kg fenthion was unconscious for about 4 days but survived (1). In another attempted suicide, a 44-year-old man was thought to have ingested 310 mg/kg fenthion. He showed only a few mild signs of poisoning when hospitalized 3 hours after ingestion. However, he experienced two relapses in spite of adequate drug therapy and required tracheotomy during recovery (1).

Fenthion blood levels and plasma cholinesterase activity were followed in a 41-year-old male who ingested an unknown amount of fenthion and died after 7 days (354). Blood fenthion concentration was 0.27 mg/L on admission (20 hours after ingestion) but rapidly increased to 0.78 mg/L coincident with worsening cholinergic symptoms. Even after 5 days, fenthion blood concentration still varied within the 0.2–0.3 mg/L level. In another case of fenthion poisoning, a 43-year-old man ingested about 30 mL of Lebaycid, corresponding to about 18 g fenthion (355). Signs of cholinergic toxicity were seen 31 hours after ingestion at which time RBC acetylcholinesterase were totally inhibited. The relatively long half-life of fenthion was illustrated in another case report of a woman who experienced severe poisoning after ingesting fenthion in a suicide attempt. A fat biopsy obtained 22 days after ingestion, after recovery from an acute cholinergic phase of poisoning but before experiencing a delayed intermediate type syndrome, indicated fat residues of about 0.15 ppm fenthion. By day 31 when all symptoms had been resolved, fat residues had decreased to zero.

Neurological symptoms that ranged from occasional tingling and numbness of the hands and feet to

multiple shooting pain, back pain, numbness, and generalized muscle weakness were reported by five employees in a veterinary hospital who routinely used topical applications of a 20% fenthion solution on dogs and took no precautions to avoid dermal contract (356, 357). When the use of fenthion was discontinued, the symptoms stopped.

The characteristics of an intermediate syndrome (respiratory insufficiency, weakness of muscles, innervated by cranial nerves and weakness of proximal limb muscles) were described in four cases of fenthion poisoning (two of the people died) that occurred 2–6 days following resolution of an acute cholinergic crises and which lasted 5–18 days (358). Unusual transient dystonic movements also occurred in two of these cases. Symptoms that comprised an "intermediate syndrome" (i.e., weakness of external ocular, facial, neck, proximal limb, and respiratory muscles) and extrapyramidal signs (dystonia, rest tremor, cog-wheel rigidity, and choreoathetosis), occurred from 4 to 40 days after acute poisoning with fenthion, and resolved after 1 to 4 weeks in survivors were described in six cases of people who ingested 15–60 mL of fenthion (359).

Several publications report an association between an increased incidence of adverse visual effects (myopia and a visual disease syndrome termed "Saku" disease) and agricultural use of organophosphates, including fenthion, in Japan. The recently reviewed studies vary in quality and usefulness, but nevertheless suggest that the association is probable (327). However, only one study is available that suggests a specific link between fenthion exposure and ocular toxicity. In this study, neurological function, visual acuity, refraction, color vision, and the condition of the fundus oculi were assessed in 79 individuals who worked 5–6 h/day spraying an aqueous suspension of fenthion and were compared to equivalent observations of 100 control subjects (327). Macular changes (hypopigmentation, irregularity of background pigmentation, and dull foveal relex) were evident in 15 (19%) workers and in 3 (3%) control subjects. Other visual symptoms reported in workers who had macular change included visual impairment, reduced visual acuity, abnormal color vision, and constriction of visual fields. Pathological myopia (associated with "Saku") disease was not observed.

Symptoms reported among thirty-one workers who sprayed aqueous suspensions of fenthion (100 mg in 100 L water) by a hand-operated sprayer for 5–6 hours/day, 6 days/week included headache (56%) giddiness (44%), eye irritation (20%), anorexia and paresthesia (11%), but no signs specific for cholinergic toxicity (360). On neurological examination, two subjects had loss of ankle reflex, and one had coarse tremors. Additionally, subtle subclinical effects on psychometric tests and event related potentials were observed. However, no estimate of exposure was provided.

Fenthion administered to human volunteers at dose levels of 0.02 or 0.07 mg/kg daily for up to 4 weeks produced no physical signs or symptoms; no alterations in clinical chemistry, hematology or urinalysis; and no inhibition of RBC cholinesterase activity (361).

16.5 Standards, Regulations, or Guidelines of Exposure

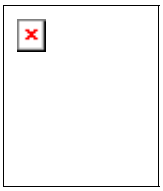
Fenthion has been reregistered for use by the EPA. The ACGIH TLV for fenthion is 0.2 mg/m^3 with a skin notation (154). There is no OSHA PEL-TWA or NIOSH REL-TWA for fenthion. Other countries have Occupational Exposure Limits of 0.2 mg/m^3 for fenthion (Australia, Belgium, Germany, and Japan); others have OELs of 0.1 mg/m^3 (Denmark, The Netherlands, and Switzerland).

Organophosphorus Compounds
Jan E. Storm, Ph.D

17.0 Fonofos

17.0.1 CAS Number:

[*944-22-9*]
17.0.2 Synonyms:
(*O*-ethyl-*S*-phenyl ethylphosphonodithioate; *O*-ethyl *S*-phenyl ethyldithiophosphonate; Ethyl *S*-phenylethylphosphonothiolthionate; Diphonate; Fonophos; *O*-ethyl *S*-phenylethylphosphonothiolothionate; ethylphosphonodithioic acid *O*-ethyl *S*-phenyl ester; Dyfonate II; N-2790; *O*-ethyl *S*-phenylethylphosphonodithioate; Stauffer N-2790; ethyl *s*-phenyl ethylphosphonodithioate; Dyphonate
17.0.3 Trade Names:
Dyfonate®; Difonate; Dyphonate
17.0.4 Molecular Weight:
246.32
17.0.5 Molecular Formula:
$C_{10}H_{15}OPS_2$
17.0.6 Molecular Structure:



17.1 Chemical and Physical Properties
Fonofos is a light yellow liquid.

Specific gravity	1.154 at 20°C
Boiling point	130°C at 0.1 mmHg
Flash point	>94°C, closed cup
Vapor pressure	0.00021 torr at 25°C
Solubility	very slightly soluble in water (13 mg/L at 20°C); miscible with organic solvents such as kerosene, xylene, and isobutyl ketone

17.1.2 Odor and Warning Properties Pungent, mercaptan-like odor.
17.2 Production and Use
Fonofos was introduced in 1967 for use as a soil insecticide to control corn borers, rootworms, cutworms, symphylans (garden centipedes), wireworms, and other soil and foliar pests. It is formulated as an emulsifiable concentrate and as granules. Registration of fonofos in the U.S. has been voluntarily cancelled.
17.4 Toxic Effects
17.4.1.1 Acute Toxicity Fonofos has high oral toxicity, and oral LD_{50}s are 3–18.5 mg/kg for rats (64a). Cholinergic signs and death occur rapidly after lethal exposure (364). The oral LD_{50} for a racemic mixture of fonofos was 14 mg/kg, which was less than the oral LD_{50} of 32 mg/kg for the $(S)_p$ isomer but greater than the oral LD_{50} of 9.5 mg/kg for the $(R)_p$ isomer (362). The acute i.p. LD_{50} for the fonofos racemic mixture was 4.8 mg/kg, suggesting an overall detoxification role of first-pass hepatic metabolism. The dermal LD_{50} for rats is 147 mg/kg and for guinea pigs is 278 mg/kg (363). Application of 0.5 ml undiluted fonofos to the skin of rabbits caused on dermal irritation, but all animals died within 24 hours (154). The 4-hour LC_{50} of fonofos for rats is 900 mg/m^3, and the 1-hour LC_{50} is 460 mg/m^3 (363).

Technical fonofos (0.1 mL) instilled into the eye of albino rabbits caused death during the first 24 hours after administration of the chemical, but local eye irritation was negligible (363).

17.4.1.2 Chronic and Subchronic Toxicity Dietary feeding of fonofos of groups of dogs for 14 weeks indicated a no-observed effect level of 8 ppm (approximately 0.2 mg/kg) (120a).

17.4.1.3 Pharmacokinetic, Metabolism, and Mechanisms Fonofos is well absorbed orally. After a single oral dose of fonofos, 98% was excreted in the urine (91%) and feces (7.4%) of rats within 96 hours. Prior exposure to fonofos did not change in excretion pattern. Tissue residues were very small and had virtually disappeared by day 16 (365). Similar results were obtained in white mice given the enantiomer of fonofos orally (365a). Fifty percent of the most toxic isomer and 95% of the less toxic isomer where eliminated within 96 hours.

Fonofos is first oxidized by microsomal enzymes to the oxon and also, by a different reaction, to *O*-ethyl-ethylphosphonothioic acid (ETP) and thiophenol. The oxon, in turn, is hydrolyzed to *O*-ethyl-ethylphosphoric acid (EOP) and thiophenol (366, 367). The oxon is not found *in vivo* due to its rapid hydrolysis (368). The other metabolites were much less toxic than the parent compound.

17.4.1.4 Reproductive and Developmental No adverse effects were noted on overall reproductive performance at either level among the parental animals or on the numbers, well-being, or integrity of the offspring among rats fed 10 or 31.6 ppm fonofos for three generations (95).

EPA noted a fetotoxic no-observed-effect level of 1.58 mg/kg/day in rats and a fetotoxic no-observed-effect level and lowest observed effect level of 2 and 6 mg/kg/day, respectively, in mice (95, 364).

17.4.1.5 Carcinogenesis There was no evidence of carcinogenicity when fonofos was given in the diet to rats for 105 weeks (95). This study produced a no-observed-effect level of 10 ppm (0.5 mg/kg/day) for brain acetylcholinesterase inhibition and a lowest observed effect level of 1.58 mg/kg/day based on RBC cholinesterase inhibition (95).

There was no evidence of carcinogenicity in dogs that were fed 0, 0.2, 1.5, and 12 mg/kg/day fonofos via their diet for 2 years (95). No compound-related effects were observed at 0.2 mg/kg/day; moderate (*sic*) inhibition of RBC cholinesterase, increased liver weight, tremors, lacrimation, and salivation occurred at 1.5 mg/kg/day; and, these symptoms plus microscopic lesions of the small intestines and liver occurred at 12 mg/kg/day.

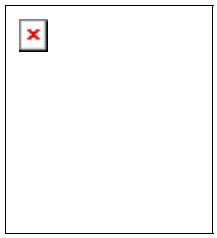
17.4.2 Human Experience Four members of a family were poisoned by pancakes mistakenly made with fonofos instead of flour; one family member died (368a). Soon after eating the pancakes, one family member developed nausea, vomiting, salivation, and sweating and was taken to a hospital where she suffered cardiorespiratory arrest. She was resuscitated and transferred to a medical center where she was artificially ventilated, exhibited muscle fasciculations, low blood pressure, pinpoint pupils, and profuse salivary and bronchial secretions. Treatment continued and she was eventually released 2 months later. Gallo and Lawryk (1) noted that, although not reported in the original paper, three other members of the family were poisoned by the pancakes, and one of them died. A fifth family member who may have mixed the batter, but did not eat pancakes, remained well.

17.5 Standards, Regulations, or Guidelines of Exposure

The registration of fonofos has been voluntarily cancelled in the United States and tolerances are being revoked. The ACGIH TLV for fonofos is 0.1 mg/m^3 with a skin notation (154). The NIOSH REL-TWA for fonophos is 0.1 mg/m^3 with a skin notation. Most other countries also have Occupational Exposure Limits of 0.1 mg/m^3 for fonophos (Australia, Belgium, France, and Switzerland).

Organophosphorus Compounds
Jan E. Storm, Ph.D

18.0 Malathion
18.0.1 CAS Number:
[*121-75-5*]
18.0.2 Synonyms:
(*O*,*O*-Dimethyl dithiophosphate of diethyl mercaptosuccinate; *O*,*O*-dimethyl-*S*-(1,2-dicarbethoxyethyl)-phosphorodithioate; diethyl [(dimethoxyphosphinothioyl)thio]butanedioate; Maldison; *O*,*O*-dimethyl phosphorodithioate ester of diethyl mercaptosuccinate; [(Dimethoxyphosphinothioyl)thio]butanedioic acid diethyl ester; mercaptosuccinic acid diethyl ester *S*-ester with *O*,*O*-dimethyl phosphorothioate; insecticide no. 4049; phosphothion; Cythion; dicarboethoxyethyl *O*,*O*-dimethyl phosphorodithioate; *O*,*O*-dimethyl *S*-(1,2-dicarbethoxyethyl) dithiophosphate; *O*,*O*-dimethyl *S*-(1,2-dicarbethoxyethyl)phosphorodithioate; diethyl mercaptosuccinate, *O*,*O*-dimethyl phosphorodithioate; 1,2-di(ethoxycarbonyl)ethyl *O*,*O*-dimethyl phosphorodithioate; chemathion; emmatos; karbofos, kop-thion; malagran; malamar; MLT; sadofos; *S*-(1,2-bis(carbethoxy)ethyl) *O*,*O*-dimethyl dithiophosphate; *S*-1,2-bis(ethoxycarbonyl)ethyl *O*,*O*-dimethyl dithiophosphate; calmathion; carbetox; carbethoxy malathion; carbetovur; celthion; cinexan; compound 4049; detmol ma; *S*-(1,2-di(ethoxycarbonyl)ethyl) dimethylphosphorothiolothionate; diethyl (dimethoxyphosphinothioylthio)succinate; diethyl mercaptosuccinate, *O*,*O*-dimethyl dithiophosphate, *S*-ester; diethyl mercaptosuccinate, *O*,*O*-dimethyl thiophosphate; diethyl mercaptosuccinate *S*-ester with *O*,*O*-dimethylphosphorodithioate; diethyl mercapatosuccinic acid *O*,*O*-dimethyl phosphorodithioate; *O*,*O*-dimethyl-*S*(1,2-bis(ethoxycarbonyl) ethyl)dithiophosphate; *O*,*O*-dimethyl-*S*(1,2-dicarbethoxyethyl) thiothionophosphate; *O*,*O*-dimethyl *S*-1,2-di(ethoxycarbonyl)ethyl phosphorodithioate; *O*,*O*-dimethyldithiophosphate diethyl mercaptosuccinate; phosphorodithioic acid, *O*,*O*-dimethyl ester, *S*-ester with diethyl mercaptosuccinate; Malaspray; dicarbethoxyethyl-*O*,*O*-dimethyldithiophosphate; diethyl mercaptosuccinic acid, *S*-ester of *O*,*O*-dimethyl phosphorodithioate; dimethyl dithiophosphate of diethyl mercaptosuccinate; dimethyl phosphorodithioate of diethyl mercaptosuccinate; Ethiolacar; Etiol; Cleensheen; Lice Rid
18.0.3 Trade Names:
Carbophos; Extermathion; Forthion; Fosfothion; Fyfanon; Malacide;Malatox; Maldison; Mercaptothion
18.0.4 Molecular Weight:
330.36
18.0.5 Molecular Formula:
$C_{10}H_{19}O_6PS_2$
18.0.6 Molecular Structure:



18.1 Chemical and Physical Properties
Malathion is a noncombustible, yellow to deep brown liquid. Malathion is rapidly hydrolyzed at pH>7 or >5 and is stable in aqueous buffered pH 5.6 solutions. It can corrode iron, steel, tinplate,

lead, and copper. It is a solid below 37°C.

Specific gravity	1.23 at 25°C
Melting point	2.85–3.7°C
Density	1.23 at 25°C
Boiling Point	156-157°C at 0.7 torr
Solubility	slightly soluble in water (145 ppm); completely soluble in alcohols, esters, ketones, ethers, aromatic solvents, and hexane, limited solubility in petroleum oils

18.1.2 Odor and Warning Properties A mild skunk-like odor.

18.2 Production and Use

Malathion is a broad-spectrum insecticide and one of the earliest organophosphate insecticides developed. It is used to control sucking and chewing insects on fruits, vegetables, and ornamental plants. It is also used to control mosquitos, flies, household insects, animal parasites, and head and body lice.

18.4 Toxic Effects

18.4.1.1 Acute Toxicity Malathion is an organophosphate compound that has low acute toxicity and rat oral LD_{50}s are generally in the 1,000–12,500 mg/kg range, depending on the formulation and gender tested (64, 268). An intraperitoneal LD_{50} of 750 mg/kg was reported, showing that route of exposure markedly impacts toxicity (369). This was also illustrated in a study where oral and intraperitoneal LD_{50}s in mice were 1025 and 420 mg/kg, respectively (370). Following lethal oral doses, maximal symptoms are often delayed for several hours, but death generally occurred within 2 days after poisoning (369). Technical grade malathion is more toxic than the pure product. Oral LD_{50}s for rats of 65% technical grade malathion, 90% technical grade malathion and 99% undiluted malathion were 369, 1156, and 5843 mg/kg, respectively (370). Commercial preparations of malathion vary in their toxicity due to the presence of impurities which bind to and inhibit acetylcholinesterase and also the carboxylesterase that detoxifies malathion (371–373).

A precise dermal LD_{50} for malathion has not been identified. The dermal LD_{50}s for rats for a 57% emulsifiable concentrate was greater than 4444 mg/kg (64a, 268). In rabbits, single dermal doses of up to 4 ml/kg 90% technical malathion or the 25% wettable powder caused no overt signs of toxicity, except for temporary irritation at the site of application (370). However, mortality occurred after four daily applications of 0.5 or 1 mL/kg/day and after two daily applications of 2 mL/kg. In each case, symptomology was characteristic of acute organophosphate poisoning (370).

An acute inhalation LC_{50} for malathion is not available, although a 4-hour LC_{50} of >5200 mg/m^3 has been reported (155). However, an intravenous LD_{50} of 50 mg/kg was reported in rats (373a) which is at least 20 times smaller than reported oral LD_{50}s. In dogs, an intravenous dose of 100 mg/kg resulted in immediate and profuse salivation and tremors (370). In a 5-hour exposure of mice of 7 mg/L 95% technical grade malathion (7000 mg/m^3), there were no signs of cholinergic toxicity and no deaths (203).

Overt toxicity has rarely been identified following single, sublethal exposures to malathion, although they cause RBC and brain cholinesterase inhibition. RBC cholinesterase activity maximally decreased in rats 45 minutes after an intraperitoneal dose of 300 mg/kg (370). Repeated daily intraperitioneal doses of 300 mg/kg produced a cumulative inhibitory action on cholinesterase activity of brain, submaxillary gland, and serum in rats so that after 5 days, activities were about 30, 50, and 25% of control, respectively (369). Rats could not tolerate longer periods of treatment.

Repeated administration of 200 mg/kg also progressively decreased cholinesterase activity of the brain and submaxillary gland.

An important characteristic of malathion acute toxicity is its potentiation by other organophosphates. When malathion and EPN were administered to rats separately, LD_{50}s were 1400 and 65 mg/kg, respectively. However, when malathion and EPN were administered simultaneously at a ratio of about 25:1, oral LD_{50}s were reduced to 167 and 7 mg/kg, respectively (184). The onset of symptoms for individual compounds was slow, and death usually occurred several hours after administration. However, when given together at or near the LD_{50}, symptoms developed much more rapidly, and death usually occurred within 1 hour. In dogs, oral doses of 2000 or 4000 mg/kg malathion alone were not fatal; however, when EPN was given simultaneously (2 or 5 mg/kg) with malathion, doses of 50, 100, and 200 mg/kg were lethal (184). Potentiation of malathion toxicity is due to the inhibition of carboxyesterase by EPN (and other organophosphates), an enzyme important in detoxifying of malathion (as well as the more toxic metabolic product malathion, malaoxon) (165, 374).

Evidence that malathion causes a paralytic type of neurotoxicity was observed in hens given 100 mg/kg or more malathion subcutaneously and observed for up to 30 days (190). Neurotoxicity, reflected by the occurrence of leg weakness that lasted for 4–14 days, occurred in atropinized chickens given single, subcutaneous doses of 100 mg/kg malathion (64a). Atropinized rats were given 600, 1000, or 2000 mg/kg malathion (88% pure) via oral gavage and were observed for signs of delayed neuropathy at 14–21 days; only the 2000-mg/kg dosed rats showed signs of gait alterations indicative of delayed neuropathy (375).

18.4.1.2 Chronic and Subchronic Toxicity Mortality was 20, 60 and 100%, respectively, among rats given 100, 200 or 300 mg/kg/day malathion intraperitoneally for 60 days (369). Rats fed lentil diets that contained 0.95 or 6.51 ppm malathion (equivalent to about 0.06 and 0.44 mg/kg/day) exhibited no signs of cholinergic toxicity (376). However, both exposure levels were associated with increased blood urea nitrogen and increased white blood cells, and the 0.44-mg/kg/day group had decreased serum cholinesterase activity. Brain and RBC cholinesterase activity were unaffected. Similarly, mice fed soybean seeds contaminated with 7 ppm malathion of 75 days exhibited no signs of cholinergic toxicity and no effect on RBC cholinesterase activity (376).

There is evidence that malathion is a sensitzer. In a field study, 3% of workers involved in spraying malathion for mosquito control and 5% of poultry ranchers who had used malathion for at least one season showed positive reactions when malathion (95%) was applied under adhesive tape to the skin of the upper arm and allowed to remain in place for 2 days (406). In another study of ten subjects who had reported skin reactions to malathion bait, none had a reaction to patch testing of malathion. Only one exhibited a positive reaction to the bait and another had irritant reactions to both bait and malathion (407).

18.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Approximately 90% of ingested malathion is relatively slowly absorbed and excreted in urine (1, 106, 389). Six hours after an oral dose of malathion, 75% remained in the stomach, 8% was in the small intestine, and 7% was in saliva. Thus a very small amount had been absorbed. Similar results were obtained in rats fed a lentil diet contaminated with malathion (376). After 48 hours, about 35% of the dose was excreted in urine; 45% in feces, 1.5% in exhaled air, and tissues contained about 9%. In rats given malathion orally, it is distributed to blood, adipose tissue, muscle, liver, and brain and then eliminated from these tissues at half-lives of 1.4, 2.4, 3.7, 19.4, and 17.6 days, respectively (101, 388).

Absorption of malathion via inhalation is expected to be high and elimination via urine extremely rapid and nearly complete based on pharmacokinetic studies following intravenous dosing. Among male volunteers, approximately 90% of an intravenous dose of malathion was excreted in urine within 5 days and the an elimination half-life was 3 hours (66). Thirty minutes following intravenous

administration of malathion to rats most had been distributed to tissues; liver, small intestine, lung, urinary tract, and kidney accumulated extremely high levels (389). Distribution pattern at 1 and 2 hours were similar.

In mice, 25% of a 1-mg/kg dermal dose of malathion was absorbed within 60 minutes, and 67% of the dose was absorbed by 8 hours (213). Distribution of malathion was equal in liver and blood; slightly greater in urine, feces, and expired air; and greatest in the rest of the carcass at 60 minutes. By 8 hours, 30% of the dose had been excreted, 30% remained in the carcass, and about 2.5% was distributed to lungs, kidney, bladder, stomach, intestine, liver, and blood. Whole body autoradiography of rats treated dermally with a single dose of malathion indicated that after 8 hours most of the dose was equally distributed between the application site (28%), remaining skin (29%), and the small intestine and urinary bladder (23%) (389).

Among human volunteers, about 8% of an applied malathion dermal dose of 4 mg/cm^2 was absorbed by 120 hours after application to the ventral forearm (66). *In vitro* absorption by human skin was about 9% from an aqueous ethanol solution and about 0.6 to 4% from cotton sheets to which malathion had been added (389a).

Malathion is either oxidized in the liver to malaoxon by microsomal cytochrome P450 enzymes or to monoacids by a microsomal carboxyesterase. Malaoxon is the toxic metabolite of malathion that binds and inhibits acetylcholinesterase and leads to the typical cholinergic sequelae associated with organophosphate poisoning. The other products of malathion and malaoxon metabolism are detoxification products. Malaoxon is also subject to hydrolysis and carboxyesterase (105, 390, 391). There is evidence that the linkage at P–S is enzymatically broken by another cytosolic esterase as well (*A*-esterase) and forms *O*,*O*-dimethyl phosphorothioate (390). There is some evidence the monoacids can then be S-methylated, and that the C–S bond of either malaoxon or malathion can be further hydrolyzed (392, 393).

The rate of malathion desulfuration is not as critical as the rate of hydrolysis by carboxyesterase or hydrolysis of the C–S bond, both of which are detoxication reactions, in determining the toxicity of malathion (393). Female rats that are more sensitive to malathion toxicity have relatively lower levels of liver carboxylesterase activity (394). Further, pretreatment of mice with the microsomal inducer phenobarbital failed to decrease the mouse intraperitoneal LD_{50} (i.e., failed to increase the toxicity) of malathion, whereas it did decrease the i.p. LD_{50} of dimethoate which is not subjected to detoxification reactions as extensive as those for malathion (391). Additionally, oral LD_{50}s for rats and three strains of mice were significantly correlated with their carboxyesterase titer in liver and plasma (371). Carboxyesterase activity (also termed hydrolase B) occurs in mouse, rat, and human liver microsomal preparations and it has been shown, is markedly inhibited by a common impurity of malathion, isomalathion (372). This inhibition is associated with the potentiation of malathion toxicity (395a). Finally, it is believed that malathion and/or malaoxon inactivate carboxyesterase, so that additional dose of malathion are less effectively detoxified. This contributes to the phenomenon whereby pretreatment with malathion increases the toxicity of subsequent doses (374).

No polymorphism of carboxylesterase was detected in 12 human livers, but the range of individual activity toward malathion was about 10-fold (395). In humans, carboxyesterase is expressed only, in the liver, whereas in rodents, carboxyesterase is expressed in the serum and liver. This could provide a basis for a greater sensitivity of humans to malathion compared to rodents, although that has not been adequately explored.

18.4.1.4 Reproductive and Developmental Viability and growth decreased in fetuses of rats fed diets that contained about 4000 ppm technical grade (95%) malathion (240 mg/kg) for 5 months (377). Pregnant rats on protein-deficient or protein-adequate diets given 500 mg/kg/day malathion orally on gestation days 6, 10, and 14 showed decreased maternal weight gain, a decreased number of implantations and live fetuses, and decreased brain acetylcholinesterase activity (392a). Protein

deficiency enhanced an effect of malathion on fetal crown to rump and tail length, fetal body weight, and retardation of skeletal ossification. No detectable increases in the number of resorptions, fetal size, and external or visceral anomalies occurred in rabbits given malathion (70%) at 100 mg/kg by gavage on gestation days 7 through 12 (378).

Pregnant rats given 600 or 900 mg/kg malathion via intraperitoneal injection on gestation day 11 showed signs of maternal toxicity but did not produce malformed or low birth weight pups (379). Malathion caused a dose-dependent inhibition in brain acetylcholinesterase activity in dams and pups among rats given 138, 276, and 827 mg/kg/day malathion via intraperitoneal injection on gestation days 6 through 13 (380).

18.4.1.5 Carcinogenesis No cholinergic toxicity or inhibition of whole blood cholinesterase activity occurred in rats fed diets that contained 100 or 200 ppm (2.5 or 6.25 mg/kg/day) for 8 weeks (194). However, when the diet contained 25 ppm (0.625 mg/kg/day) EPN, as well as 500 ppm malathion, whole blood cholinesterase was significantly inhibited. No cholinergic signs occurred in dogs fed diets that contained 25, 100, or 250 ppm malathion for 12 weeks, but RBC cholinesterase was significantly inhibited in dogs fed 250 ppm (194). In rats fed 100, 1000, or 10,000 ppm 65% technical malathion, 90% technical malathion, or 99%+ malathion in the diet (equivalent to about 6, 60, or 600 mg/kg/day) for 2 years, cholinergic toxicity was not described, but among rats given the more toxic 65% and 90% technical products, RBC and brain cholinesterase activities were inhibited in the 1000- and 10,000-ppm groups and were unaffected in the 100-ppm group (370).

There was no evidence of carcinogenicity in rats given diets that contained 4700 or 8150 ppm (about 270 mg/kg and 466 mg/kg) for 80 weeks and observed for an additional 33 weeks, in rats given diets that contained 2000 or 4000 ppm malathion (about 115 mg/kg/day and 230 mg/kg/day) for 103 weeks, or in rats given diets that contained 500 or 1000 ppm malaoxon for 103 week (482). There was no evidence of carcinogenicity in mice given diets that contained 8,000 or 16,000 malathion (about 800 and 1600 mg/kg/day) for 80 weeks and observed for an additional 14 or 15 weeks (482). During the second year, clinical signs including alopecia, rough and discolored coats, poor food consumption, hyperexcitability, and abdominal distension occurred with increasing frequency in dosed animals. A few animals appeared hyporeactive, and some had hunched appearances. During weeks 71 to 79, five high-dose females exhibited generalized body tremors.

18.4.1.6 Genetic and Related Cellular Effect Studies Mammalian *in vivo* and *in vitro* studies of technical or commercial grade malathion and its metabolite malaoxon show a pattern of induced chromosomal damage, as measured by increased chromosomal aberrations, sister chromatid exchanges, and micronuclei (381, 382), as well as increased mutations (383, 384). Purified (>99%) malathion gave weak or negative results in cytogenetic assays. Technical malathion was generally negative in mammalian gene mutation assay, but malaoxon was positive. Studies of human lymphocytes indicated that *in vitro* incubation with malathion increased the frequency of DNA mutations (383, 384). Malathion were positive in a modified SOS microplate assay in which the induction of b-galactosidase in *E-coli* PQ37 was used as a qualitative measure of genotoxic activity (385).

Dermal exposure caused cytogenetic damage in test animals at doses near those that produce positive results by intraperitoneal injection (381). Workers involved in a Mediterranean fruit fly aerial spraying eradication program in California in the early 1990's exhibited no increase in micronuclei formation or mutation frequency assessed by the glycophorin A (GPA) assay (386, 387). However, a significant increase in micronuclei occurred in whole blood cultures and in human lymphocytes at dose levels that also caused cytotoxicity and strong inhibition of proliferation (386, 387).

18.4.2 Human Experience 18.4.2.2 Clinical Cases There have been many reports of organophosphate poisoning from the intentional or accidental ingestion of malathion (1). There are a few reports of poisoning from dermal exposure of children that occurred when their hair was washed with a 50% solution of malathion to eliminate lice. Poisoning following inhalation exposures have

been reported but were probably confounded by simultaneous ingestion (1). Cholinergic symptoms appear rapidly from minutes to 3 hours following ingestion, but may be delayed by 12–14 hours after dermal exposure.

Estimates of lethal doses of malathion obtained from case study reports range from 68 to 3855 mg/kg (1). Actual estimates of ingestion obtained from reports of poisonings where the quantity was approximately known indicated that a life-threatening dose is 500–1000 mg/kg (371). Doses associated with serious but sublethal toxicity have ranged from approximately <1 mg/kg (in a two-year-old boy) to 357 mg/kg (396).

Large-scale occupational poisoning by malathion occurred among sprayers, mixers, and supervisors involved in a mosquito control program that used a water-wettable powder formulation of malathion (397). An estimated 2810 cases of poisoning including five deaths were recorded during the peak month of the epidemic. Symptoms and clinical histories were consistent with organophosphate intoxication and the most severe illness were associated with the formulation that contained high levels of isomalathion and other contaminants. Exposures were primarily dermal and estimates ranged from 1 to 200 mg/cm^2. Respiratory exposure was estimated to considered less important—peak air concentrations measured during spraying were about 1.5 mg/m^3. RBC cholinesterase decreased at the end of the workday in workers, who used the two formulations that contained 2–3% isomalathion, but not in workers who used the uncontaminated formulation.

An intermediate-type syndrome characterized by weakness of proximal limb muscles, cranial nerve palsies, and respiratory depression has sometimes followed initial acute symptoms associated with malathion poisoning (1). Typical of a case that showed such delayed symptoms is that of a woman who experienced a typical cholinergic crisis about 1 hour after ingesting 300 mL malathion. She was successively treated with atropine and pralidoxime iodide but suffered a “relapse” characterized by diaphoresis, miosis, mental confusion, and respiratory dysfunction 47 hours later (398). Measurements of plasma and RBC cholinesterase activities in this patient suggested that they were 26–38% and 28–40% of normal, respectively for the 15 days following malathion ingestion. Initial plasma concentrations were quite high in this patient, and an elimination half-life of 7.6 hours was determined suggesting to the authors that because of its lipophilicity, malathion may have been retained in adipose tissues and then was released more slowly into circulation, causing the delayed effects.

No signs of cholinergic toxicity have been reported as a result of the aerial spraying of malathion to control mosquitos or the Mediterranean fruit fly (399, 400, 405). However, chronic dose rates calculated from spraying to eradicate the Mediterranean fruit fly in California were quite low—about 0.001–0.246 mg/kg/day via dermal contact, about 0.01 to 0.1 mg/kg/day via inhalation, and about 0.030–0.080 mg/kg/day via ingestion of backyard vegetables (401). Average and upper bound estimates of environmental levels of malathion during aerial spraying derived from mass deposition rates and air monitoring in affected areas were 0.09 and 0.2 mg/m^3 in air immediately after spraying, 22 and 52 mg/m^2 on outdoor surfaces, 3.8 and 9.6 mg/g in plants, and 1.5 and 3.5 mg/g in soil. Estimated average and upper bound estimates of malaoxon levels were 0.04 to 0.110 mg/m^3 in air, 0.15 and 0.46 mg/m^2 on outdoor surfaces, 0.03 and 0.08 mg/g in plants, and, 0.01 and 0.03 mg/g in soil (402).

To test the safety of malathion in controlling lice, the bodies and clothing of thirty-nine men were dusted five times a week for 8–16 weeks with talcum powder that contained 0, 1%, 5%, or 10% malathion. Complaints about odor and skin irritation were roughly proportional to dosage. No change in blood cholinesterase activity was found, except occasionally with 10% powder (403).

Exposure to malathion via dermal contact and inhalation was estimated in six entomologists who were exposed to windborne aerosols of malathion drifting downwind from generators as they moved

along pastures where they were working (404). Measures of respiratory exposure were made using midget impingers at the breathing zones of the entomologists, by measuring malathion in absorbent filters in cartridge type respirators, and by measuring atmospheric concentrations. Dermal exposures were estimated from malathion contained in cotton gloves and absorbent cellulose surface patches placed in various locations on the skin. Estimates of total dermal exposures during a two week period ranged from 0.5–1.3 mg/kg (0.05–0.13 mg/kg/day assuming two 5-day weeks), and estimates of respiratory exposures ranged from 0.2–0.3 mg/kg (0.02–0.03 mg/kg/day assuming two 5-day weeks). Average air concentrations of malathion were 0.5 to 4 mg/m^3 although they ranged as high as 56 mg/m^3. None of the men exposed during the study exhibited any cholinergic clinical signs or inhibition of plasma or RBC cholinesterase activity.

18.4.2.3.4 Reproductive and Developmental No association was found between malathion exposure and spontaneous abortion, intrauterine growth retardation, stillbirth, and most categories of congenital anomalies in a cohort of 7450 pregnancies potentially exposed to malathion applied aerially to control the Mediterranean fruit fly (405).

Five men given gelatin capsules delivering 8, 16, or 24 mg/malathion each day (equivalent to roughly 0.11, 0.23, or 0.34 mg/kg/day) for 32, 47 or 56 days, respectively, experienced no cholinergic toxicity (294). RBC cholinesterase activity was not affected in either the 8- or 16-mg/day group, but it was inhibited by exposure to 24 mg/day.

No adverse symptoms or inhibition of RBC cholinesterase occurred among volunteers exposed to dust containing 1, 5, or 10% malathion five times/week for 8 weeks (403). The estimated maximum dosage received was about 224 mg/day or 3.2 mg/kg/day.

Groups of four men received two 1-hour exposures to aerosols that contained variable amounts of malathion in unventilated rooms on each of 42 consecutive days (408). Based on the decreased weight of the aerosol containers used to spray the exposure rooms, malathion air concentrations were estimated at 0.15 g, 0.60 g, or 2.4 g of malathion per 1000 ft^3—which is equivalent to about 5, 21, and 85 mg/m^3 malathion. No cholinergic toxicity occurred during the study, nor was RBC cholinesterase activity reliably depressed in any of the exposed subjects.
18.5 Standards, Regulations, or Guidelines of Exposure
Malathion is undergoing reregistration by the EPA (154). The ACGIH TLV for malathion is 10 mg/m^3 with a skin notation. The OSHA PEL-TWA is 15 mg/m^3 total dust with a skin notation. The NIOSH REL-TWA is 10 mg/m^3 with a skin notation. Other countries have Occupational Exposure Limits of 15 mg/m^3 (Austria, Germany, The Philippines, Thailand, and Turkey), 10 mg/m^3 (Egypt, Australia, Belgium, Finland, France, Japan, The Netherlands, and Switzerland), or 5 mg/m^3 (Denmark). In Poland the TWA is 1 mg/m^3, STEL 10 mg/m^3 (1998), and in Russia the STEL is 0.5 mg/m^3 (Jan. 93).

Organophosphorus Compounds
Jan E. Storm, Ph.D

19.0 Methyl Parathion
19.0.1 CAS Number:
[*298-00-0*]
19.0.2 Synonyms:
Axophos; *O*,*O*-Dimethyl *O*-(*p*-nitrophenyl) phosphorothioate; Parathion-methyl; phosphorothioic acid *O*,*O*-dimethyl *O*-(4-nitrophenyl) ester; *O*,*O*-dimethyl *O*-*p*-nitrophenyl thiophosphate; dimethyl parathion; Metaphos; E 601; Penncap-M; Metafos; dimethyl 4-nitrophenyl phosphorothionate;

dimethyl *p*-nitrophenyl monothiophosphate; *O*,*O*-dimethyl O-(*p*-nitrophenyl) thionophosphate; dimethyl *p*-nitrophenyl thionophosphate; *p*-nitrophenyldimethylthionophosphate; Dalif; nitrox 80; nitrox; wofatox; bay e-601; folidol-80; Metaphor; parathion methyl homolog; dimethyl *O*-*p*-nitrophenyl thiophosphate

19.0.3 Trade Names:

Bladan M®; Metron®; Nitrox®; Dalf®; Diithion 63; Ketokio 52; Foidol-M®; Metacide®; Metron®; Seis-Tres 6-3; Metaspray 5E; Paraspray 6-3

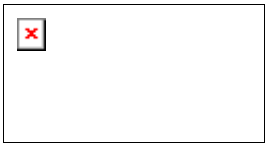
19.0.4 Molecular Weight:

263.23

19.0.5 Molecular Formula:

$C_8H_{10}NO_5PS$

19.0.6 Molecular Structure:



19.1 Chemical and Physical Properties

Pure methyl parathion is a white crystalline solid. The technical grade product contains about 80% methyl parathion and is a brown liquid. Methyl parathion is hydrolyzed by alkaline materials; may react with strong oxidizers; decomposes rapidly above 100°C (creating an explosion hazard) and may release fumes of dimethyl sulfide, sulfur dioxide, carbon monoxide, carbon dioxide, phosphorus pentoxide, and nitrogen oxides

Specific gravity	1.36 at 20°C
Melting point	37–38°C
Boiling point	143°C at 1.0 mmHg
Vapor pressure	0.5 torr at 20°C
Solubility	soluble in water (0, 005 g/100 mL) ethanol, chloroform, aromatic and aliphatic solvents

19.1.2 Odor and Warning Properties Rotten egg or garlic ordor (technical product); odor threshold 0.012 ppm.

19.2 Production and Use

Methyl parathion is a broad-spectrum insecticide and acaracide used to control boll weevils and many biting or sucking insect pests on cotton, field vegetables, rice, fruit trees, alfalfa, soy beans, forest trees, and aquatic food crops. It is also used for mosquito control. Methyl parathion is generally applied to the leaves or aerial portion of the crop by either aircraft or ground spray equipment (53). Methyl parathion is available as an emulsifiable concentrate or microencapsules (155). Methyl parathion may be formulated in combination with other pesticides (53).

19.3.5 Biomonitoring/Biomarkers Immediately after exposure, the concentration of methyl parathion in serum is the most specific biomarker for exposure (409). Urinary concentrations of two metabolites of methyl parathion, *p*-nitrophenol and dimethyl phosphate, may also indicate exposure to methyl parathion. However, they are not unique to methyl parathion. *p*-Nitrophenol is also a breakdown product of parathion, and alkylphosphates are metabolic products of a number of organophosphates (410, 411).

19.4. Toxic Effects

19.4.1.1 Acute Toxicity Methyl parathion is highly toxic and has oral LD_{50}s of 8–24 mg/kg for rats

(64, 268, 252, 412). Dermal LD_{50}s are 6–67 mg/kg (268). Dermal LD_{10}, LD_{50}, and LD_{90}s of 506, 566, and 632 mg/kg for rats indicate a very steep dose–lethality curve (413). One-hour and 4-hour LC_{50}s of 200–287 mg/m^3 and 120 mg/m^3, respectively, were reported for rats. A 4-hour LC_{50} of <163 mg/m^3 and a 4-hour LC_{50} of 135 mg/m^3 were reported for rats for the 80% technical formulation (243). On a milligram per kilogram basis, methyl parathion via intravenous injection was up to eight times more potent than via oral gavage indicating detoxification via first-pass hepatic metabolism (414, 415). Generally, lethal doses cause death quickly within one hour.

An intraperitoneal LD_{50} of 4 mg/kg was reported for adult rats (248, 416, 417), but is <1 mg/kg and <4 mg/kg in neonatal and 12 to 13-day-old rats, respectively, showing enhanced susceptibility of young animals of methyl parathion toxicity. Subcutaneous maximum tolerated doses (MTD, the highest dose that causes no mortality) of 8 and 18 mg/kg were reported for neonate and adult mice, respectively (204).

Among rats given single oral doses of 0, 0.025, 7.5, 10 (males only), or 15 mg/kg (females only) methyl parathion, cholinergic toxicity occurred at doses of 7.5, 10, or 15 mg/kg (243). Neuropathology (focal demyelination) was also evident at these levels.

Methyl parathion caused neurotoxicity, indicated by leg weakness, that lasted from 3–28 days after dosing when given subcutaneously to atropinized chickens at a dose of 64 mg/kg, but not at a dose of 32 mg/kg (64). This shows that methyl parathion may cause a delayed neuropathy but only at doses substantially above a lethal dose and is consistent with a study submitted to EPA in which hens were given an oral dose of 215 mg/kg (243). No signs of ataxia typical of delayed neurotoxic effects were seen in treated hens, nor were neural degenerative changes observed histologically.

Immunotoxicity was observed in mice that were treated with a single oral dose of 9 mg/kg or with 0.9 or 0.4 mg/kg/day, 5 days/week for 4 weeks with the industrial product used to produce Wofatox 50 (60% methyl parathion) and that were immunized with sheep red blood cells (418). Significant increases in the number of splenic plaque forming cells (PFC) occurred among mice treated acutely with 9 mg/kg or repeatedly with 0.9 mg/kg, but not among mice treated repeatedly with 0.4 mg/kg. Immunotoxic effects were also observed in rabbits given diets that contained doses of 0.6 mg/kg/day, but not 0.2 mg/kg/day (419), and in rats given 1.25 mg/kg/day (420).

19.4.1.2 Chronic and Subchronic Toxicity Repeated oral exposure of rabbits to methyl parathion (1.78 mg/kg/day for 28 days) was associated only with decreased body weight gain and slightly decreased plasma acetylcholinesterase activity by day 21 (421).

Cholinergic signs were not noted in rats given 0, 0.5, 1, 1.5, 2, or 2.5 mg/kg/day methyl parathion via their diet for 7 weeks followed by a 1-week observation period (421a). One female died in each of the 0.5-, 1.5- or 2-mg/kg groups, and two females died in the 2.5 mg/kg group; no deaths occurred in males. When methyl parathion was given to rats in the diet at 0, 2.5, 25, or 75 ppm (about 0, 0.12–0.16, 1.24–1.55, and 4.46–5.15 mg/kg/day) for 90 days, fourteen females and one male fed 75 ppm died by 4 weeks (243). Subjects fed 75 ppm also exhibited a variety of hematologic and clinical chemistry effects. Rats fed the 25- or 75-ppm diet exhibited inhibited RBC and/or brain cholinesterase activity. When parathion was given to rats in the diet at 0.5, 5, or 50 ppm (about 0.029–0.037, 0.295–0.365, or 3.02–3.96 mg/kg/day for 13 weeks, cholinergic toxicity and RBC and brain cholinesterase inhibition occurred (243). Among rats fed the 5-ppm diet, RBC cholinesterase inhibition occurred. No treatment related neuropathy was observed at any dose.

When mice were given 0, 2.6, 5.2, 7.8, 10.4, 13, 16.2, 32.5, or 65 mg/kg/day methyl parathion via their diet for 7 weeks followed by a 1-week observation period (421a), the only clinical signs noted were rough hair coat and arched back, but all males in the 32.5- and 65-mg/kg/day group died as did all females in the 65-mg/kg/day group. When methyl parathion was given to mice in the diet at 0, 10,

30, or 60 ppm (about 0, 2.1–2.5, 6.5–8.6, and 13.5–16.3 mg/kg/day) for 90 days, body weight decreased, absolute brain weight increased, and testes weight decreased in males given 60 ppm (243). In females fed the 60-ppm diet, brain and ovary weight decreased; in females fed the 30-ppm diet, only ovary weight decreased; no other adverse effects were recorded.

There was no evidence of cholinergic toxicity in rabbits given dermal doses of 0, 1, 5, 10, or 100 mg/kg/day methyl parathion for 21 days, although RBC cholinesterase was inhibited in rabbits given 10 or 100 mg/kg/day (243). Slight erythema and edema occurred in females at all doses. Rats exposed to methyl parathion via dermal application of 2 mg/kg/day for 30 days experienced cholinergic toxicity and 40% lethality. Treatment was associated with severe liver injury, severe renal tubular injury, and Purkinje cell necrosis, as well as a decrease in brain and RBC cholinesterase activity.

No cholinergic signs or treatment-related effects on clinical chemistry, hematologic, or urinalytic parameters occurred in dogs exposed to 0, 0.30, 1.0, or 300 mg/kg/day methyl parathion via the diet for 13 weeks (243). Dogs given 3 mg/kg/day exhibited decreased brain and RBC cholinesterase activity, and, dogs given 1 mg/kg/day exhibited decreased RBC cholinesterase activity. No adverse effects occurred in dogs given 0.3 mg/kg/day. When dogs were treated with methyl parathion in the diet at 0, 0.03, 0.3, or 3.0 mg/kg/day for 13 weeks, two high-dose males exhibited emaciation, dehydration, and thin appearance (242). RBC and brain cholinesterase activity were inhibited in high-dose males and females.

Dogs fed diets that provided 0.03, 0.1, or 0.3 mg/kg/day methyl parathion for 1 year exhibited no adverse effects at any dose other than decreased RBC cholinesterase activity at all doses (243). Cholinergic toxicity, thymic lymphoid depletion, and decreased RBC and brain cholinesterase activity occurred in dogs given 4.0 mg/kg/day via the diet for 1 year. Only decreased RBC and brain cholinesterase activity occurred in dogs given 3.5 mg/kg/day, and only decreased RBC cholinesterase activity occurred in dogs given 1.0 mg/kg/day (243). No effects occurred in dogs given 0.3 mg/kg/day, and no treatment-related effects on survival, food efficiency, hematologic and urinalytic findings, ophthalmoscopic findings, intraocular pressures, or electroretinograms occurred in any dogs at any dose (243).

When methyl parathion was given to rats via diets containing 0, 0.5, 2.5, 12.5, and 50 ppm (about 0, 0.02–0.03, 0.11–2.5, 0.53–0.70, and 2.21–3.09 mg/kg/day) for one year cholinergic signs, neuropathology (in peripheral nerve preparations), and decreased RBC and brain cholinesterase activity occurred in rats given 50 ppm (243). Among rats fed the 12.5 ppm diet, RBC and brain cholinesterase was significantly inhibited. No ocular effects were observed at any dietary level.

19.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Absorption, distribution, and elimination of methyl parathion via either oral or inhalation exposure is rapid and extensive. Eighty-five percent of an oral dose of methyl parathion was eliminated by mice in urine by 72 hours (425). Similarly, oral methyl parathion was rapidly absorbed by rats and guinea pigs. Concentrations in blood and brain were maximal in about 1–3 hours, and it was nearly completely eliminated in urine (mostly as dimethyl phosphoric and dimethyl phosphorothioic acid) by 7 days (415). Absorption following intravenous or oral dosing of dogs with methyl parathion was 63–78% and 80–95%, respectively, and urinary elimination was rapid and extensive. Bioavailability after oral exposure was much lower (6–30%) than after intravenous exposure due to extensive metabolism and a high extraction ratio in the liver, as well as extensive serum protein binding (426, 427). Maximum serum concentrations after oral exposure occurred 2–9 hours after dosing. Following intravenous injection of dogs with methyl parathion, serum concentrations initially declined rapidly and then more slowly, and the apparent volume of distribution exceeded total body water, indicating distribution to peripheral tissues (427). The mean terminal serum half-life was 7.2 hours, although one dog had a half-life of 16.4 hours. Similar results were obtained in rats and guinea pigs treated intravenously with methyl parathion—absorption, distribution, and elimination were rapid and complete (428).

Following oral exposure, methyl parathion is distributed to blood, liver, adipose tissue, muscle, and brain (429). Distribution coefficients were highest in adipose tissue 8 days after exposure (0.99), in liver 20 days after exposure (0.17), and in brain 16 days after exposure (0.35), but they were always <1.0, indicating no long-term accumulation of methyl parathion in tissues. Concentrations of methyl parathion are maximum 12 days after exposure in blood and liver and 8 days after exposure in adipose tissue and brain. Half-lives of elimination were 15 days for blood, 13 days for adipose tissue, 15 days for liver, and 15 days for brain (429).

Methyl parathion is oxidatively desulfurated to methyl paraoxon or dearylated to dimethyl thiophosphorothioic acid and *p*-nitrophenol via cytochrome p450 enzymes (20, 416, 417). Alternatively, methyl parathion is hydrolyzed to form *O*-methyl-*O*-*p*-nitrophenyl thiophosphate by esterase (termed A-esterase). Methyl paraoxon can also be dearylated to dimethyl phosphoric acid and *p*-nitrophenol or hydrolyzed to *O*-methyl-*O*-*p*-nitrophenyl phosphate. All of these oxidative and hydrolytic products are excreted in urine (425), except methyl paraoxon that is rarely detected in tissues. These metabolic conversions occur primarily in the liver but also occur in the lung and brain (13, 21, 434–436).

Methyl paraoxon binds to and irreversibly inhibits acetylcholinesterase. Noncatalytic, stoichiometric binding to other esterase (aliesterases) in liver and plasma also occurs, however, and may represent a significant detoxification mechanism because it may reduce the amount of methyl paraoxon that leaves the liver and/or blood to enter target tissues (14, 21, 435). Binding to hepatic and plasma esterase may not be as significant a detoxification mechanism for methyl parathion as it is for parathion and chlorpyrifos, however, because the affinity of methyl paraoxon is considerably greater for brain acetylcholinesterase than for hepatic esterase. The reverse is true for parathion and chlorpyrifos (14). Thus, even though methyl paraoxon has a lower affinity for acetylcholinesterase than paraoxon, the relatively weaker protection afforded by the aliesterases could allow lethal levels of the hepatically generated methyl paraoxon to reach the nervous system (14).

Differences in the relative rats of toxification and detoxification reactions of methyl parathion contribute to differences in its toxicity compared to other organophosphates, as well as to differences in toxicity between sexes and among different ages (20). For example, female rats, who are slightly less sensitive to the toxicity of methyl parathion than males, metabolized less methyl parathion to methyl paraoxon than male rats in *in situ* perfused liver (21). Age-related differences in the oral LD_{50} also correlated with rates of detoxification pathways of methyl paraoxon rather than with rates of direct metabolism of methyl parathion (417). Differences in the relative rates of toxification and detoxification also contribute to interspecies differences in toxicity. However, the primary factor that accounts for interspecies differences is species-specific differences in the affinity of acetylcholinesterase for methyl paraoxon (20, 437, 438).

19.4.1.4 Reproductive and Developmental When rats were fed diets that contained 0.5, 5.0, and 25 ppm methyl parathion (0.04, 0.4, and 2 mg/kg/day) for two generations, no treatment-related histopathological effects occurred, nor were there any effects on reproductive parameters, except for maternal weight gain at 25 ppm which decreased significantly in both generations during lactation (243). Reproductive effects, however, occurred in male mice given 0, 9.4, 18.8 and 75.0 mg/kg by gavage (422). Treated animals showed a dose-related increase in the percentage of abnormal sperm. Because there was no appreciable change in testis to body weight ratio and because greater damage was induced when cells were treated as spermatocytes, the authors concluded that methyl parathion acts as a germ cell mutagen. Reproductive effects were also reported in rats treated intraperitoneally with 2.5, 3.5, 4.0, and 5.0 mg/kg methyl parathion (423). Treatment with 4.0 or 5.0 mg/kg caused a significant decrease in ovarian weight and the number of healthy follicles but no change in atretic follicles. The number and duration of estrous cycles was significantly affected at 3.5 mg/kg and higher.

When pregnant rats were given 0.3, 1.0 or 3.0 mg/kg/day methyl parathion via gavage on gestation

days 6 through 15, developmental toxicity (increased postimplantation loss and embryonic resorptions, decreased fetal body weight, and delayed ossification) occurred at 3.0 mg/kg/day, but this dose was also maternally toxic (243). Pregnant rats given 1.5 mg/kg/day methyl parathion via gavage on gestation days 6 through 15 exhibited cholinergic toxicity, decreased body weight gain, and an increased number of fetal resorptions (243). When rabbits were given 0.3, 1.0, 3.0, or 5.0 mg/kg/day methyl parathion on gestation days 6 to 18, no maternal or developmental toxicity occurred, other than RBC cholinesterase inhibition at all doses 243.

Pregnant rats given 5, 10, or 15 mg/kg and pregnant mice given 20 or 60 mg/kg methyl parathion via intraperitoneal injection on gestation days 12 and 10, respectively, showed signs of toxicity at all doses (592). Some of the severely affected animals that were treated with the highest dose died. There were no fetotoxic effects in rats. The mice, however, showed more lethality and external malformations (cleft palate) at the highest dose (60 mg/kg). Among pregnant rats given 4.0 mg/kg methyl parathion on gestation days 9 or 15 or 6.0 mg/kg on gestation day 9 via intraperitioneal injection, marked RBC cholinesterase inhibition and some deaths occurred within 30 minutes after injection of 6 mg/kg (424). Embryos of both treated groups had diminished cerebral cortical cholinesterase activity, but there were no effects on fetal mortality or fetal weight and no gross anomalies or developmental defects occurred at either dose.

19.4.1.5 Carcinogenesis Methyl parathion was not carcinogenic in rats or mice given 0, 1, or 2 mg/kg/day (rats) or 0, 4.5–8, or 9.7–16.2 mg/kg/day (mice) methyl parathion via their diet for 2 years (421a). Methyl parathion was not carcinogenic in mice given diets containing 0, 1, 7, or 50 ppm methyl parathion (0, 0.2–0.3, 1.6–2.1, and 9.2–13.7 mg/kg/day) for 2 years, although RBC and brain cholinesterase were decreased in mice given 7 or 50 ppm (243). Nor was methyl parathion carcinogenic when diets that contained 0, 0.5, 2, 5, 10, or 50 ppm methyl parathion were given to rats for 2 years (equivalent to 0.02–0.03, 0.09–0.14, 0.21–0.26, 0.46–0.71, and 2.6-5.0 mg/kg/day) (243). Cholinergic symptoms, hematologic effects, bilateral retinal degeneration, posterior subcapsular cataract, decreased body weight, increased food consumption, and some deaths occurred in rats given 50 ppm. Brain and RBC cholinesterase activity were inhibited in males given the 10- or 50-ppm diets and in females given the 50-ppm diet; RBC cholinesterase activity was inhibited in females given the 10-ppm diet. At 5 ppm, cholinergic toxicity was apparent in one female, hematologic effects were apparent in males only, and RBC cholinesterase activity decreased slightly. Neurological changes (in particular sciatic nerve degeneration) were pronounced in rats that received 50 ppm, and lesions in 5-ppm treated rats were considered significant.

19.4.1.6 Genetic and Related Cellular Effects Studies Assays for mutagenicity of methyl parathion using prokaryotic systems have been both positive and negative. Methyl parathion was both positive and negative in *S. typhimurium* with or without metabolic activation, negative in *S. cerevisiae* for reverse mutation and gene conversion, negative for reverse mutation but positive for 5-methyl tryptophan resistance in *E. coli*, positive for mitotic recombination in *S. cerevisiae* (53, 243); positive for DNA damage in *S. typhimurium* and *E. coli*, and negative for unscheduled DNA synthesis in cultured human lung fibroblasts (53, 408a).

Increases in sister chromatid exchange were observed in Chinese hamster ovary cells with metabolic activation but not in Chinese hamster V79 cells, cultured human lymphoid cells, or lymphoma cells without metabolic activation (53).

Methyl parathion was negative in a mouse dominant lethal assay in which mice were fed diets that contained methyl parathion for 7 weeks, and a dominant lethal effect was not observed in mice given methyl parathion in drinking water for 7 weeks (53).

Increased percentages of lymphocytes that had chromosomal breaks were not found among workers from a pesticide factory that manufactured methyl parathion, but chromosomal aberrations were detected in lymphocytes of individuals who were acutely intoxicated by methyl parathion via oral ingestion, inhalation, or dermal contract (53).

19.4.2 Human Experience 19.4.2.2 Clinical Cases Numerous cases of death and serious toxicity have been reported following acute oral exposure to methyl parathion or following a combination of acute dermal and inhalation exposure (439). Minimal lethal doses were in the range of about 5–10 mg/kg (53).

The degree of RBC acetylcholinesterase inhibition was reported in several cases of combined parathion and methyl parathion poisoning (440). Levels of RBC acetylcholinesterase activity on the day of maximum depression, which ranged from day 1 to day 9 after poisoning, ranged from about 1 to 31% of normal values. This is consistent with RBC cholinesterase activity determined in a pesticide applicator who complained of headache, light headedness, increasing malaise, insomnia, anorexia, and decreased sexual drive, that was 13% of normal (441).

Seven children displayed signs of organophosphate poisoning (lethargy, increased salivation increased respiratory secretions, pinpoint pupils, and respiratory arrest) following their apparent exposure to methyl parathion as a result of its inappropriate use as an insecticide indoors. Significant residues of methyl parathion were found in water used for drinking, orange drink mix, and indoor air (441a). Two of the children died. Upon admission to the hospital, plasma and RBC cholinesterase activities ranged from 20–70% and from 0–26% of normal, respectively.

The occurrence of symptoms consistent with an "intermediate syndrome" began 1 to 3 days after recovery from an acute cholinergic crisis precipitated by ingestion of parathion and methyl parathion (442–444). Symptoms compatible with a diagnosis of an "intermediate syndrome" were respiratory paresis, external ophthalmoparesis, ptosis, proximal limb and neck flexor muscle weakness, and absent or depressed tendon reflexes. Plasma and RBC cholinesterase activities were <5% and <15% of control values, respectively, for as long as this syndrome persisted, and the authors noted that this degree of severe cholinesterase inhibition was not observed in individuals who recovered from a cholinergic crisis without subsequently experiencing this type of syndrome.

Dermal exposure to an estimated 0.06 or 0.11 mg/kg methyl parathion on arms and hands did not result in cholinergic effects in two entomologists who entered a cotton field two hours after it was sprayed with methyl parathion, although RBC cholinesterase activities were markedly depressed in both individuals (432).

Methyl parathion air concentrations ranged from 1–30 mg/m^3 and concentrations from surface wipe samples ranged from 50–980 mg/100 cm^2 in 64 residences that had been sprayed with methyl parathion within the previous 31 days. Although absorption of methyl parathion was evident by the presence of *p*-nitrophenol in the urine of 142 individuals who lived in the affected residences, no adverse clinical effects were reported.

No cholinergic toxicity of RBC or plasma cholinesterase inhibition occurred after two male volunteers ingested 2 mg/day (0.03 mg/kg) methyl parathion for 5 days or 4 mg/day (0.06 mg/kg) for 5 days 1 to 8 weeks later. Nor were clinical signs of cholinergic toxicity apparent among other volunteers who participated in a metabolic study of methyl parathion and were given a single dose of approximately 0.06 mg/kg methyl parathion (410).

Neurological signs did not occur among men who ingested daily doses of methyl parathion that ranged from 1 to 19 mg during a 30-day period. Nor were there any uniform changes in plasma or RBC cholinesterase levels reported at any of these doses (260). By increasing the concentrations of methyl parathion administered to the same experimental population and using the same protocol, a dose that inhibited RBC cholinesterase activity by 55% in one of five subjects was 24 mg/day (76). Assuming that this individual weighed 70 kg, this would be equivalent to about 0.3 mg/kg/day. This dose and higher levels of 28 and 30 mg/day (equivalent to about 0.4 mg/kg/day) did not result in any overt clinical signs of cholinergic toxicity (76, 78).

In a study where methyl parathion (and several organophosphate pesticides) were tested for the frequency of irritant or allergic contact dermatitis in 652 subjects, one subject (described as a farmer who had occupational hand dermatitis) exhibited allergic contract dermatitis (445).

19.4.2.2.3 Pharmacokinetics, Metabolism, and Mechanisms Rapid absorption, metabolism, and elimination of methyl parathion occurred in human volunteers given single oral doses of methyl parathion for 5 consecutive days (410). Metabolites detected in urine 24 hours after dosing included *p*-nitrophenol and dimethyl phosphate. Excretion of the primary metabolite, *p*-nitrophenol, was 60% complete in 4 hours, 86% complete in 8 hours, and 100% complete by 24 hours. Urinary excretion of dimethylphosphate followed a similar pattern and was essentially complete by 24 hours after ingestion.

Absorption of methyl parathion following combination dermal and inhalation exposures was demonstrated in a series of field studies of cotton field workers who reentered a field sprayed with methyl parathion. Urinary *p*-nitrophenol and serum methyl parathion were detected up to 12 hours after exposure, confirming that absorption of methyl parathion had occurred (409, 430, 431). Based on methyl parathion residues measured on skin, dermal exposure were probably much less than 0.1 mg/kg, and based on measured air concentrations, (<0.2 mg/m^3) inhalation exposures probably resulted in absorbed doses much less than 0.02 mg/kg (409, 430, 431). Dermal absorption of 0.06 to 0.11 mg/kg methyl parathion adsorbed on forearms and hands of entomologists (combined with likely inhalation exposure) who worked in a cotton field 2 hours after it was treated with an ultra low volume spray was demonstrated by a concurrent, marked (40% decrease) inhibition of RBC cholinesterase activity (432).

About 5% of an applied dose of a commercial preparation of methyl parathion (*sic*) penetrated human cadaver skin placed in an *in vitro* diffusion cell during a period of 24 hours, whereas only about 1% of an applied dose of methyl parathion in acetone penetrated during 24 hours (433).
19.5 Standards, Regulations or Guidelines of Exposure
Methyl parathion is undergoing reregistration by the EPA for use as a restricted pesticide (154). The ACGIH TLV for methyl paration is 0.2 mg/m^3 with a skin notation. There is no OSHA PEL-TWA for methyl parathion. The NIOSH REL-TWA is 0.2 mg/m^3 with a skin notation. Most other countries have Occupational Exposure Limits for methyl parathion of 0.2 mg/m^3 (Australia, Belgium, Denmark Finland, France, The Netherlands, Switzerland, and the United Kingdom) or 0.1 mg/m^3 (Hungary, Poland, and Russia).

Organophosphorus Compounds
Jan E. Storm, Ph.D

20.0 Mevinphos
20.0.1 CAS Number:
[*7786-34-7*]
20.0.2 Synonyms:
Carboxymethoxy-1-methylvinyl dimethyl phosphate; *O*,*O*-dimethyl 1-carbomethoxy-1-propen-2-yl phosphate; 3-hydroxycrotonic acid methyl ester dimethyl phosphate; *mevinphos*; Duraphos; apavinphos; 2-carbomethoxy-1-1methylvinyl dimethyl phosphate; CMDP; *O*,*O*-dimethyl *O*-(2-carbomethoxy-1-methylvinyl) phosphate; dimethyl 1-carbomethoxy-1-propen-2-yl phosphate; dimethyl 2-methoxycarbonyl-1-methylvinyl phosphate; dimethyl methoxycarbonylpropenyl phosphate; dimethyl phosphate of methyl 3-hydroxy-cis-crotonate; fosdrin; gesfid; gestid; dimethyl phosphate 3-hydroxycrotonoic acid methyl ester; meniphos; menite; 2-methoxycarbonyl-1-methylvinyl dimethyl phosphate; *cis*-2-methoxycarbonyl-1-methylvinyl dimethylphosphate; *cis*-

phosdrin; phosphoric acid, dimethyl ester, ester with methyl 3-hydroxycrotonate; phosphoric acid, (1-methoxycarbonylpropen-2-yl) dimethyl ester; methyl 3-((dimethoxyphosphinyl)oxy)-2-butenoate; methyl 3-hydroxycrotonoate dimethyl phosphate; (*E*)-3-hydroxycrotonic acid, methyl ester, dimethylphosphate; Mevinphos trans+cis isomers; butenoic acid, 3-((dimethoxyphosphinyl)oxy)-, methyl ester; 1-carbomethoxy-1-propen-2-yl dimethyl phosphate; crotonic acid, 3-((dimethoxyphosphinyl)oxy)-, methyl ester; dimethyl *O*-(1-carbomethoxy-1-propen-2-yl) phosphate; methoxycarbonyl-1-methylvinyl dimethyl phosphate; 1-methoxycarbonyl-1-propen-2-yl dimethyl phosphate; Methyl 3-hydroxy-alpha-crotonatedimethyl phosphate

20.0.3 Trade Names:

Menite®; Mevinox®; OS-2046®; Phosdrin®; Phosfene®

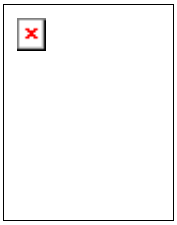
20.0.4 Molecular Weight:

224.16

20.0.5 Molecular Formula:

$C_7H_{13}O_6P$

20.0.6 Molecular Structure:



20.1 Chemical and Physical Properties

Mevinphos is a pale yellow to orange liquid. The commercial product is a mixture of cis and trans isomers; the cis isomer is also referred to as the alpha or E isomer, and the trans isomer is also referred to as the beta or Z isomer. The cis isomer (which is ten times more toxic than the trans isomer) comprises about 60% of the commercial material (445a). Mevinphos is corrosive to black iron, drum steel, stainless steel, and brass. Mevinphos is hydrolyzed in water at pH 11 and has a half-life of 1.4 hours; as the pH is reduced, the rate of hydrolysis is also reduced, so the half-life in water at pH 6 is 120 days.

Specific gravity	1.25 at 20°C
Melting point	21°C (cis); 6.9°C (trans)
Boiling point	325°C at 760 torr
Vapor pressure	2.9×10^{-3} torr at 21°C (trans)
Flash point	79.44°C, open cup
Solubility	miscible with water, acetone, and benzene; slightly soluble in aliphatic hydrocarbons

20.1.2 Odor and Warning Properties Weak Odor.

20.2 Production and Use

Mevinphos was initially registered as a pesticide in the United States in 1957 and was classified as a Restricted Use Pesticide in 1978 (297). It was formulated as a ready-to-use liquid and concentrate and applied to foliage using aerial, boom spray, and airblast equipment to control aphids, mites, thrips, and lepidopterous larvae on a wide variety of crops. Largely as a result of a high incidence of human poisonings, mevinphos is no longer registered for use in the United States (297).

20.4 Toxic Effects

20.4.1.1 Acute Toxicity Mevinphos is an organophosphate that has extremely high oral toxicity and

has LD_{50}s of 3.4–6.8 mg/kg for rats and mice (64a). The dermal LD_{50} is 4.2–4.7 mg/kg for rats, and 33.8 mg/kg for rabbits (64a, 446). In a comparative study, the oral LD_{50} for female rats was 6.0 mg/kg compared to the intraperitoneal LD_{50} of 1.5 mg/kg (446). Intraperitoneal, oral, intravenous, and subcutaneous LD_{50}s were 2.5, 12.3, 0.6, and 1.2 mg/kg, respectively, indicating that mevinphos is less toxic when administered via "hepatic" routes (intraperitoneal and oral) than via "peripheral" routes (intravenous and subcutaneous) (122). This suggests that the process of oral absorption and/or first-pass metabolism by the liver slightly decreases the acute toxicity of mevinphos. One-hour LC_{50} values are 9.8–92 mg/m^3 (155, 448).

Poisoning following oral or intraperitoneal exposure is rapid. Moderate cholinergic signs occur within 5 to 10 minutes. Peak toxicity occurs within 15 to 30 minutes, lasts about 10 minutes, and most deaths occur in 45 minutes. Symptoms develop faster following intraperitoneal exposure. Signs of distress occur in 1 minute, and death usually occurred in 10 minutes or less (446).

Mevinphos does not cause delayed neuropathy in the hen (448).

20.4.1.2 Chronic and Subchronic Toxicity To assess the potential for cumulative toxicity, rats were given intraperitoneal injections of 10, 25, or 50% of the intraperitoneal LD_{50} (1.5 mg/kg) for 5 days/week for 17 to 22 days (446). Cumulative effects were not evident because the only sign observed was slight trembling of the head in rats that received 50% of the LD_{50} immediately after injection. No deaths occurred in any group.

When rats were fed diets that contained 0, 6.3, 12.5, 50, or 100 ppm mevinphos (about 0, 0.5, 1.0, 4.0, or 8.0 mg/kg/day) for 60 days all rats fed 100 ppm died within 3 weeks (446). Rats in all dosed groups showed slight tremors. In another study, rats were fed diets that contained 0, 0.3, 2, 5, 25, 50, 100, or 200 ppm (about 0, 0.02, 0.16, 0.4, 2.0, 4.0, 8.0, or 16 mg/kg/day) for 13 to 18 weeks or a diet that contained 150 ppm for 5 weeks followed by a diet that contained 300 ppm for 2 weeks and a diet that contained 400 ppm for 6 weeks (447). Cholinergic signs were "minimal" (*sic*) at 25 ppm and increased progressively with increasing dietary level; signs were not reported in rats given the 5-ppm diet. Additionally, nonspecific, diffuse, toxic degeneration of the liver and renal tubular epithelium and degeneration of the epithelial cells that line ducts and acini of the exocrine glands occurred. RBC cholinesterase activity progressively decreased during the experimental period in rats fed diets that contained 2 ppm mevinphos or more. Brain cholinesterase was inhibited in rats fed diets of 25 ppm mevinphos or more.

When dogs were fed diets that contained 0, 0.3, 1.0, 2.5, 5.0, 75, or 200 ppm mevinphos (about 0, 0.0075, 0.025, 0.0625, 0.125, 1.875, or 5 mg/kg/day) for 14 weeks, cholinergic signs occurred in dogs given the 75- and 200-ppm diets (447). Dogs fed the 2.5- or 5-ppm diet had inhibited RBC cholinesterase activity. The 1-ppm diet had no effect on RBC cholinesterase activity. Brain cholinesterase activity was inhibited in dogs given 7.5 or 200 ppm.

20.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms The similarity of LD_{50} values and the rapid occurrence of cholinergic signs regardless of route of exposure indicates that mevinphos is well absorbed via all relevant routes of exposure. Indeed, approximately 94% of an orally administered dose to rats was absorbed, and dermal absorption of mevinphos in the rats was reportedly approximately 16.8% of an applied dose (448).

In the first 24 hours, 18% of an orally administered dose of mevinphos was excreted in the urine, at 76% was excreted in expired air. Mevinphos was distributed to all human organs within 45 minutes of ingestion of a lethal dose.

Mevinphos is rapidly hydrolyzed *in vivo* in humans to dimethyl phosphate which subsequently

appears in the urine (449–451). In two cases of occupational mevinphos poisoning, peak urinary dimethylphosphate concentrations occurred within 12 hours of exposure, and elimination in urine was essentially complete within 50 hours of initial exposure (449). Initial urine concentrations of dimethyl phosphate in mevinphos-poisoned individuals wee 4.7 and 4.0 mg/L. Total excretion of dimethyl phosphate, it was estimated, was equivalent to 7.7 or 9.2 mg mevinphos. These findings are similar to that observed in two mevinphos poisonings where urine concentration of dimethyl phosphate at hospital admission was about 5 mg/L (411).

20.4.1.4 Reproductive and Developmental Mevinphos did not cause reproductive toxicity in rats fed a diet that contained mevinphos for two generations (448). Other studies indicated that no developmental toxicity occurred in rats or rabbits when they were administered mevinphos during gestation (448). No other details were provided.

20.4.1.5 Carcinogenesis No evidence of carcinogenicity was reported in chronic mice and rat studies (No other details were provided) (448).

A no-observed-effect level for inhibition of RBC cholinesterase in a chronic dog study was 0.025 mg/kg/day (448). A 1-year no-observed-effect level for inhibition of brain cholinesterase activities in rats was 0.025 mg/kg/day (lowest observed effect level = 0.35 mg/kg/day); and, a 2-year no-observed-effect level for clinical signs in rats was also 0.025 mg/kg/day (448). No other details were provided.

20.4.1.6 Genetic and Related Cellular Effects Studies Mevinphos was mutagenic with or without metabolic activation in *S. typhimurium* and in an assay with Chinese hamster ovary cell (448). Mevinphos with or without metabolic activation also caused chromosomal aberrations in Chinese hamster cells *in vitro* but did not increase unscheduled DNA synthesis (448).

20.4.2 Human Experience 20.4.4.2 Clinical Cases Initial symptoms of organophosphate poisoning (nausea, vomiting) occurred between 1 to 2 hours in a worker exposed while spraying greenhouse carnations and a worker exposed while cleaning out a spray bottle. Initial symptoms in both cases were followed by blurred vision, fasciculations, weakness, and miosis. Hospitalization occurred about 10 or 3 hours after exposure, respectively, at which time RBC and plasma cholinesterase activities were about 10% of normal laboratory values (449). The estimated intake of mevinphos based on quantification of dimethyl phosphate in urine was 7.7 and 9.2 mg which would be about 0.1 mg/kg, assuming a 70-kg body weight.

Widespread poisoning, apparently due mostly to dermal contact, occurred among nineteen farm workers who worked in a cauliflower field that had been sprayed 4 hours earlier with a mixture of mevinphos and phosphamidon (451a). Within minutes of beginning work, workers developed blurred vision and headache, followed by nausea, weakness, vomiting, abdominal pain, and dizziness; two workers collapsed, one into unconsciousness. Sequential determinations made during a 4-week period of recovery indicated the plasma and RBC cholinesterase activities had initially been inhibited by an average of 66% and 32%, respectively. Plasma and RBC cholinesterase activities in poisoned individuals returned to normal levels by about 57 and 66 days after poisoning, respectively (118). In another case of occupational poisoning, twenty-nine workers who were packing and cutting lettuce in a field 2 hours after it had been sprayed with mevinphos experienced eye irritation, headache, visual disturbances, dizziness nausea, vomiting, weakness, chest pain or shortness of breath, skin irritation, pruritis, eyelid fasciculation, arm fasciculation, excessive sweating, and diarrhea (118). Sequential determinations made during a 2-week period of recovery indicated that plasma and RBC cholinesterase activities had initially been inhibited by an average of 16% and 6% respectively.

Another case of widespread occupational mevinphos poisoning was that of twenty-six men who worked in nineteen different apple orchards where mevinphos was used to control apple aphids (454). Twenty-three of the workers who were exposed during mixing/loading or application of

mevinphos experienced nausea, vomiting, dizziness, visual disturbances, muscle weakness, abdominal pain, headache, sweating, and salivation. Seven workers were hospitalized; four required intensive care. RBC cholinesterase activity was depressed to at least 25% below the lower limit of normal in affected workers.

Among cases of accidental poisoning by dermal contact, six children were poisoned after wearing mevinphos-contaminated trousers that had been sold as "damaged goods" (452); a 17-year-old boy experienced delayed mevinphos poisoning, which appeared 2 days after initial contact, as a result of continued wearing of contaminated clothing (453); and an orchardist experienced typical signs of anticholinesterase poisoning 10 hours after mevinphos was applied as a patch test at a dose estimated at 14 mg/kg (312). In other cases, a farmer was poisoned after his boots were accidentally filled with mevinphos solution, and four formulators experienced symptoms of cholinesterase inhibition up to 48 hours after their last contact with mevinphos (450, 451).

Severe poisoning characterized by unconsciousness, pinpoint pupils, profuse sweating, and salivation and accompanied by acute pancreatis was reported for a 37-year-old woman who intentionally ingested 200 mL mevinphos (454a).

The predominant role of dermal absorption of mevinphos in occupational settings was illustrated in a study of greenhouse workers in Finland (454b). Inhalation exposure was measured during 2 days after application of mevinphos to greenhouse plants by measuring mevinphos in green house air. Workers' dermal exposure was measured with patch and hand-wash samples. Greenhouse air concentrations in breathing zones ranged from about 0.04 mg/m^3 (detection limit) to 11.4 mg/m^3 after spraying or use of automatic foggers that resulted in maximum inhalation doses up to about 0.002 mg/kg/day. Intake from dermal exposure would have been considerably more: up to 298 mg/hr mevinphos was determined by measuring mevinphos in hand-washing water from one worker and up to 20 mg/hr mevinphos was determined using patch samples. An additional study of these workers showed that decreases in plasma and RBC cholinesterase activity correlated well with estimated dermal exposure to mevinphos reflected in hand-wash water concentration (455).

Five male volunteers were given various doses of mevinphos daily for 30 days (456). A dose of 1.0 mg/day (about 0.01 mg/kg/day) had no effect during the test period, but RBC acetylcholinesterase activity decreased by as much as 17% in two subjects during the 30-day posttest period. Doses of 1.5, 2.0, or 2.5 mg/day inhibited RBC cholinesterase in all subjects. None of these doses affected plasma cholinesterase activity. No cholinergic signs were directly related to treatment, although loose stools were occasionally reported.

Mean reductions in RBC cholinesterase and plasma cholinesterase activities of 19% and 13%, respectively, occurred in eight volunteers who ingested 0.025 mg/kg/day mevinphos for 28 days (456a, 472). No signs or symptoms of organophosphate intoxication were detectable, and no changes in standard clinical chemistry parameters, other than the reductions in cholinesterase activities, were observed at this dose.

20.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV for mevinphos is 0.09 mg/m^3 with a skin notation (154). The OSHA PEL-TWA is 0.1 mg/m^3 and the NIOSH REL-TWA is 0.1 mg/m^3.

Organophosphorus Compounds
Jan E. Storm, Ph.D

21.0 Monocrotophos

21.0.1 CAS Number:

[*6923-22-4*]
21.0.2 Synonyms:
(*E*)-dimethyl 2-methylcarbamoyl-1-methylvinyl phosphate; (*E*)-*O*,*O*-dimethyl-*O*-(1-methyl-3-oxo-1-propenyl) phosphate, phosphoric acid, dimethyl (*E*)-1-methyl-3-(methylamino)-3-oxo-1-propenyl ester; Biloborn; Nuvacron; Phosphoric acid (E)-dimethyl 1-methyl-3-(methylamino)-3-oxo-1-propenyl ester; dimethyl 1- methyl-3-(methylamino)-3-oxo-1-propenyl phosphate; phosphoric acid, dimethyl 1-methyl-3-(methylamino)-3-oxo-1-propenyl ester, (*E*); Corophos; Monocil; Parryfos; dimethoxyphosphinyloxy-*N*-methyl-*cis*-crotonamide; dimethyl phosphate ester of 3-hydroxy-*N*-methyl-*cis*-crotonamide; hydroxy-*N*-methyl-*cis*-crotonamide dimethyl phosphate; phosphoric acid, dimethyl ester, ester with 3-hydroxy-*N*-methylcrotonamide
21.0.3 Trade Names:
Azodrin®; Monocron®; Nuvacron®
21.0.4 Molecular Weight:
223.16
21.0.5 Molecular Formula:
$C_7H_{14}NO_5P$
21.0.6 Molecular Structure:

21.1 Chemical and Physical Properties
Monocrotophos is a reddish brown solid.

Melting point	54–55°C; 25–30°C
Boiling point	125°C at 0.005 mmHg
Vapor pressure	7×10^{-5} mmHg at 20°C
Solubility	soluble in water, acetone, and alcohol; very slightly soluble in kerosene and diesel fuel

21.1.2 Odor and Warning Properties Possesses a mild ester odor.
21.2 Production and Use
Monocrotophos was introduced in 1965 and used as a systemic and contact organophosphorus insecticide and acaricide to control a variety of sucking, chewing, and boring insects and spider mites on cotton, sugarcane, peanuts, ornamentals, and tobacco (155). All registrations for monocrotophos have been cancelled in the United States but it is available in other countries as a soluble concentrate or an ultralow volume spray.
21.4 Toxic Effects
21.4.1.1 Acute Toxicity Monocrotophos is an organophosphate that has high oral toxicity and oral LD_{50s} of 17–20 mg/kg for rats (164a). Intraperitoneal, oral, intravenous, and subcutaneous LD_{50}s for monocrotophos were 8.9, 14.3, 9.2, and 8.7 mg/kg, respectively, for mice, indicating that it is equally potent whether exposure is via an "hepatic" (intraperitoneal and oral) or "peripheral" (intravenous and subcutaneous) route (122). Regardless of route of exposure, lethality occurs rapidly within 5 minutes. Dermal LD_{50}s are 112–129 mg/kg for rats and 270–354 mg/kg for rabbits (64a, 457). A 4-hour LC_{50} of 100 mg/m^3 and a 1-hour LC_{50} of 163–176 mg/m^3 have been reported (458).

Among mice given single oral doses of 1, 2, or 4 mg/kg monocrotophos, reduced locomotor activity occurred at 1 mg/kg and deficits in performance on a rotating rod occurred at 4 mg/kg (459). Among rats given single oral doses of 0, 2, 4, or 6 mg/kg monocrotophos, hypothermia occurred at all levels

(459). Cholinergic signs occurred in rats given 6–9 mg/kg/day for 1, 3, 7, 11, or 16 days, but only until 4 to 9 days; signs were absent after 10–11 days. Repeated exposure of rats to 4.5 or 6 mg/kg/day for 16 days also caused overt cholinergic toxicity that diminished by the seventh day of exposure and illustrated accomodation to lowered cholinesterase activity. All rats given three doses of 0.45, 0.85, 1.75, or 3.5 mg/kg/day monocrotophos on alternate days exhibited mild cholinergic signs (461).

Rabbits treated dermally with 20 or 40 mg/kg/day monocrotophos for 6 h/day, 5 days/week for 3 weeks exhibited no clinical signs of toxicity (458). Monocrotophos was not irritating to eyes or skin and was not sensitizing under conditions of current standard tests in rabbits and guinea pigs (458).

Two single doses of 6.7 mg/kg monocrotophos 3 weeks apart were fatal in nine of fourteen atropinized hens (458). The hens that survived two doses did not develop signs of delayed neurotoxicity during an observation period of 3 weeks after the second dose.

Decreased body weight and reduced brain, RBC, and plasma cholinesterase activities occurred in rats given diets that contained 8 ppm monocrotophos (about 0.6 mg/kg/day) for 8 to 13 weeks (458). Body weight gain decreased in rats given diets that contained 45 or 135 ppm and blood and brain cholinesterase were inhibited in rats given diets that contained 1.5 ppm for 12 weeks (458). Mild tremors occurred in dogs given diets that contained 135 ppm, for less than 9 weeks and blood and brain cholinesterase were inhibited in dogs given 15 ppm for 13 weeks (458). In rats treated with 0.3, 0.6, or 1.2 mg/kg/day monocrotophos by gavage for 90 days, brain and whole blood cholinesterase were inhibited at all levels (458).

21.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Monocrotophos is well absorbed orally and rapidly excreted. Sixty-three to 85% of an oral dose of monocrotophos was excreted in the urine of rats within 12–48 hours; the majority appeared within the first 6 hours (466). By 96 hours, 82%, 3%, and 6% of the dose was eliminated in urine, feces and expired air, respectively (466). An additional 5% of the dose appeared in feces within 48 hours. Most of the excreted dose in urine was present as water-soluble hydrolytic products (e.g., dimethyl phosphate), and the remainder was the parent compound or the *N*-hydroxymethyl amide analog of monocrotophos (160).

Human volunteers given a single intravenous injection of monocrotophos rapidly excreted 67 ± 5% of the dose in the urine within 4 to 8 hours. The elimination half-life was about 20 hours (66). When monocrotophos was applied dermally (4 mg/cm^2) to the forearm, 14± of the dose was found in the urine within 120 hours. When covered with a vaporproof film for 72 hours, 33% of the applied dose was absorbed.

The metabolism of monocrotophos involves three different reactions: N-demethylation, O-demethylation, and cleavage of the vinyl phosphate bond. Cleavage of the vinyl phosphate bond is the primary pathway resulting ultimately in excretion of resultant degradation products and conjugates in urine (466). Metabolism is not necessarily complete because significant amounts of unmetabolized monocrotophos are also excreted in urine and feces.

21.4.1.4 Reproductive and Developmental Rats given diets that contained 10 ppm monocrotophos for two generations had lower body weights, decreased male mating index, lengthened gestation periods, fewer litters, reduced viability and lactation indices, and decreased pup weights in both generations (458). Those given diets that contained 3 ppm had lower pup weights in the second generation, and those given 0 or 0.1 ppm exhibited no adverse reproductive or developmental effects.

When rats were given 0.3, 0.6 or 1.2 mg/kg/day monocrotophos by gavage for two weeks before mating and throughout gestation and lactation, average birth weight and crown–rump length decreased in the 1.2-mg/kg/day group, but this dose was also maternally toxic. No fetotoxicity

occurred among rats given 0.1, 0.3, 1, or 2 mg/kg/day by gavage on gestation days 6 through 15 in the absence of maternal toxicity which occurred at 1 mg/kg/day (458). No fetotoxicity occurred among rabbits given 0.1, 1, 3, or 6 mg/kg/day by gavage on gestation days 6 through 18 in the absence of maternal toxicity which occurred at 3 mg/kg/day (458).

21.4.1.5 Carcinogenesis No carcinogenicity or other adverse effects occurred in mice given diets that contained 1, 2, 5, or 100 ppm monocrotophos (about 0.15, 0.30, 0.75 or 1.5 mg/kg/day) for 2 years, other than inhibition of RBC and brain cholinesterase at all levels (458). No carcinogenicity or other adverse effects occurred in rats given diets that contained 0.01, 0.03, 0.1, 1, 10, or 100 ppm (equivalent to 0.001, 0.002, 0.005, 0.05, 0.5, or 5 mg/kg/day) other than reduced weight gain at 10 ppm and higher, and RBC and brain cholinesterase inhibition at 1 ppm and higher (458).

No carcinogenicity or other adverse effects occurred in dogs given diets that contained 0.16, 1.6, or 16 ppm monocrotophos (about 0.004, 0.04, or 0.4 mg/kg/day) for 2 years, other than inhibition of RBC cholinesterase at 16 ppm and brain cholinesterase activity at 100 ppm (458).

21.4.1.6 Genetic and Related Cellular Effects Studies Monocrotophos is consistently mutagenic in *in vitro* test systems (458). It was positive in the Ames assay (458a). A dose- and incubation-time-dependent increase in the frequency of chromosomal aberrations occurred in human lymphocytes incubated with monocrotophos. The incidence of sister chromatid exchanges also increased in a dose- and time-dependent manner.

In vivo studies also indicate that monocrotophos is mutagenic. Significant increases is chromatid breaks occurred in bone marrow cells of rats given monocrotophos (462). Chromosomal aberrations in bone marrow cells increased in rats treated orally with monocrotophos (463). Monocrotophos caused somatic mutations and also induced sex-linked recessive lethal mutations among *D. melanogaster* fed contaminated diets (464). In chicks, monocrotophos increased the occurrence of micronuclei in erythrocytes of bone marrow and peripheral blood when administered once daily for 30 days (465).

21.4.2 Human Experience 21.4.2.2 Clinical Cases Death followed ingestion of an estimated dose of 1200 mg monocrotophos by a woman (about 20 mg/kg assuming 60 kg body weight). The highest concentrations of monocrotophos were found in brain and lung, followed by blood, kidney, and liver (467). Accidental ingestion has also resulted in coma, but patients have recovered without sequelae after prolonged hospitalization (468). A 19-year-old man splashed about 570 mL monocrotophos on his bare chest and arms. He initially experienced no symptoms but within 28 hours he vomited and experienced muscular weakness, chest pain, and blurred vision. Later, he experienced blackouts and intervening lucid intervals. By 38 hours, he could not stand and experienced dry retching, sweating, and confusion. He was hospitalized, treated, and discharged from the hospital 10 days later (469).

Monocrotophos is one of a group of organophosphate compounds associated with the “intermediate syndrome” that is characterized by sudden respiratory distress, proximal limb muscle weakness, and motor cranial nerve palsies that occur 1 to 4 days after acute poisoning. In one case, an individual was poisoned when a bottle containing monocrotophos was thrown at his head and broke, creating a laceration and spilling liquid over his head and face (470). After 6 to 7 hours, he experienced nausea, vomiting, abdominal pain, miosis, fasciculations, and excessive sweating. He was successfully treated with atropine and pralidoxime, but on the fourth day he developed respiratory distress with cyanosis and bradycardia along with weakness of limbs. He was artificially ventilated and eventually recovered. In another case, a male who had ingested monocrotophos and been treated with atropine and pralidoxime developed respiratory distress after 70–80 hours and required ventilatory support (471). He had bilateral facial paresis and weakness of the neck muscles and proximal limb muscles. Fasciculations were seen in the limbs. Deep tendon reflexes were absent in the upper limbs but were normal in the lower limbs. He gradually improved and was discharged after 16 days. In another report, an “intermediate syndrome” was described in an individual who ingested monocrotophos in a suicide attempt and in a worker who was poisoned while spraying monocrotophos (358). In both

cases, a well-defined cholinergic phase was followed after 24–96 hours by respiratory difficulty and cranial nerve weakness which lasted 16 to 18 days.

Exposures to monocrotophos experienced by farmers during the spraying of cotton fields were roughly estimated at between 0.007 and 0.02 mg/kg/day based on concentrations of dimethyl phosphate excreted in urine during a 24-hour period after exposure. No overt symptomology was recorded, and RBC cholinesterase activity was unaffected (472a).

Volunteers who had worked for 5 hours in cotton fields treated with monocrotophos either 48 or 72 hours earlier showed no signs of organophosphate poisoning and no RBC cholinesterase inhibition (409).

When groups of volunteers were given oral monocrotophos at 0.0036 and 0.0057 mg/kg/day for 1 month, plasma cholinesterase was reduced, but RBC cholinesterase activity was not changed (472). Signs or symptoms of cholinergic toxicity that could be ascribed to monocrotophos were not reported in the volunteers.

21.5 Standards, Regulations, or Guidelines of Exposure

All registrations of monocrotophos in the United States have been cancelled, and tolerances are being revoked. The ACGIH TLV for monocrotophos is 0.25 mg/m^3 with a skin notation (154). There is no OSHA PEL-TWA for monocrotophos. The NIOSH REL-TWA is 0.25 mg/m^3.

Organophosphorus Compounds

Jan E. Storm, Ph.D

22.0 Naled

22.0.1 CAS Number:

[*300-76-5*]

22.0.2 Synonyms:

Dimethyl-1,2-dibromo-2,2-dichloroethyl phosphate; Ortho 4355; Bromochlorphos, dimethyl-1,2-dibromo-2,2-dichlorethyl; Dibrom; phosphoric acid 1,2'2-dibromo-2,2-dichloroethyl dimethyl ester; Alvora; Bromex; Dibromfos; 1,2-dibromo-2,2-dichloroethyl dimethyl phosphate; dimethyl *O*-(1,2-dibromo-2,2-dichloroethyl) phosphate; Hibrom

22.0.3 Trade Names:

Bromchlophos®; Bromix®; Dibrom®

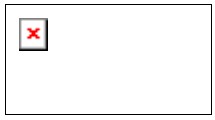
22.0.4 Molecular Weight:

380.79

22.0.5 Molecular Formula:

$C_4H_7Br_2Cl_2O_4P$

22.0.6 Molecular Structure:



22.1 Chemical and Physical Properties

Pure naled is a white solid; the technical form is 60% pure, and it is usually obtained as a liquid. Naled is completely hydrolyzed (90% to 100%) within 48 hours at room temperature in the presence of water. It is degraded by sunlight and should be stored in lightproof containers.

Specific	1.96 at 25°C (technical)

gravity	
Melting point	26°C (pure)
Boiling point	110°C at 0.5 torr (technical)
Vapor pressure	0.002 torr at 20°C; 2×10^{-4} mmHg at 20°C
Solubility	practically insoluble in water; slightly soluble in aliphatic solvents; very soluble in aromatic and oxygenated solvents

22.1.2 Odor and Warning Properties Has a slightly pungent odor.

22.2 Production and Use

Naled is a liquid insecticide and acaricide used to control mosquitoes and insects on many field crops, on plants in greenhouses, and in mushroom cultivation. It is formulated as a soluble concentrate/liquid (85% a.i.), an emulsifiable concentrate (36–58% a.i.), liquid ready to use (1–35% a.i.), ultra low volume (1–35% a.i.), dust (4% a.i.), and an impregnated collar (7–15% a.i.) Dichlorvos is frequently an impurity of technical naled.

22.4 Toxic Effects

22.4.1.1 Acute Toxicity Naled is an organophosphate that is moderately toxic and has oral LD_{50s} of 92 to 375 mg/kg for mice and rats (62, 64a, 203). Dermal LD_{50}s of naled are 800 mg/kg for rats and, 360–390 mg/kg for rabbits (64a). A 4-hour LC_{50} of 190–200 mg/m^3 was reported for rats (471a).

When rats were given a single oral dose of 25, 100, or 400 mg/kg naled, the 400-mg/kg dose produced mortality and transient decreases in body weight gain (471a). Rats of both sexes given 100 or 400 mg/kg and females given 25 mg/kg showed marked cholinergic effects. No treatment-related neurological effects were observed 7 or 14 days after treatment at any dose level.

When rats were exposed to 3.4, 7.2, or 12.1 mg/m^3 naled for 6 hours/day, 5 days/week for 3 weeks, a dose-dependent inhibition of brain, RBC, and plasma cholinesterase occurred at all concentrations (473).

Hens treated with atropine sulfate and pralidoxime and then given two acutely toxic doses of naled 21 days apart showed clinical signs of neurotoxicity but no locomotor ataxia characteristic of delayed neurotoxicity (471a). However, axonal degeneration in the spinal cord increased in naled-treated hens.

Naled caused severe eye and dermal irritation in rabbits and was weakly positive in a skin sensitization test in guinea pigs (471a).

22.4.1.2 Chronic and Subchronic Toxicity When rats were exposed to 0.2, 1, or 6 mg/m^3 naled for 6 hours/day, 5 days/week, exposure to 6 mg/m^3 resulted in cholinergic signs of toxicity (471a). Brain cholinesterase was inhibited at 6 mg/m^3, and RBC cholinesterase was inhibited at 1 and 6 mg/m^3.

When rats were fed diets delivering 0, 0.25, 1, 10, 100 mg/kg/day naled for 28 days, cholinergic effects occurred at 10 mg/kg/day, but not at lower doses (471a). When rats were exposed to naled by dermal application of 1, 20, or 80 mg/kg/day naled for 6 hours/day, 5 days/week for 28 days, the two highest doses were irritating to the skin (471a). Exposure to 20 and 80 mg/kg/day also produced systemic toxicity. Body weight gain by males was depressed, RBC and brain acetylcholinesterases were inhibited at 20 and 80 mg/kg/day, liver and adrenal weights of 80-mg/kg treated females increased, and mild renal effects were observed.

When 0.4, 2.0, or 10.0 mg/kg/day naled was given to rats by gavage for 90 days, cholinergic effects

occurred in three of ten high-dose females (471a). No other clinical effects occurred in either sex at any other dose level.

23.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms No data quantifying absorption after oral, inhalation, or dermal exposures to naled are available, but absorption via all routes of exposure is expected to be nearly equal based on the relatively low oral and dermal LD_{50}s and inhalation LC_{50}s reported.

O,*O*-Dimethyl-2,2-dichlorovinyl phosphate (dichlorvos) is a metabolite of naled as are other hydrolytic products such as methyl phosphates (mono- and di-), *O*-methyl 2,2-dichlorovinyl phosphate (desmethyl dichlorvos), and inorganic phosphate (471a). Three metabolites were identified were in an *in vitro* study using the rat liver homogenates, dichlorvos, dichloroacetaldehyde, and bromodichloroacetaldehyde (471a).

Metabolism of naled to dimethyl phosphate was demonstrated indirectly in individuals who were outdoors during aerial spraying with a naled and temephos mixture for mosquito control (1). Urinary dimethyl phosphate concentrations increased from a maximum of 0.06 ppm to a maximum of 0.50 ppm within 3 hours after spraying.

22.4.1.4 Reproductive and Developmental When rats were given 2, 6, or 18 mg/kg/day naled by gavage for two generations, body weight gain was depressed at 18 mg/kg/day for F_0 males and at all dose levels for F_1 males (471a). Reproductive indexes were unaffected in both generations. Survival of pups was reduced at 18 mg/kg/day in the F_1 and F_{2b} generations, and a consistent pup weight consistently decreased during lactation in both generations.

When naled was given to pregnant rats at doses of 2, 10, or 40 mg/kg/day by gavage on gestation days 6 through 19, 40 mg/kg/day was maternally toxic produced cholinergic signs, and reduced weight gain. No developmental toxicity occurred at any dose. There was a marginal effect on resorptions at 40 mg/kg/day, but, because this dose was also maternally toxic it was not considered significant (471a). When pregnant rats were treated orally with 25 to 100 mg/kg naled on gestation days 6 through 15, no adverse teratogenic effect was evident (471b). No maternal or developmental toxicity occurred in rabbits given 0.2, 2, or 8 mg/kg/day naled by gavage on gestation days 7 through 19, although mild cholinergic signs occurred in adults at 2 mg/kg/day.

22.4.1.5 Carcinogenesis When dogs were given 0.2, 2.0, or 20 mg/kg/day naled by gavage for one year, cholinergic signs, increases in mineralization of spinal cord, and mild testicular degeneration in males occurred at 2 and 20 mg/kg/day (471a). RBC and brain cholinesterase activities were depressed at these same dose levels. Anemia also occurred at 2 and 20 mg/kg/day, and RBC count, hemoglobin, and hematocrit were reduced. At 20 mg/kg/day, liver and kidney weights increased but were unaccompanied by histopathological changes.

There was no evidence of carcinogenicity among rats given 0.2, 2, or 10 mg/kg/day naled by gavage for 2 years, although there was a reduction in brain and RBC cholinesterase activity at 2 or 10 mg/kg/day (471a).

Cholinesterase activity of rats treated at 0.2 mg/kg/day was unaffected. Cholinergic signs occurred on isolated occasions after dosing in four females given 10 mg/kg/day; no other adverse effects were observed at any dose.

There was no evidence of carcinogenicity when mice were administered 3, 15, or 75 mg/kg/day naled by gavage for 89 weeks (471a). The high dose was reduced to 50 mg/kg/day after 26 weeks due to cholinergic signs and high mortality. The only other treatment-related finding was a slight reduction in weight gain by males that showed a dose-related trend at the middle- and high-dose

levels. Cholinesterase activity was not determined.

22.4.1.6 Genetic and Related Cellular Effects Studies Naled was positive for gene mutation in the *S. typhimurium* reverse mutation assay but did not induce DNA damage in a *rec*-type repair test with *Proteus mirabilis* strains PG713 (*rec*-, *hcr*-) and PG273 (wild-type) (471a). The mutagenicity of naled is due to the direct alkylating ability of the parental molecule and to mutagenic metabolites (e.g., dichlorvos) generated by enzymatic splitting of the side chain. Glutathione-dependent enzymes in the S9 mix eliminate the mutagenic activity of naled completely (474).

Naled exhibited no potential to induce mutations in an *in vivo* gene mutation study (mouse spot test) that used mice given 3, 20, or 150 mg/kg/day naled by gavage on gestation days 8 to 12 (471a).

Naled produced no nuclear anomalies in a mouse bone marrow micronucleus assay in mice and had no clastogenic effect in an *in vivo* cytogenetic study in which rats were given naled by gavage (471a).

22.4.2 Human Experience Acute symptoms following accidental or intentional poisoning by naled include typical cholinergic signs that disappear after 2 days (475).

Dermal exposures to naled caused residual papular dermatitis on the arm, glazing on the skin of the cheek, mild irritation of the neck skin, and a maculopapular eruption of the abdomen that caused a contact sensitization type dermatitis (476). Dermatitis was also caused by picking flowers sprayed with naled. In another case, contact dermatitis was reported in an aerial applicator who had used naled (477).

22.5 Standards, Regulations, or Guidelines of Exposure

The 90% technical product of naled is currently registered with EPA and is undergoing reregistration. The ACGIH TLV for naled is 3 mg/m^3 with a skin notation (154). The OSHA PEL-TWA and NIOSH REL-TWA is 3 mg/m^3 with a skin notation.

Organophosphorus Compounds

Jan E. Storm, Ph.D

23.0 Parathion

23.0.1 CAS Number:

[*56-38-2*]

23.0.2 Synonyms:

O,*O*-Diethyl *O*-*p*-nitrophenyl phosphorothioate; DNTP; Ethyl parathion; ethyl parathion; parthion; Foliclal; Fostox; Rhodiatox; diethyl *p*-nitrophenyl monothiophosphate; SNP; E 605; ac 3422; Etilon; phoskil; deoxynucleoside 5'-triphosphate; Parathion-E; Aqua 9-Parathion; phosphorothioic acid *O*,*O*-diethyl-*O*-(4-nitrophenyl) ester; diethyl *p*-nitrophenyl thiophosphate; *O*,*O*-diethyl-*O*-(*p*-nitrophenyl) thionophosphate; diethylparathion; *p*-nitrophenol *O*-ester with *O*,*O*-diethylphosphorothioate; AAT; AATP; acc 3422; American Cyanamid 3422; Aralo; B 404; bay e-605; bayer e-605; bladan f; compound 3422; corothion; corthione; danthion; ecatox; fosfive; fosova; fostern; genithion; kolphos; kypthion; lirothion; murfos; nitrostygmine; niuif-100; nourithion; oleofos 20; oleoparathion; Orthosphos; panthion; Paramar; paramar 50; parathene; Parawet; pestox plus; pethion; phosphemol; phosphenol; phosphostigmine; RB; stathion; strathion; sulfos; T-47; thiophos 3422; TOX 47; vapophos; diethyl *para*-nitrophenol thiophosphate; diethyl 4-nitrophenyl phosphorothionate; diethyl *p*-nitrophenyl thionophosphate; drexel parathion 8E; E 605 F; e 605 forte; ekatin wf & wf ulv; ekatox; ethlon; folidol e605; folidol e & e 605; folidol oil; fosfermo; fosfex; gearphos; lethalaire g-54; oleoparaphene; OMS 19; PAC; Pacol; Paradust; rhodiasol; rhodiatrox; selephos; sixty-three special e.c.; soprathion; super rodiatox; vitrex; penncap e; thiomex; tiofos; Viran; Durathion;

Thionspray No. 84; diethyl *O*-*p*-nitrophenyl phosphorothioate; Fosferno 50; Niran; *O*,*O*-diethyl-*O*-*p*-nitrophenylthiophosphate

23.0.3 Trade Names:

Paraphos®; Alkron®, Alleron®, Aphamite®, Etilon®, Folidol®, Bladan® (Registered); Fosferno®, Niram®, Parapos®, Rhodiatos®

23.0.4 Molecular Weight:

291.27

23.0.5 Molecular Formula:

$C_{10}H_{14}NO_5PS$

23.1 Chemical and Physical Properties

Parathion is a pale yellow liquid. Parathion is stable in acids but hydrolyzes readily in alkaline solutions. It slowly decomposes in air to paraoxon. At temperature above 120°C, parathion decomposes and may develop enough pressure to cause containers to explode. Thermal decomposition may release toxic gases such as diethyl sulfide, sulfur dioxide, carbon monoxide, carbon dioxide, phosphorus pentoxide, and nitrogen oxides.

Specific gravity	1.26 at 25°C
Melting point	6°C
Boiling point	375°C at 760 mmHg
Vapor pressure	3.78×10^{-5} torr at 20°C
Solubility	very slightly soluble in water (20 ppm); completely soluble in esters, alcohols, ketones, ethers, aromatic hydrocarbons, and animal and vegetable oils; insoluble in petroleum ether, kerosene, and spray oils

23.1.2 Odor and Warning Properties Faint odor of garlic at temperatures above 6°C.

23.2 Production and Use

Parathion is a broad-spectrum pesticide and acaracide with a wide range of applications on many crops against many insect species. In 1992 the U.S. Environmental Protection Agency (EPA) cancelled all uses of parathion on fruit, nut, and vegetable crops. The only uses continued are those on alfalfa, barley, corn, cotton, sorghum, soybeans, sunflowers, and wheat (477a).

23.4 Toxic Effects

23.4.1.1 Acute Toxicity Parathion is a highly toxic organophosphate compound that has oral LD_{50s} of 1–30 mg/kg for rats, mice, and guinea pigs (62, 64, 268). Dermal LD_{50s} for rats are 7–21 mg/kg (64, 268). Approximate lethal dermal doses to the rabbit ranged from 150 to 2800 mg/kg, depending on the formulation applied (252). A 4-hour LC_{50} of 32 mg/m^3 was reported for rats (123). Two-hour exposures to 3–4 mg/m^3 of a spray of commercial parathion were lethal to the female rat (252). Death occurs rapidly at lethal oral or inhalation exposures. In dermal exposures, death is often delayed, and in rabbits an “intermediate-type syndrome” occurred characterized by paralysis that affect the muscles of the neck and the extensor muscles of the forelegs (“foot drop”) (252).

Intraperitoneal LD_{50}s were 3–7 mg/kg for adult rats and mice, but 1 mg/kg for neonates (Benke and Murphy 1975); and subcutaneous maximum tolerated doses (MTD, the highest dose that causes no mortality) of 2 and 18 mg/kg were reported for neonate and adult mice, respectively (204), suggesting that immature animals are more sensitive to parathion than mature animals.

When rats were given 0, 2, 4, or 7 mg/kg parathion by gavage, tremors, ataxia, and 10% mortality occurred in the 7-mg/kg group, whereas only decreased tail-pinch responsivity occurred in the 2-

mg/kg group (324). When rats were given single oral doses of 0, 0.025, 0.5, 2.5, or 10.0 mg/kg/day, mortality, cholinergic toxicity, and decreased RBC and brain cholinesterase activity occurred in males given 10 mg/kg/day (477a). Males given 2.5 mg/kg had only decreased RBC cholinesterase activity. One female given 2.5 mg/kg died, and another in this group exhibited cholinergic effects and inhibition of RBC and brain cholinesterase. The time for peak effect was 4 hours and partial to full recovery occurred by 14 days.

Single-dose oral exposure to 6 mg/kg parathion caused deficits in passive avoidance learning in mice and depression in brain and RBC acetylcholinesterase activity after 0.5 h; subcutaneous exposures to 1, 2, or 4 mg/kg/day for 6 days had no effect on this type of behavior, despite a decrease in brain and RBC acetylcholinesterase activity (479). Response rates for schedule controlled behavior decreased in rats given 0.75 or 1.0 mg/kg paraoxon (the active metabolite of parathion) intraperitoneally for 3 days, but not in rats given 0.05 mg/kg. All levels of exposure, however, caused marked inhibition of brain cholinesterase (39). Similarly, among rats given 1.5, 2.5, and 4.5 mg/kg/day every other day, no sign of cholinergic toxicity occurred on days 1–5, 7–13, and 15–21, respectively, despite inhibition of brain cholinesterase (40). Rats given single oral doses of 2, 3.5, or 5 mg/kg parathion showed altered conditioned taste aversion behavior even though brain cholinesterase activities were inhibited only at 3.5 and 5 mg/kg (479a). Monkeys given a single oral dose of 2.0 mg/kg showed cholinergic toxicity, whereas monkeys given 1.5, 1.0, or 0.5 mg/kg did not (480). Performance of a visual discrimination task, however, was disrupted at 1.0 mg/kg and was associated with inhibition of blood acetylcholinesterase activity (480).

23.4.1.2 Chronic and Subchronic Toxicity A calculated 90-dose LD_{50} was 3.1–3.5 mg/kg/day for rats given feed that contained parathion for 90 days and then observed until death (196). Using the 90-dose LD_{50} and the single-dose LD_{50} of 3–4 mg/kg, a "chronicity factor" (single-dose LD_{50}/90-dose LD_{50}) of about 1 was calculated, indicating that parathion is not expected to exhibit a cumulative toxic effect.

A diet that contained 125 ppm parathion (15.4 mg/kg/day) given to rats for 15 weeks caused severe illness, growth suppression and death, as well as severe RBC and brain cholinesterase inhibition (481). Exposure to a diet that contained 25 ppm (2.4 mg/kg/day) had no toxic effect, but RBC and brain cholinesterase activities were depressed (81). Cholinergic toxicity did not occur among rats fed diets that contained 0.05, 0.5, or 5.0 ppm parathion (about 0.005, 0.05, or 0.5 mg/kg/day) for 84 days; however, RBC cholinesterase was inhibited in the 0.05- and 0.5-mg/kg/day groups. Brain cholinesterase activity was unaffected at any exposure level. In a subchronic neurotoxicity study, rats given feed that delivered 0.05, 1.25, 2.5, or 5.0 mg/kg/day showed a RBC cholinesterase inhibition at the lowest dose tested (477a).

When rats and mice were given diets containing 5, 10, 20, 40, 80, 160, 320, 640 (mice only), or 1280 (mice only) ppm parathion for 6 weeks and then observed for two additional weeks, diets of 80 ppm or more were associated with decreased body weight and increased mortality in rats, and diets of 320 ppm or more were associated with decreased body weight and increased mortality in mice (479b). Diets that contained 5 to 40 ppm had no effect on rats, and diets that contained 5 to 160 ppm had no effect on mice.

When dogs were given 0.02, 0.08, or 8 mg/kg/day parathion via gelatin capsule, 7 days/wk for 6 months, no cholinergic signs or ocular toxicity occurred at any dose (483). However, RBC and retinal cholinesterase activities were intermittently depressed in dogs given 8 mg/kg/d.

23.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Absorption of parathion is rapid and complete following oral exposure. Based on the plasma concentration–time curve in rabbits given 3 mg/kg parathion orally, a and b elimination rate constants are about 5 ± 2 and 0.7 ± 0.1 hr^{-1}, respectively, and the b elimination half-life is about 1 ± 0.3 h (494). Urinary excretion was rapid, accounted for 46% and 85% of the administered dose 3 and 6 hours after exposure, respectively, was

directly correlated with levels of parathion in plasma (494). Maximum cholinergic effects following oral exposure were slightly delayed compared to i.v. administration, and occurred 30–90 minutes after oral dosing. Similar results were observed in dogs given 10 mg/kg and in mice given 1 mg/kg parathion orally (106, 426).

Rapid absorption and elimination of parathion following oral exposure was confirmed in human volunteers given single oral doses of 1–2 mg parathion for 5 consecutive days (410). Metabolites detected in urine 24 hours after dosing included *p*-nitrophenol, diethylphosphate, and diethyl thiophosphate. Excretion of the primary metabolite, *p*-nitrophenol, was 60% complete in 4 hours, 86% complete in 8 hours, and was directly correlated with exposure. Urinary excretion of diethyl phosphate was more prolonged and reached maximum rates 4 to 8 hours after ingestion.

Absorption, distribution, and elimination are also rapid and complete following inhalation, as evidenced by results of studies where parathion was given intravenously. This is a route of exposure whose distribution and excretion characteristics are similar to those of inhalation because it allows parathion to bypass the extensive "first-pass" metabolic effect of the liver. In humans, 46% of an intravenous dose was excreted in urine by 120 hours, and an elimination half-life of 8 hours was determined (66). Intravenous administration of parathion to dogs demonstrated high serum protein binding, a very high liver extraction ratio (82–97%), rapidly decreasing serum levels, rapid excretion of 85–92% of the dose in urine by 14 hours, and a plasma half-life of 8.5 to 11.2 hours (427, 493). In atropinized rats, parathion was rapidly distributed to tissues (brain, fat, and liver) and eliminated from blood following intravenous administration; the elimination half-life was 3.4 hours (493). Absorption, distribution, and elimination were also rapid in rabbits given intravenous doses of parathion (494). The plasma concentration–time curve followed a three-compartment kinetic model, two very rapid distribution phases followed by a final slower disposition phase that had a b elimination half-life of 5 ± 3 h. Maximal cholinergic effects, including one death, occurred 10–20 minutes after injection. In 8-week-old pigs, parathion had distributed to plasma, kidney, liver, lung, brain, heart and muscle, and about 82% of the dose had been eliminated in urine by 3 hours after dosing, (495). Urinary excretion of metabolites was much lower in newborn (1–2 days old) and neonatal (1-week-old) pigs administered the same dose, and parathion tended to accumulate in newborn and neonatal tissues to a much greater extent than in the 8-week-old pigs, providing a possible partial basis for the apparent sensitivity of developing mammals to parathion (204, 417).

Dermal absorption of parathion is extensive and has been the major cause of occupational disease. In one study, humans absorbed about 20–30% of a dermally applied emulsion of parathion (approximately 2.5 mg) after 300 minutes (496), from 0.1 to 2.8% of parathion dermally applied using an absorbent pad in another (497), and 10% of an applied dose of 4 mg/cm^2 in acetone in another (66). In another study, 5 grams of 2% parathion dust was placed on the right hand and forearm of a volunteer for 2 hours, after which the hand and arm were thoroughly washed, and urinary *p*-nitrophenol (the major parathion metabolite) was monitored for 40 hours (498). Dermal absorption was indicated by increases in urinary *p*-nitrophenol that peaked after 5–6 hours and decreased to very low levels within 40 hours. Marked differences in dermal absorption depending on the anatomic site of exposure were observed among six men who were dosed with 4 mg/cm^2 ^{14}C parathion in thirteen different locations and requested not to wash the site of application for 24 hours (499). After 5 days, the following percentages of applied dose had been absorbed from each anatomic site tested: forearm: 9%; palm: 12%; ball of the foot: 14%; abdomen: 18%; back of the hand: 21%; jaw angle: 34%; postauricular area: 34%; forehead: 36%; axilla: 64%; and scrotum: 102%. Maximum rates of absorption occurred 1–2 days after exposure but were still significant 5 days after exposure.

Location-specific absorption rates were observed in pigs in an experiment that showed that absorption rates ranged from 30–50% occluded skin to 8–25% for nonoccluded skin, depending on the site of application (500). Times of maximum excretion were 8–13 h for occluded skin and 12–17 h for nonoccluded skin. Rats treated dermally with 1.7–2.0 mg/kg (44–48 mg/cm^2) parathion

reached steady state and absorbed 1.4% of the applied dose within 1 hour and 57–59% of the applied dose during a period of 168 hours (501). The skin absorption rate was 0.33 and 0.49 mg/h/cm^2, and the permeability constant was 7.5×10^{-3} and 1.0×10^{-2} cm/h for males and females, respectively. Absorbed parathion was rapidly distributed to heart, liver, and kidneys. Elimination half-times were 39.5 and 28.6 h for males and females, respectively. Mice absorbed nearly 100% of a 1-mg/kg dose of parathion from 1-cm^2 area on their shaved backs by 2 days after treatment (213). Eight hours after treatment nearly 50% of the absorbed dose was excreted in urine, and the rest was distributed primarily to intestine, liver, blood, stomach, kidney, lungs, fat, ear, spleen, and bladder.

Once absorbed, parathion is widely distributed regardless of the route of exposure. Distribution coefficients are highest in the liver (4.1–20.8) and adipose tissue (1.3–2.9) but also exceed one in the brain (1.0–1.4) and muscle (1.5–1.9), indicating retention of parathion by these tissues (101). Maximum concentrations in all tissues is reached 10–20 days after dosing. Extensive distribution of parathion to the liver was demonstrated in mice following intraperitoneal, subcutaneous, oral, or dermal exposure (106, 213, 436, 502) and in pigs following i.v. exposure (495). This is consistent with its rapid hepatic metabolism and high affinity for hepatic esterase (13, 220). Placental transfer has been demonstrated *in vitro* using term perfused human placentas (503).

Parathion is converted to paraoxon by cytochrome P450 enzymes (primarily CYP3A4, but possibly also CYP1A2 and CYP2B6 (48, 504). Binding to other cytochromes also occurs (e.g., CYP3A2, CYP2C11) and is accompanied by their inactivation (48, 504). Alternatively, parathion is dearylated to form diethyl phosphorothioic acid and *p*-nitrophenol in a reaction catalyzed by microsomal enzymes or hydrolyzed by paraoxonase (also termed A-esterase) to form *O*-ethyl-*O*-*p*-nitrophenyl thiophosphate (13). Paraoxon can also be dearylated to diethyl phosphoric acid or hydrolyzed to *O*-ethyl-*O*-*p*-nitrophenyl phosphate. *p*-Nitrophenol, the primary dearylation metabolic product formed from parathion, is eliminated in the urine and quantifying it provides an index of parathion exposure (154). These metabolic conversions occur primarily in liver, but also in the lung and brain (435, 436, 504, 505), and a significant "first-pass" metabolic effect in skin has been demonstrated (506).

Paraoxon binds to and irreversibly inhibits acetylcholinesterase. Binding to other hepatic and plasma esterases also occurs, however, and represents a significant detoxication mechanism because it prevents much of the hepatically generated paraoxon from entering the general circulation and target tissues (13, 14). Comparative differences in the rates of hepatic esterase binding, as well as rates of dearylation, have been implicated as contributors to the greater sensitivity of female rats to parathion toxicity compared to male rats (15, 19, 221), to the greater sensitivity of some tissues (e.g., brain) to parathion toxicity compared to other tissues (17), and, to the greater sensitivity of young animals to parathion toxicity compared to adults (18). Differences in the relative rates of parathion desulfuration, dearylation, hydrolysis, and esterase binding probably also contributes to interspecies differences in sensitivity to parathion toxicity; however, the primary factor that accounts for interspecies differences appears to be species-specific differences in the affinity of acetylcholinesterase for paraoxon (218, 437, 438, 507).

Interindividual differences in paraoxonase activity may contribute to interindividual differences in human sensitivity to parathion because this enzyme is polymorphic in the human population. Its expression is determined by two codominant alleles that represent high and low activity (218, 222, 508). Individuals whose paraoxonase activity is low might be expected to detoxify relatively less of an absorbed dose of parathion and therefore experience greater toxicity than individuals whose paraoxonase activity is high, although that has not been demonstrated. The low-activity phenotype is apparently more common than the high-activity phenotype. In a Southeast Asian population, 4–18% of individuals expressed the high-activity form (508). In another population, 6% were homozygous for high activity, 42% were homozygous for low activity, and 53% were heterozygous (222). Differences in baseline levels of plasma cholinesterase activity may also contribute to interindividual differences in sensitivity. Plasma cholinesterase activity in pregnant women was about 76% of the activity in nonpregnant women, and the plasma cholinesterase activity of renal patients was about

77% of normal (509).

23.4.1.4 Reproductive and Developmental No adverse reproductive outcomes occurred in rats given feed that contained 1, 10, or 20 ppm parathion (0.05, 0.5, or 1.0 mg/kg/day) for two generations (477a). The only developmental effect observed was reduced body weight and body weight gain in pups fed the 20-ppm diet. However, excess mortality occurred among pups of second-generation rats when given diets that contained 10 ppm parathion once per (486). To further explore these findings, six additional second-generation exposed females were mated with two second-generation exposed males, and six second-generation exposed females were mated with a single second-generation control male. Only four of the twelve females produced litters. Survival of pups was 27% in litters from females mated to the exposed males, and 38% in litters mated to the control male. Thus parathion interfered with both reproductive success and developmental viability.

When rats were given 0, 0.25, 1.0, or 1.5 mg/kg/day parathion on gestation days 6 through 19, mortality occurred and body weight gain decreased in 1.5-mg/kg doses dams (477a). No fetotoxic effects were observed at any dose. When rabbits were given 0, 1, 4, or 16 mg/kg/day parathion via gavage on gestation days 7 through 19, mortality occurred and body weight gain decreased in 16-mg/kg dosed dams (477a). A decrease in litter size also occurred at the 16-mg/kg dose. Conception and litter size were not affected in wild rabbits given two oral 8-mg/kg doses of parathion 30 days apart, although brain acetylcholinesterase activity was reduced, and dosed animals had lower perirenal and kidney fat weights (487).

Intraperitoneal injection of pregnant mice with 4, 8, 10, 11, or 12 mg/kg parathion on gestation days 12, 13, and 14 caused increased resorptions and a reduction in fetal weight at doses of 8 mg/kg and higher. The highest dose was associated with 90% fetal mortality. At 4 mg/kg, fetal body weight was reduced, although the incidence of resorptions was normal (488). Intraperitoneal injection of 10 mg/kg parathion on gestation days 8, 9, and 10 had no impact on fetal weight. Intraperitoneal injection of pregnant rats with 3 or 3.5 mg/kg parathion on gestation day 11 produced increases in resorptions, decreased fetuses/litter, and reductions in fetal and placental weight (123). However, this treatment was also associated with maternal toxicity. Subcutaneous injection of pregnant rats for 4 days during the first, second, or third trimester of gestation resulted in inhibition of brain acetylcholinesterase in dams, but not in pups. However, all pups of parathion-treated rats displayed delays in development of the righting reflex (489).

Altered electrocardiographic patterns (decreased heart rates) occurred in 24-day-old progeny of spontaneously hypertensive strain rats given oral doses of 0.01, 0.1, or 1.0 mg/kg/day parathion from day 2 of pregnancy through day 15 of lactation (490). Dose-related decreases in acetylcholinesterase activity and muscarinic agonist binding occurred in the cerebral cortexes of 21- and 28-day-old rat pups treated subcutaneously with either 1.3 or 1.9 mg/kg/day parathion on postnatal days 5–20 (490a). Slight alterations also occurred in the development of memory; however, no deficits in the development of most reflex behaviors occurred. Acetylcholinesterase activity and muscarinic agonist binding also decreased in the hippocampi of 12-day-old rat pups treated subcutaneously with 0.882 mg/kg/day parathion on postnatal days 5–20 (491). Additionally, cellular disruption and necrosis occurred in the hippocampi of 21-day-old treated pups. When neonatal rats were given subcutaneous injections of 0.5, 1.0, 1.5, or 2.0 mg/kg parathion on postnatal days 8–20, doses of 1.0 mg/kg/day or more caused decreases in body weight gain, mild tremor, brain acetylcholinesterase inhibition decreases in muscarinic receptor density, and mortality (492).

23.4.1.5 Carcinogenesis Cholinergic toxicity was not observed in dogs given feed that delivered parathion doses of 0, 0.01, 0.03, or 0.10 mg/kg/day for 12 months (477a). RBC cholinesterase activity was intermittently depressed at all doses; brain cholinesterase activity was decreased only in dogs given 0.03 mg/kg/day. When dogs were orally dosed by capsule with parathion at 0, 0.0024, 0.079, or 0.7937 mg/kg/day for 6 months, only dogs given 0.7937 mg/kg/day had decreased RBC and brain cholinesterase activity.

There was no evidence of carcinogenity in rats given feed that contained 10, 25, or 50 ppm parathion for 64–88 weeks or in rats given 50 (about 3 mg/kg/day) or 100 ppm (about 6 mg/kg/day) parathion for 104 weeks (370, 484). Rats fed the 100-ppm diet occasionally showed peripheral tremors and irritability during the first few weeks, but were normal later. At 50 ppm no adverse effects occurred. However, when rats were given food that contained 10, 20, 50, 75 or 100 ppm parathion once a day for 1 year, those given food containing 75 or 100 ppm experienced serious poisoning and lethality, so that exposures were discontinued (486). Excess mortality occurred at 50 ppm and higher by 1 year. No signs of poisoning occurred in either the 20-ppm or 10-ppm groups.

No evidence of carcinogenity occurred when mice were fed diets that contained 80 or 160 ppm parathion (equivalent to about 12 and 23 mg/kg/day) for 62–80 weeks and were observed for an additional 9–28 weeks (479b). Cholinergic toxicity occurred at both exposure levels. However, when rats were fed diets that averaged 23–32 and 45–63 ppm parathion (delivering doses of 1.3 or 2.6 mg/kg/day) for 13–67 weeks and observed for 9–28 additional weeks, there was an increased incidence of adrenal cortical adenomas and carcinomas in the high-dose group. Cholinergic toxicity occurred at both doses. Based on these results, the NCI concluded that the evidence for carcinogenicity was equivocal in rats (479b). Noting that the exposure duration of these experiments was less than lifetime, that adrenal cortical adenomas sometimes spontaneously arise in aged rats, and that most tumors were adenomas rather than carcinomas, the International Agency for Research on Cancer (IARC) concluded that these data provided inadequate evidence to evaluate the carcinogenicity of parathion in animals (485). No evidence of carcinogenicity occurred in another study when rats were maintained on diets that contained 0, 0.5, 5.0, and 50.0 ppm parathion for 100 (males) and 120 (females) weeks (477a).

23.4.1.6 Genetic and Related Cellular Effects Studies Parathion was negative in the *rec*-assay (differential killing assay utilizing H17 *rec*+ and M45 *rec*– strains of *Bacillus subtilis*) and the *E. coli Pol*-assay without metabolic activation (485). In a large number of tests, it did not induce gene mutations in *E. coli, S. typhimurium, Serratia marcescens, S. cerevisiae*, or *Schizosaccharomyces pombe* with or without metabolic activation (485).

p-Nitrophenol, a metabolite of parathion, was not mutagenic to *S. marcescens* or *S. typhimurium* G46 in a mouse host-mediated assay following i.p. administration of 75 mg/kg (485). *p*-Nitrophenol, but not parathion, induced mitotic gene conversion in *S. cerevisiae*. Paraoxon reportedly in two abstracts was weakly mutagenic to *S. typhimurium* TA98 and TA1538 without metabolic activation (485) and induced lethal mutations in mice treated with 0.3 mg/kg (485).

No excess of sex-linked recessive lethal mutations was induced in *D. melanogaster* by parathion. Negative results have also been reported for the induction of unscheduled DNA synthesis by parathion in WI38 human fibroblasts, with or without uninduced mouse liver microsomal fractions (485). No dominant lethal mutation was induced in mice fed parathion for 7 weeks at 62.5, 125, or 250 mg/kg of diet or following a single i.p. injection (485).

Radiolabeled metabolites of ^{14}C parathion bound to DNA *in vitro* in the presence of a rat liver microsomal metabolizing system (485).

23.4.2 Human Experience 23.4.2.2 Clinical Cases Parathion is a potent cholinergic poison in humans. Upon oral exposure, initial symptoms of poisoning usually occur within 1–2 h. Massive oral exposures can cause death within 5 minutes (33). Estimates of lethal parathion exposures in adults range from 120–900 mg (about 2–13 mg/kg assuming a 70-kg body weight), but are much lower in children and range from 0.1–1.3 mg/kg (1). The heightened sensitivity of children to parathion is illustrated by instances in which parathion-contaminated food was eaten by people of different ages, but death occurred mainly or exclusively among children (1, 510). Research has suggested that the sensitivity of young animals to parathion is due, at least in part, to their relatively lower levels of detoxifying enzyme activity compared to adults (18).

RBC cholinesterase activities among fifty-one mild-to-moderately poisoned individuals averaged 58–64% of normal levels, although some individuals showed essentially no cholinesterase inhibition (18). RBC cholinesterase activities among seven severe-to-fatal poisoning cases averaged 14–29% of normal levels, and all affected individuals exhibited marked depression. Clinical symptoms in all moderately and severely poisoned individuals were thoroughly documented and were characterized especially by gastrointestinal signs (abdominal pain, anorexia, diarrhea, nausea, and vomiting), fatigue, malaise, miosis or visual disturbances, headache, diarrhea, and respiratory difficulty. Giddiness, ataxia, drowsiness, paresthesia and loss of consciousness also occurred.

Occurrence of symptoms consistent with an "intermediate syndrome" began 2 days after recovery from an acute cholinergic crisis precipitated by ingestion of parathion. Symptoms included acute respiratory paresis, severe nystagmus, weakness in proximal limb muscles, and depressed tendon reflexes. Symptoms occurred in the absence of muscarinic signs, lasted for approximately 3 weeks, and were not influenced by atropine. Five instances of "intermediate syndrome" were also reported in individuals who ingested or inhaled a combination of methyl parathion and parathion (442, 443). In two reports, an intermediate syndrome was reportedly followed by axonal polyneuropathy in individuals who were severely poisoned by ingesting parathion (511).

Parathion levels in air during various operations in a parathion manufacturing plant ranged from 0.2–0.8 mg/m^3 during 6-month period. During this same period, repeated measurements were made of RBC cholinesterase activity in thirteen workers. Although there were no preexposure baseline levels of cholinesterase activity against which to compare these levels, activities markedly increased 5 months after parathion manufacture ceased, suggesting that parathion exposure had markedly depressed them in the first place (512).

Several studies simply reported depressions in cholinesterase activity associated with different work environments. Field workers or pilots involved in spraying parathion on agricultural fields have had cholinesterase activities that ranged from 60–70% of baseline and RBC activities from 30–50% of baseline (509, 513, 514).

In a poorly described report, oral intake of 0.07 mg/kg produced no clinical signs of toxicity; 0.1 mg/kg produced uneasiness, warmth, tightness of the abdomen, frequent urination, and a 12% depression in whole blood cholinesterase activity; and 0.4 mg/kg resulted in increased peristalsis, tightness of the chest, and 47% cholinesterase activity inhibition in whole blood (515).

Ten male volunteers given 0.003, 0.010, 0.025, and 0.050 mg/kg/day parathion in capsules sequentially for 3 days at each dose exhibited no signs or symptoms of toxicity at any dose. RBC cholinesterase levels were monitored before, during, and after exposure and showed no effect (516). In another study, five men given 3.0, 4.5, 6.0, or 7.5 mg/day (0.04, 0.06, 0.08, or 0.10 mg/kg/day) for up to 30 days exhibited no clinical signs. RBC cholinesterase activity decreased in three individuals to 63, 78, and 86% of their preexposure levels. RBC cholinesterase activity in all individuals recovered to preexposure levels by 37 days after exposure stopped (260). No inhibition occurred in lower doses. Women given 7.2 mg/day (0.1 mg/kg/day assuming a 60-kg body weight) orally for 5 days/week for 6 weeks exhibited no clinical signs, a 16% decrease in RBC cholinesterase activity, and a 33% decrease in whole blood cholinesterase activity (517), and men given 1 or 2 mg/kg orally for five days (0.01 or 0.03 mg/kg/day assuming a 70-kg body weight) exhibited no clinical signs and no change in RBC cholinesterase activity (410).

RBC and plasma cholinesterase activity was measured and correlated with urinary *p*-nitrophenol excretion for 112 hours following dermal exposure in an individual covered with 2% parathion dust and placed in a rubberized suit for 7–7½ hours (518). No signs or symptoms of toxicity were observed. Maximum depression of plasma and RBC cholinesterase activity occurred 12–24 hours from the start of exposure but did not exceed 56 or 16% depression, respectively (518). Based on

measurements of *p*-nitrophenol excretion, the authors estimated that 18.2 mg parathion had been absorbed over a period of 103 hours (514), which is equivalent to about 0.06 mg/kg/day, assuming a 70-kg body weight.

To assess parathion toxicity and cholinesterase inhibition following inhalation exposures, a single volunteer was exposed to vapors generated from technical parathion (*sic*) spread over a 36 in^2 area and heated to 105–115°F for 30 minutes/day for 4 days (515). No signs of toxicity were observed by day 4 of exposure, although RBC cholinesterase activity was 71% of preexposure baseline activity. Based on measurements of 24-hour urinary *p*-nitrophenol excretion, the authors estimated that 2.5 mg parathion had been absorbed each day during the 4-day period, an amount equivalent to about 0.04 mg/kg/day, assuming a 70-kg body weight. This is consistent with the occupational study noted before in which RBC cholinesterase activities rebounded 5 months after cessation of exposure to about 0.03 mg/kg/day (512).

23.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV for parathion is 0.1 mg/m^3. The OSHA PEL-TWA is 0.1 mg/m^3 with a skin notation. The NIOSH REL-TWA is 0.05 mg/m^3 with a skin notation. Most other nations have Occupational Exposure Limits of 0.1 mg/m^3 (Australia; Belgium, Denmark, Finland, France, Germany, Japan, The Netherlands, The Philippines, Switzerland, Thailand 0.11 mg/m^2, Turkey, and the United Kingdom) or 0.05 mg/m^3 (Hungary and Russia).

Organophosphorus Compounds
Jan E. Storm, Ph.D

24.0 Phorate

24.0.1 CAS Numbers:

[*298-02-2*]

24.0.2 Synonyms:

(*O*,*O*-Diethyl (*S*-ethylmercaptomethyl) dithiophosphate; *O*,*O*-diethyl (*S*-ethylthiomethyl) phosphorodithioate; phosphorodithioic acid *O*,*O*-diethyl *S*-[(ethylthio)methyl] ester; *O*,*O*-diethyl *S*-(ethylthio)methyl phosphorodithioate; *O*,*O*-diethyl *S*-ethylmercaptomethyl dithiophosphate; American Cyanamid 3911; EI 3911; CL 35,024; diethyl *S*-((ethylthio)methyl) phosphorodithioate

24.0.3 Trade Names:

Granatox®; Rampart®; Thimet®; Timet®

24.0.4 Molecular Weight:

260.40

24.0.5 Molecular Formula:

$C_7H_{17}O_2PS_3$

24.0.6 Molecular Structure:

24.1 Chemical and Physical Properties

Technical phorate is a colorless to light yellow clear liquid. Phorate is stable at room temperature; it is hydrolyzed in the presence of moisture and by alkalis.

Specific gravity	1.17 at 25°C
Melting point	–43.7°C

Boiling point	125° to 127°C at 2 mmHg
Vapor pressure	0.00084 mmHG at 20°C; 6.380×10^{-4} mmHg at 25°C
Saturated vapor pressure	11.8 mg/m^3 (1.1 ppm) at 20°C
Solubility	insoluble in water, miscible with carbon tetrachloride, dibutyl phthalate, 2-methoxyethanol, dioxane, xylene, and vegetable oils

24.1.2 Odor and Warning Properties Skunk-like odor.

24.2 Production and Use

Phorate is a systemic and contact insecticide and acaracide registered for use on corn, sugar beets, cotton, brassicas, and coffee. It is available as a 2 to 95% emulsifiable concentrate and in granular form at 6.5% to 20% active ingredient although it is currently only used in granular formulation (1). Phorate is not registered for greenhouse or indoor uses. Phorate can be applied by aircraft and ground equipment; only one application per season is allowed for most uses, although two applications are allowed for irrigated cotton, sorghum, peanuts, and sugar beets.

24.4 Toxic Effects

24.4.1.1 Acute Toxicity Phorate is an organophosphate that has extremely high oral, dermal and inhalation toxicity and oral LD_{50}s of 1–4 mg/kg, dermal LD_{50}s of 2–9 mg/kg, and a 1-hour LC_{50} of 11–60 mg/m^3 (64a, 518a).

There are no data on primary eye or dermal irritation or on the primary dermal sensitization properties of phorate. However, the high acute toxicity of phorate would make the conduct of these types of experiments problematic (518a).

No signs of delayed neurotoxicity occurred in hens treated with two LD_{50} doses (14.2 mg/kg) of phorate 21 days apart (518a).

24.4.1.2 Chronic and Subchronic Toxicity When rats were given diets that contained 0, 0.22, 0.66, 2, 6, 12, or 18 ppm phorate (about 0, 0.01, 0.03, 0.1, 0.3, 0.6, or 0.9 mg/kg/day) for 90 days, mortality and reduced body weight gain occurred at 12 and 18 ppm. RBC cholinesterase activity inhibition occurred at 2 ppm and higher (518a). When dogs were given capsules that delivered 0, 0.01, 0.05, 0.25, 1.25, or 2.5 mg/kg/day for 6 days/week for 13–15 weeks, dogs given 1.25 or 2.5 mg/kg/day showed typical signs of organophosphate poisoning and subsequently died (518a). RBC cholinesterase was inhibited in dogs given 0.25 mg/kg/day or more.

24.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Phorate is well absorbed both orally and dermally, as evidenced by the low oral and dermal LD_{50}s. About 77% of an oral dose was excreted in the urine of rats within 24 hours, and 12% was excreted in the feces (518a). Rats given oral phorate at 2 mg/kg or six daily oral doses at 1 mg/kg/day eliminated up to 35% of the dose in urine and up to 6% in feces in 6 days. Rats treated at the rate of 1 mg/kg/day for 6 days excreted only 12% in the urine and 6% in the feces within 7 days (319). The major hydrolytic products that appeared in urine were *O*,*O*-diethylphosphoric acid (17%), *O*,*O*-diethyl phosphorothioic acid (80%), and *O*,*O*-diethyl phosphorodithioic acid (3%).

Rats metabolize phorate to the corresponding sulfoxide and sulfine and produce the phosphorothiolic and phosphoric acids that appear in urine (518a).

Metabolites of phorate were quantified in daily urine specimens obtained from employees of a pesticide formulating plant (184). The predominant alkyl phosphates found in urine were diethyl phosphate, diethyl phosphorothiolate, and diethyl thiophosphate.

24.4.1.4 Reproductive and Developmental Pup survival and pup body weight decreased among rats given diets that contained 4 or 6 ppm phorate (equal to about 0.4 and 0.6–0.7 mg/kg/day) for three generations (518a). No adverse developmental or reproductive effects occurred when rats were fed diets that contained 1 or 2 ppm phorate (equal to about 0.1 or 0.2 mg/kg/day) for three generations. Slight reductions in lactation and viability indexes occurred in the second generation of mice fed diets that contained 3 ppm phorate (equal to about 0.45 mg/kg/day) for three generations (518a). No reproductive effects occurred in mice fed 0.6 or 1.5 ppm (equal to about 0.09 or 0.23 mg/kg/day).

Neither fetotoxicity nor adverse developmental effects independent of maternal toxicity occurred in progeny of rats given 0.1, 0.125, 0.2, 0.25, 0.3, 0.4, or 0.5 mg/kg/day phorate via gavage on gestation days 6 to 15 (518a). Decreased fetal weights and increased incidence of skeletal variation occurred at 0.4 mg/kg/day, and enlargement of the fetal heart occurred at 0.5 mg/kg/day, but both of these doses were also associated with maternal cholinergic signs and mortality. Similarly, a marginal increase in resorptions occurred in rats exposed to 1.94 mg/m^3 phorate for 1 hour/day on gestation days 7 through 14, but this exposure also caused maternal phorate poisoning (518a). Exposures to 0.15 or 0.40 mg/m^3 phorate for 1 hour/day on gestation days 7 through 14 had no maternal or fetal effect.

Neither fetotoxicity nor adverse developmental effects occurred in rabbits given 0.15, 0.5, 0.9, or 1.2 mg/kg/day phorate on gestation days 6 to 18 (518a).

24.4.1.5 Carcinogenesis When dogs were given phorate via capsules at doses of 0.005, 0.01, 0.05, or 0.25 mg/kg/day for 1 year, slight body tremors, marginal inhibition of body weight gain, and RBC and brain cholinesterase inhibition occurred in males given 0.25 mg/kg/day (518a).

No evidence of carcinogenicity occurred in rats given diets that contained 0, 1, 3, or 6 ppm phorate (equal to about 0, 0.05, 0.15, or 0.3 mg/kg/day) for 2 years (518a). RBC and brain cholinesterase inhibition occurred at exposures of 3 and 6 ppm. No evidence of carcinogenicity or other adverse effects occurred in mice given diets that contained 0, 1, 3, or 6 ppm phorate (equal to about 0, 0.15, 0.45, and 0.9 mg/kg/day) for 78 weeks, other than a slight decrease in body weight gain in females that were fed 6 ppm (518a).

24.4.1.6 Genetic and Related Cellular Effects Studies Phorate was negative for mutagenicity in *S. typhimurium*, in *E. coli*, and at the HGPRT locus in cultured Chinese hamster ovary (CHO) cells with or without metabolic activation (45). Phorate was negative in a mitotic recombination assay with *S. cerevisiae* D3 with and without metabolic activation (45). Preferential toxicity assays in DNA repair proficient and deficient strains of *E. coli* and *B. subtillis* were negative (518a).

Phorate was negative for chromosomal aberrations in a dominant lethal test in mice and did not cause chromosomal aberrations in mammalian (rat) bone marrow cells (518a).

An unscheduled DNA synthesis (UDS) assay in human fibroblasts did not show a mutagenic respone (518a).

24.4.2 Human Experience Poisoning as a result of handling phorate-treated cotton seed led to coma, pinpoint pupils, blood-tinged, frothy sputum, and occasional convulsions in a worker (Hayes, 1963). The next day, RBC cholinesterase activities were 49% of normal. Treatment continued until day 15, at which time RBC cholinesterase activity was 24% of normal. In another study, 60% of a group of 40 workers engaged in formulating 10% phorate granules experienced cholinergic symptoms (514). Exposure levels were not reported.

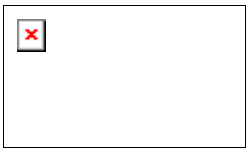
In a pesticide formulating plant where phorate concentrations ranged from 0.07 to 14.6 mg/m^3, two workers experienced cholinergic toxicity (520). After appropriate treatment, recovery was prompt and uncomplicated.

24.5 Standards, Regulations, or Guidelines of Exposure

Phorate is undergoing reregistration by the EPA. The ACGIH TLV for phorate is 0.05 mg/m^3 (154). The NIOSH REL-TWA is 0.05 mg/m^3 with a skin notation and a 15-minute STEL of 0.2 mg/m^3. Most other countries have Occupational Exposure Limits of 0.05 mg/m^3 (Australia, Belgium, Denmark, France, The Netherlands, Switzerland, and the United States).

Organophosphorus Compounds
Jan E. Storm, Ph.D

25.0 Ronnel
25.0.1 CAS Number:
[*299-84-3*]
25.0.2 Synonyms:
O,*O*-Dimethyl *O*-(2,4,5-trichlorophenyl)phosphorothioate: dimethyl trichlorophenyl thiophosphate; Trichlorometaphos; Blitex; Dermafos; dimethyl(2,4,5-trichlorophenyl)phosphorothionate; dimethyl *O*-(2,4,5-trichlorophenyl)thiophosphate; Gesektin K; Moorman's medicated RID-EZY; Nankor; phenol, 2,4,5-trichloro-, *O*-ester with *O*,*O*-dimethyl phosphorothioate; Remelt; *O*,*O*-dimethyl *O*-(2,4,5-trichlorophenyl) phosphorothioate; Rovan; Trichlorometafos; Fenclofos
25.0.3 Trade Names:
Fenchlorophos®; Ectoral®; Etrolene®; Korlan®; Nankor®; Trolene®; Viozene®
25.0.4 Molecular Weight:
321.57
25.0.5 Molecular Formula:
$C_8H_8Cl_3O_3PS$
25.0.6 Molecular Structure:



25.1 Chemical and Physical Properties
Ronnel is a white, noncombustible powder

Specific gravity	1.48 at 25°C
Melting point	41°C
Boiling point	decomposes; 97° at 0.013 mbar
Vapor pressure	0.0008 torr at 25°C
Solubility	practically insoluble in water; very soluble in acetone, carbon tetrachloride, ether, methylene chloride, toluene, and kerosene

25.2 Production and Use
Ronnel was introduced in 1954, and until 1991 when all registered uses of ronnel in the United States were cancelled by the EPA. It was used as an oral or contact insecticide to control insects that affect cattle. It has also been used as a systemic antiparasitic in humans (1).
25.4 Toxic Effects
25.4.1.1 Acute Toxicity Ronnel is an organophosphate that has low oral toxicity and oral LD_{50}s of 1250–2630 mg/kg for rats and mice, >500 mg/kg for dogs (larger doses caused emesis), 640 mg/kg

for rabbits, and 3140 mg/kg for male guinea pigs (41, 64a). In rats given single oral doses of 250, 500, or 1000 mg/kg ronnel by gavage, RBC acetylcholinesterase was unaffected 24 hours after dosing (41).

A specific dermal LD_{50} could not be determined but was larger than 5000 mg/kg for rats (64a). The rabbit dermal LD_{50} was 1600 to 2000 mg/kg (445a). When ronnel was dermally applied to rabbits under an impervious cuff for 24 hours, one of twelve died at a dose of 1000 mg/kg, six of twelve died at a dose of 2000 mg/kg, and eight of eight died at a dose of 4000 mg/kg (41).

No cholinergic effects occurred in rats given 25, 50, 100, or 200 mg/kg ronnel via intraperitoneal injection, although brain and RBC cholinesterase were inhibited at the 200-mg/kg dose (165). Plasma carboxyesterases were markedly inhibited even at the 25-mg/kg dose. Similar effects occurred in cows given 100 mg/kg via gelatin capsule (521).

When rats were given diets that contained 5, 10, or 30 ppm ronnel for 30 days or, 10, 30, 100, 300, or 500 ppm ronnel for 7 days, adverse cholinergic effects were not reported, and only the rats fed 300- or 500-ppm diets (equivalent to about 0.5, 1.0, 3.0, 10.0, 30.0, or 50.0 mg/kg/day) for 7 days exhibited significantly inhibited brain and RBC cholinesterase (165). Other esterases, however, were significantly inhibited in all rats except those fed 5-ppm diets. Overall, plasma and liver carboxyesterases were about ten times more sensitive to ronnel inhibition than brain or RBC cholinesterase. Moreover, 30-ppm diets had no effect on brain or RBC cholinesterase activity regardless of whether exposures were for 7 or 30 days, suggesting that ronnel lacks a cumulative effect. However, though the 30-ppm diet for 7 days did not inhibit brain cholinesterase, it increased the degree of cholinesterase inhibition produced by a challenge dose of malathion. The percentage inhibition of brain cholinesterase produced by 200 mg/kg malathion was three times as great as expected on the basis of additive effects in ronnel-fed rats.

A small (unspecified) amount of ronnel powder placed in the eye of a rabbit caused slight discomfort and a transient conjunctival irritation that disappeared in 48 hours (41). “A very slight hyperemia of the skin” was produced in rabbits whose skin was treated ten times during 14 days with ronnel under a gauze bandage (519).

25.4.1.2 Chronic and Subchronic Toxicity Albino rats that received 328 and 164 mg/kg ronnel developed cholinergic signs of poisoning within 2 weeks. Some of the rats died. No signs were observed in rats that received 16.4 and 8.2 mg/kg (522).

Among steers given diets that contained 0, 44, 88, or 176 ppm ronnel (equivalent to about 0, 1, 2, or 5 mg/kg/day), growth was promoted and thyroid function was altered (increased plasma T4) only in the 176-ppm group—no other effects were reported (523).

Repeated dermal exposure to ronnel apparently cured generalized demodicosis in eighteen of twenty dogs treated for 5–20 weeks, although it also caused lethal organophosphate poisoning in one of twenty (524).

25.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms In rats given three acute oral doses of about 18.6 or 186.5 mg/kg/day ronnel 24 hours apart, approximately 14 and 8% of the dose was eliminated in urine as the alkyl metabolites dimethyl phosphoric acid and dimethyl phosphorothioic acid, and 41 and 47% of the dose was eliminated as 2,4,5-trichlorophenol within 48 hours of the last dose. On the third day of dosing, ronnel was distributed to body fat (370 ppm) but by the eighth day the concentration dropped significantly (0.40 ppm) (280). Maximum concentrations in fat occur after 12 hours, and residues at 7 days are equivalent and persist longest in subcutaneous and mesenteric fat, followed by spleen, kidney, and liver.

25.4.1.4 Reproductive and Developmental Ronnel treatment did not alter the number of total

implants, live fetuses, dead fetuses, resorptions, or fetal weight in pregnant rats given 0, 400, 600, or 800 mg/kg ronnel via gavage on gestation days 6 through 15 (525). However, increases in the incidence of extra ribs were observed in fetuses from dams given 600 or 800 mg/kg.

When pregnant rabbits were given oral doses of 0, 12.5, 25, and 50 mg/kg ronnel on gestation days 6 through 18, an increase in malformed fetuses occurred in the 12.5- and 50.0-mg/kg group, an increase in fetuses that had malformations in the cardiovascular system occurred in the 50-mg/kg treated group, and fetuses that had cerebellar hypoplasia increased in the 25.5- and 50.0-mg/kg group (526).

25.4.1.5 Carcinogenesis A single female dog given 25 mg/kg ronnel for 11 months reportedly experienced no adverse effects, although RBC and brain cholinesterase activity were below normal (41). Dogs given 0.3, 1, 3, or 10 mg/kg ronnel via their diet for 1 year exhibited no adverse effects, although RBC cholinesterase activity was inhibited in dogs given 10 mg/kg.

No evidence of carcinogenicity, cholinergic toxicity, or adverse effects were seen in dogs given diets that contained 15, 45, or 150 ppm ronnel (equivalent to daily doses of 1, 3, or 10 mg/kg/day) for 2 years (587). Neither brain nor RBC cholinesterase activities were inhibited.

There was no evidence of carcinogenicity in rats fed diets that delivered doses of 0.5, 1.5, 5, 15, or 50 mg/kg/day ronnel for 2 years (41). Among rats given 50 mg/kg/day, there was some evidence of slight granular degeneration or cloudy swelling of the parenchymal cells of the liver and cloudy swelling and vacuolation of renal tubular epithelium of the kidney. RBC and brain acetylcholinesterase were inhibited at 15 or 50 mg/kg/day.

25.4.2 Human Experience There was no indication of sensitization among thirty men and twenty women given three patch applications of ronnel per week for 3 weeks and then challenged 2 weeks after the last application (41).

Five of twenty-one patients treated orally for creeping eruptions (larva migrans) with ronnel at 10 mg/kg/day for 5 or 10 days, reported nausea, weakness, blurred vision, and/or serpiginous ulcers (527). After ronnel was discontinued, the side effects spontaneously disappeared.

Nausea, headaches, and irritations of the throat and facial skin were occasionally reported by veterinarians who treated group infestations in cattle with pour-on applications of ronnel or other organic phosphorus pesticides (famphur, coumaphos, fenthion, trichlofon) in poorly ventilated areas. Neither plasma nor RBC cholinesterase activities were reduced in these cases, although correlations between specific exposures and cholinesterase measurements appeared imprecise. In support of this, alkyl phosphate metabolites were only occasionally found in the urine at the same times at which blood was drawn for cholinesterase determinations (528).

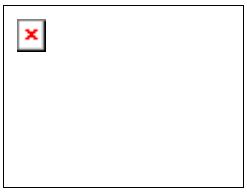
25.5 Standards, Regulations, or Guidelines of Exposure

Ronnel is no longer registered by the EPA for use (EPA, 1998). The ACGIH TLV for ronnel is 10 mg/m^3 (154). The OSHA PEL-TWA is 15 mg/m^3. The NIOSH REL-TWA is 10 mg/m^3. Most other countries have Occupational Exposure Limits for ronnel of 10 mg/m^3 (Australia, Belgium, Denmark: 5 mg/m^3 (Jan 93), Russia: STEL 0.3 mg/m^3 (Jan 93), France, The Netherlands, The Philippines, Switzerland, and the United Kingdom).

Organophosphorus Compounds
Jan E. Storm, Ph.D

26.0 Sulfotepp

26.0.1 CAS Number:
[*3689-24-5*]
26.0.2 Synonyms:
Tetraethyl dithionopyrophosphate; tetraethyl dithiopyrophosphate; tetraethyl dithiopyrophosphate; tetraethyl pyrophosphorodithionate; thiodiphosphoric acid tetraethyl ester; Bladafum; Dithione; thiopyrophosphoric acid, tetraethyl ester; ASP-47; bay-g-393; bayer-e 393; bis-*O*,*O*-diethylphosphorothionic anhydride; bladafun; dithiodiphosphoric acid, tetraethyl ester; dithiofos; dithiophos; di(thiophosphoric) acid, tetraethyl ester; dithiotep; E393; ethyl thiopyrophosphate; lethalaire g-57; pirofos; plant dithio aerosol; plantfume 103 smoke generator; pyrophosphorodithioic acid, tetraethyl ester; pyrophosphorodithioic acid, *O,O,O,O*-tetraethyl ester; sulfatep; Tedtp; *O,O,O,O*-tetraethyl dithiopyrophosphate; tetraethyl thiodiphosphate; Dithio Insecticidal Smoke; dithiopyrophosphoric acid, tetraethyl ester; thiopyrophosphoric acid ($[HO)_2P(S)]_2O$), tetraethyl ester
26.0.3 Trade Names:
Dithion®; Dithiophos®; Sulfotepp®; TEDP; Thiotepp®
26.0.4 Molecular Weight:
322.30
26.0.5 Molecular Formula:
$C_8H_{20}P_2S_2O_5$
26.0.6 Molecular Structure:



26.1 Chemical and Physical Properties
Sulfotepp is a pale yellow, noncombustible liquid.

Specific gravity	1.196 at 25°C
Boiling point	136–139°C
Vapor pressure	0.00017 torr at 20°C
Solubility	slightly soluble in water (25 mg/L); soluble in alcohol and most organic solvents

26.1.2 Odor and Warning Properties Possesses a garlic odor.
26.2 Production and Use
Sulfotepp is registered for use in greenhouses only as a fumigant formulation to control aphids, spider mites, whiteflies, and thrips (529a). It is formulated as impregnated material in smoke generators (canisters) containing 14 to 15% active ingredient. Smoke generators are placed in greenhouses and then ignited using inserted sparklers to generate a thick white smoke for fumigation.
26.4 Toxic Effects
26.4.1.1 Acute Toxicity Sulfotepp is extremely toxic following oral, dermal or inhalation exposures. Oral LD_{50}s are 5–13.8 mg/kg for rats (529, 530). Oral LD_{50} values are 21.5–29.4 mg/kg for mice; 25 mg/kg for rabbits, 3 mg/kg for cats, and 5 mg/kg for dogs (530). In rats, maximum acetylcholinesterase inhibition occurred 24 hours after an oral dose, was greater in RBCs than in plasma, and returned to normal after 7 days (530). Intraperitoneal LD_{50}s are about one-half oral LD_{50}s for mice and rats, suggesting delayed oral absorption and/or an overall detoxifying role for the liver. Rat dermal LD_{50}s of 65 and 262 mg/kg have been reported (530). A rabbit dermal LD_{50} of

20 mg/kg has also been reported. One-hour and 4-hour LC_{50}s for rats were 160–330 mg/m^3 and 38–59 mg/m^3, respectively. One-hour and 4-hour LC_{50}s for mice were 155 mg/m^3 and 40 mg/m^3, respectively. Typical symptoms of organophosphate poisoning were observed, and animals died in 24 hours (530). Following any route of exposure, symptoms occur within 1 hour and death occurs within 24 hours; surviving animals completely recover in 1–4 days.

Sulfotepp applied to the skin of rabbits at 0.4 gm for a period of 24 hours produced no noticeable effects on the skin (530). When sulfotepp was instilled into a rabbit eyes, the conjunctiva reacted slightly but returned to normal within 24 hours (530).

Nonatropinized and atropinized hens that received single oral doses of sulfotepp that ranged from 10 to 50 mg/kg body weight exhibited no signs of ataxia or paralysis of extremities during a 4-week observation period (530).

26.4.1.2 Chronic and Subchronic Toxicity When rats were exposed to 0, 0.89, 1.94, and 2.83 mg/m^3 sulfotepp aerosols for 6 hours/day, 5 days/week for 12 weeks, no changes in appearance, behavior, or body weight gain occurred at any dose. RBC acetylcholinesterase was not inhibited at any dose; however, plasma cholinesterase activity was inhibited in rats exposed to 2.83 mg/m^3. Absolute and relative lung weights of females exposed to 2.83 mg/m^3 were significantly higher than those of controls due to edema. No effects were observed at sulfotepp concentrations less than 2.83 mg/m^3 (530).

When rats were fed diets that contained sulfotepp at concentrations of 0, 5, 10, 20, and 50 ppm for 3 months, plasma cholinesterase activity was significantly reduced in female rats at 20 and 50 ppm and in male rats at 50 ppm. RBC acetylcholinesterase activity was significantly reduced in both sexes at 20 and 50 ppm (530). The highest dietary concentration tested for 12 weeks that was reportedly without symptoms in rats was 60 ppm; 180 ppm produced both illness and histological change (529).

When dogs were given diets that contained 0, 0.5, 3, 15, or 75 ppm sulfotepp (equivalent to about 0, 0.014, 0.11–0.12, 0.55–0.57, or 2.75–3.07 mg/kg/day) for 13 weeks, food consumption and body weight gain decreased at 75 ppm (529a). Plasma cholinesterase activity was inhibited at 3 ppm or higher, whereas RBC cholinesterase was inhibited at 15 ppm sulfotepp or higher. Occasional diarrhea and vomiting occurred in dogs at 15 ppm and were common in dogs at 75 ppm. RBC and plasma cholinesterase activity was inhibited at 75 ppm, and plasma cholinesterase was inhibited at 3 ppm and more. Brain cholinesterase was unaffected at any dose.

26.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms There are no available data on the absorption, distribution, elimination, or metabolism of sulfotepp. However, based on what is known about other organophosphates, it is likely to be well absorbed via all routes of exposures, rapidly oxidatively desulfurated to oxon derivatives, and/or hydrolyzed to dimethyl thiophosphoric acid or diethyl phosphoric acids.

26.4.1.4 Reproductive and Developmental No embryo toxic or teratogenic effects occurred in rats given 0.1, 0.3, or 1.0 mg/kg/day sulfotepp by gavage on gestation days 9 to 15 (593). No embryo toxic or teratogenic effects occurred in rabbits given 0.1, 1.0, or 3.0 mg/kg/day on gestation days 6 to 18 (533).

26.4.1.5 Carcinogenesis No signs of carcinogenicity or other adverse effects occurred at any dose level in mice or rats given diets that contained 0, 2, 10, or 50 ppm (equivalent to 0, 0.29, 1.43, or 7.14 mg/kg/day (mice); 0.13, 0.67 or 3.33 mg/kg/day (rats)) sulfotepp for 2 years (531). There were no signs of toxicity other than inhibition of plasma and RBC cholinesterase at 50 ppm.

26.4.1.6 Genetic and Related Cellular Effects Studies Sulfotepp was mutagenic in *S. typhimurium* strain TA1535 with metabolic activation (78). However, sulfotepp was not mutagenic to *S. typhimurium* strains TA100, TA98, TA1537, and TA1535 with or without metabolic activation (534, 535). A micronucleus test in rats was negative (536). A dominant lethal assay, in which sulfotepp was administered orally to mice, was also negative (537).

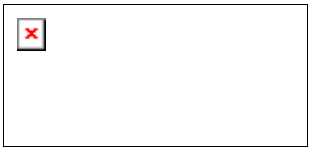
26.4.2 Human Experience Two men suffered from acute poisoning when spraying a mixture of sulfotepp and tetraethylpyrophosphate which had decomposed from diazinon. Symptoms were similar to those observed from organophosphorus insecticide poisonings (nausea, vomiting, burning eyes and blurred vision, difficulty breathing, headache, muscle twitching in arms and legs, and weakness). Blood cholinesterase activity showed a marked reduction but recovered 20 days after the poisoning incident in one individual and 28 days in the other individual (538).

In a review of available epidemiological information on sulfotepp EPA described an instance where a greenhouse worker experienced symptoms of organophosphate poisoning (headache, nausea, diarrhea, vomiting, cough, dizziness, sweating, fatigue, abdominal pain, anxiety, muscle aches, chest tightness, drowsiness, restlessness, shortness of breath, and excessive salivation) when applying the compound.

Skin lesions have been reported during the spraying of sulfotepp.
26.5 Standards, Regulations, or Guidelines of Exposure
Sulfotepp is undergoing reregistration by the EPA. The ACGIH TLV for sulfotepp is 0.2 mg/m^3 with a skin notation. The OSHA PEL-TWA for sulfotepp is 0.2 mg/m^3 with a skin notation; the NIOSH REL-TWA for sulfotepp is 0.2 mg/m^3 with a skin notation.

Organophosphorus Compounds
Jan E. Storm, Ph.D

27.0 Sulprofos
27.0.1 CAS Numbers:
[*35400-43-2*]
27.0.2 Synonyms:
O-Ethyl *O*-(4-(methylthio)phenyl)-*S*-propyl phosphorodithioate; BAY NTN 9306; Phosphorodithioic acid *O*-ethyl *O*-[4-(methylthio)phenyl] *S*-propyl ester; merdafos; *O*-ethyl *O*-(4-(methylthio)phenyl) *S*-propyl phosphorodithioate; *O*-ethyl *O*-[4-(methylthio)phenyl]phosphorodithioic acid *S*-propyl ester; Bolstar 6; *O*-ethyl *O*-(4-methylthiophenyl) *S*-propyl dithiophosphate; Heliothion; ethyl *O*-(4-(methylthio)phenyl) *S*-propyl phosphorodithioate; Morpafos
27.0.3 Trade Names:
Bolstar®; Helothion®
27.0.4 Molecular Weight:
322.43
27.0.5 Molecular Formula:
$C_{12}H_{19}O_2PS_3$
27.0.6 Molecular Structure:



27.1 Chemical and Physical Properties
Sulprofos is a tan colored liquid that hydrolyzes in basic conditions and is stable in acid or neutral conditions.

Specific gravity	1.20 at 20°C
Melting point	<–50°C
Boiling point	125°C at 0.0075 torr (pure active ingredient) (155°C at 0.1 mmHg)
Vapor pressure	<7.88 torr at 20°C (6.3×10^{-7} mmHg at 20°C)
Solubility	soluble in organic solvents; slightly soluble in water (310 mg/L at 20°C)

27.1.2 Odor and Warning Properties Possesses a sulfide or phosphorus-like odor.
27.2 Production and Use
Sulprofos is a selective organophosphate used to control foliar lepidopterous, dipterous, and hemipterous insects Registration of sulprofos in the United States was voluntarily cancelled by the registrant in 1997.
27.4 Toxic Effects
27.4.1.1 Acute Toxicity Sulprofos is a moderately toxic organophosphate via oral, dermal or inhalation exposure. Oral LD_{50}s are 65–275 mg/kg and 107–304 mg/kg for female and male rats, respectively (539). Intraperitoneal LD_{50}s for male and female rats are 305 and 224 mg/kg, respectively, indicating that sulprofos is well absorbed orally (539). Oral LD_{50}s are 1831 and 1617 mg/kg in male and female mice, respectively (539). Dermal LD_{50}s are 5491 and 1064 mg/kg in male and female rats, and dermal LD_{50}s are 820 and 994 mg/kg in male and female rabbits, respectively (539). A 4-hour LC_{50} >4130 mg/m^3 and a 1-hour LC_{50} >3840 mg/m^3 were reported for rats; a 4-hour LC_{50} of >490 mg/m^3 was reported for mice and hamsters (539). Five 4-hour exposures of rats to 37, 94, or 259 mg/m^3 sulprofos caused cholinergic signs and inhibition of RBC and plasma cholinesterase activities.

In rats given single doses of 0, 29, 71, or 206 mg/kg sulprofos, cholinergic signs occurred in females at all dose levels and in males at the two higher doses (539). RBC cholinesterase activity was inhibited at all doses. No lesions were seen at necropsy or during histopathological examination of skeletal muscles, peripheral nerves, and tissues from the central nervous system. Following single oral exposures, the no-observed-effect-levels for plasma and brain cholinesterase inhibition were 7.5 and 30 mg/kg, respectively, in male rats (a no-observed-effect level for RBC cholinesterase inhibition was not identified). The lowest observed effect levels for plasma, RBC, and brain cholinesterase inhibition were 15, 30, and 90 mg/kg, respectively. In female rats, no-observed-effect levels for plasma, RBC, and brain cholinesterase inhibition were 4.5, 8.5, and 17 mg/kg, respectively. The lowest observed effect levels for plasma, RBC, and brain cholinesterase inhibition were 8.5, 17, and 50 mg/kg, respectively (539). In female dogs, no-observed-effect levels for plasma and RBC inhibition were 1 and 10 mg/kg, respectively. A lowest observed effect level for plasma inhibition was 5 mg/kg, but a lowest observed effect level for RBC cholinesterase inhibition was not identified. Inhibition was most severe within the first 24 hours after the acute oral dose, and brain cholinesterase was less affected than plasma and RBC cholinesterase (539).

A combination of sulprofos and malathion caused a fivefold potentiation of acute oral toxicity in rats, based on oral LD_{50}s (539). Similarly, a simultaneous dosing of sulprofos and azinphos-ethyl yielded a threefold potentiation of toxicity (539).

In rats exposed to 6, 14, or 74 mg/m^3 sulprofos aerosol for 6 hours/day, 5 days/week for 3 weeks, cholinergic signs (“general health impairment”, trembling) occurred only at 74 mg/m^3 (539).

Exposures of 6 or 14 mg/m^3 reportedly had no detrimental effects on behavior, physical appearance and growth rate, hematology, clinical chemistry, urinalysis, macroscopic pathology, or histopathology. Plasma, RBC, and brain cholinesterase activities were inhibited in males exposed to 74 mg/m^3 and in females exposed to 14 or 74 mg/m^3.

When rats were given 0.1, 1.0, and 10 mg/kg/day sulprofos by gavage for four weeks, the only parameters affected were dose- and time-dependent depressions of plasma, RBC, and brain cholinesterase enzymes (539). Plasma cholinesterase activity was inhibited in the 1.0-mg/kg/day group, and RBC and brain cholinesterase activity were inhibited in the 10-mg/kg/day group. No other treatment-related changes were seen in weight gain, blood chemistry urinalysis, gross pathology, or histopathology.

Sulprofos was not an eye or dermal irritant when tested in rabbits and did not cause dermal sensitization in guinea pigs (539).

Hens given antidote doses of pyridine-2-aldoxime methiodide and atropine sulfate followed by two doses of 65 mg/kg sulprofos (the LD_{50} for the hen) 3 weeks apart exhibited no ataxia or paralysis, nor any changes in the histopathological examinations of brain, spinal cord, or sciatic nerves. There was no evidence of delayed neurotoxicity (539).

27.4.1.2 Chronic and Subchronic Toxicity When groups of twenty male and female Sprague–Dawley rats were fed diets that contained 10, 30, 100, or 300 ppm (0.54–0.65, 3.0–3.5, and 15–17 mg/kg/day) for 90 days, reduced body weight gain occurred in females given the 300-ppm diet (539). Plasma cholinesterase activity was depressed at 30 ppm and above in both sexes. RBC cholinesterase activity was depressed at 100 ppm in males and 30 ppm in females. Brain cholinesterase activity was depressed in both sexes at 100 ppm and higher. No other effects were noted in blood parameters, urine parameters, or pathology examinations.

In rats fed diets that contained 0, 9, 47, or 226 ppm sulprofos (equivalent to 0, 0.54–0.65, 3.0–3.5, or 15–17 mg/kg/day) for 90 days, cholinergic signs occurred only in rats given the 226-ppm diet (539). Brain cholinesterase activity was inhibited at 226 ppm, RBC cholinesterase was inhibited at 47 and 226 ppm, and plasma cholinesterase was inhibited at 9 ppm (females only). No treatment-related effects were seen during gross pathology or histopathological examination of skeletal muscle, peripheral nerves, eyes, and tissues from the central nervous system.

In dogs given diets that contained 0, 10, 20, or 200 ppm (equivalent to 0, 0.26–0.32, 0.52–0.64, 5.2–6.4 mg/kg/day) for 90 days, diarrhea and regurgitation occurred at 200 ppm (539). Reduced body weights, and decreased plasma, RBC, and the brain cholinesterase activity also occurred at 200 ppm, as well as thickening of the small intestinal wall; decreased liver, kidney, brain and lung weights (males only); increased brain and liver weights, relative to body weight; increased relative lung weights (females only); and increased relative heart weights (males only). Plasma and RBC cholinesterase were also inhibited at 20 ppm. No treatment-related effects were seen in ophthalmic examinations.

No changes occurred in blood or urine parameters, behavior, clinical signs, food consumption, body weights, organ weights, mortality, or in necropsied tissues in mice given diets that contained 0, 2.5, 5, 100, 200, or 400 ppm (equivalent to 0, 0.38–43, 0.76–0.86, 15.2–17.2, 30.4–34.4, or 60.8–68.8 mg/kg/day) for 10 months (539). At 5 ppm and higher, plasma and RBC cholinesterase were inhibited and, at 200 ppm and higher.

27.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Sulprofos is rapidly and nearly completely absorbed following oral exposures. In rats, more than 98% of an oral dose of sulprofos was eliminated within 48–72 hours after dosing (539). Rats that received one 11-mg/kg dose or ten 10-mg/kg doses of sulprofos during 15 days also excreted >96% of the dose (or last dose) within 24

hours. The primary route of excretion was through the urine, and less than 11% was excreted in the feces. Conjugated and nonconjugated phenol accounted for 11% of the administered dose, conjugated phenol sulfide accounted for 33–36% of the administered dose, and conjugated phenol sulfone accounted for 41–45% of the administered dose (539). Tissues and organs retained □2% of the dose; the highest residues were in the fat, ovaries, skin, and liver. Less than 1% of the dose was expired as CO_2 or volatile organic compounds from any exposure. A previous study had demonstrated that female Sprague–Dawley rats dosed at 10 mg/kg excreted >92% within 24 hours (540).

Pigs rapidly excreted an oral dose of sulprofos. More than 95% of the dose was excreted in urine by 24 hours. The major urinary excretion metabolites were the conjugated phenol, free and conjugated phenol sulfoxide, and free and conjugated phenol sulfone. Maximum blood levels occurred 4 hours posttreatment, at which time tissue levels were <0.01 ppm, except for 0.27- and 0.53- ppm levels in liver and kidney, respectively. Traces of sulprofos and its sulfoxide were found in the omental fat (539). All tissue residues were <0.05 ppm of sulprofos equivalents at 48 hours posttreatment (539).

Sulprofos is involved in a series of oxidation reactions that may result in replacing the thiono sulfur with oxygen and/or the addition of first one and then two oxygen atoms to the thioether sulfur. The phosphorous-O-phenyl ester of sulprofos and any of these materials may be hydrolyzed to the free phenols, which are then conjugated and eliminated, usually in the urine. The oxidation of the thioether sulfur to its sulfoxide is catalyzed by microsomal flavin-contain monooxygenase (352, 541). The major sulprofos metabolites are phenol, phenol sulfoxide, phenol sulfone, and their conjugates. Sulprofos sulfoxide, sulprofos sulfone, O-analog and O-analog sulfone were also identified in pigs, goats and cows but not in the rat or hen (539, 540).

27.4.1.4 Reproductive and Developmental No adverse effects on reproduction or development occurred in three generations of rats given diets that contained 0, 30, 60, or 120 ppm sulprofos (539). Third-generation parents of both sexes given the 120-ppm diet had decreased plasma and RBC cholinesterase activity, and third-generation female parents had decreased brain cholinesterase activity. Mean body weights of all treated F1a offspring were lower at weaning, but this was not evident in subsequent litters or additional generations.

No treatment-related reproductive or teratogenic effects were seen in rats given 0, 3, 10, or 30 mg/kg/day sulprofos by gavage on gestation days 6 through 15 (539). At 30 mg/kg/day, signs of maternal toxicity included clinical signs, reduced food consumption, and lower body weights. Fetal body weights were also reduced at the 30-mg/kg/day level. No maternal toxicity, embryo toxicity, or teratogenic effects occurred in rats given 0, 1, 3, or 10 mg/kg/day sulprofos on gestation days 6 through 15 (539). No developmental effects occurred in rabbits given 0, 3, 10, or 30 mg/kg/day sulprofos on gestation days 6 through 18 (539). The 30-mg/kg/day dose was maternally toxic and caused mortality, decreased weight gain, diarrhea, drowsiness, occasional salivation, and "proneness" (*sic*).

27.4.1.5 Carcinogenesis No evidence of carcinogenicity or overt cholinergic toxicity occurred in rats given diets that contained 6, 60, or 250 ppm sulprofos (0.28–0.27, 2.46–2.74, or 10.25–11.43) for 2 years (539). Plasma, RBC, and brain cholinesterase were inhibited at 250 ppm; only plasma and RBC cholinesterase were inhibited at 60 ppm. There were no other differences in behavior, physical condition, mortality, other blood chemistry parameters, hematology, urine parameters, gross pathology, or histological findings for any treatment level other than decreased absolute and relative male kidney gonad weights at 250 ppm.

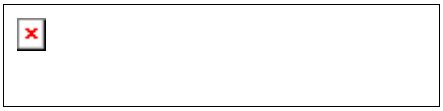
There was no evidence of carcinogenicity or overt cholinergic toxicity in dogs given diets that contained 10, 100, or 150 ppm sulprofos (0.23–0.24, 2.99–3.82, and 4.49–5.73 mg/kg/day) for 2 years (539). Plasma, RBC, and brain cholinesterase activities were inhibited at 100 ppm.

There was no evidence of carcinogenicity or other adverse effects in mice given diets that contained 2.5, 25, 200, and 400 ppm sulprofos (0.28–0.32, 2.8–3.2, 22.4–24.8, and 44.849.6 mg/kg/day) for 22 months (539). No changes were observed in food consumption, body weights, clinical signs, or mortality. Plasma and RBC cholinesterase activities decreased at dietary levels of 25 ppm, and brain cholinesterase activity decreased at 400 ppm (females only).

27.4.1.6 Genetic and Related Cellular Effects Studies Sulprofos is neither mutagenic nor genotoxic. Sulprofos was negative in the reversion assay using *S. typhimurium* with or without metabolic activation, in the CHO/HGPRT mutation assay, in the Pol DNA repair test using *E. coli*, and did not increase the incidence of sister chromatid exchange in Chinese hamster ovary cells (308, 539). Sulprofos was negative in the micronucleus test and in a dominant lethal test using mice (539).
27.5 Standards, Regulations, or Guidelines of Exposure
Registrations for sulprofos have been cancelled by the EPA, and all tolerances are being revoked (www.epa.gov/opsrd1/op/status.htm accessed 10/99). The ACGIH TLV for sulprofos is 1 mg/m^3 (154). There is no OSHA PEL-TWA. NIOSH REL-TWA is 1 mg/m^3. Most other countries have Occupational Exposure Limits of 1 mg/m^3 for sulprofos (Australia, Belgium, Denmark: 1 mg/m^3, France, The Netherlands, and Switzerland).

Organophosphorus Compounds
Jan E. Storm, Ph.D

28.0 Temephos
28.0.1 CAS Number:
[*3383-96-8*]
28.0.2 Synonyms:
O,*O*,*O*′,*O*′-Tetramethyl-*O*,*O*′thiodi-*p*-phenylene phosphorothioate; Temephosn; Abate; *O*,*O*′-(thiodi-4,1-phenylene)phosphorothioic acid *O*,*O*,*O*′,*O*′-tetramethyl ester; *O*,*O*′-(thiodi-4,1-phenylene)bis (*O*,*O*′-dimethylphosphorothioate); phosphorothioic acid, *O*,*O*′-(thiodi-4,1-phenylene) *O*,*O*,*O*′,*O*′-tetramethyl ester; Tempephos; *O*,*O*,*O*′,*O*′-tetramethyl *O*,*O*′-(thiodi-4,1-phenylene)phosphorothioate; temefos; Abaphos; Tetrafenphos; tetramethyl *O*,*O*′-thiodi-*p*-phenylene phosphorothioate
28.0.3 Trade Names:
Abate®; Abathion®; Biothion®; Difenthos®; Difos®; Nephis 1G®; Swebate®
28.0.4 Molecular Weight:
466.46
28.0.5 Molecular Formula:
$C_{16}H_{20}O_6P_2S_3$
28.0.6 Molecular Structure:



28.1 Chemical and Physical Properties
Pure temephos is a white crystalline solid; technical grade temephos (90–95% pure) is a brown, viscous liquid.

Melting point	30°C
Solubility	insoluble in hexane or water; soluble in toluene, ether, dichloroethane, carbon tetrachloride, and acetonitrile

Reactivity	undergoes hydrolysis at high or low pH
Specific gravity (technical)	1.3
Vapor pressure (technical)	7.17×10^{-8} mmHg at 25°C

28.2 Production and Use

Temephos is a nonsystemic larvicide used to control mosquitoes, chironomid midges, blackflies, biting midges, moths, and sandflies. It is used on crops to control cutworms, thrips, and lygus bugs and on humans as a 2% powder to control body lice. Temephos is formulated as emulsifiable concentrates (10, 43, or 50%), wettable powders (50%) or granules (1). It can be applied by fixed-wing aircraft, helicopter, handheld sprayers, power backpack blowers, and by spoon.

28.4 Toxic Effects

28.4.1.1 Acute Toxicity Temephos has low acute oral, dermal, and inhalation toxicity. Oral LD_{50}s are 1226–13,000 mg/kg for rats and mice although an LD_{50} value of 444 mg/kg was reported to EPA (42, 64a, 539a). Rats showed typical signs of organophosphate poisoning (*sic*) when given single oral doses of temephos as low as 500–750 mg/kg. Death of rats usually occurred after 6–7 days and after 3 days in mice. In rats given a single oral dose of 8600 mg/kg, brain acetylcholinesterase inhibition was maximum on day 3 and showed partial recovery by day 7 after dosing (542).

The dermal LD_{50} for rats was >4000 mg/kg (larger doses could not be practicably applied) (42). Systemic toxicity was apparent after a much lower dermal exposure of 1200 mg/kg (1). The dermal LD_{50} in rabbits is 970–1850 mg/kg (539a). A 4-hour LC_{50} of >1300 mg/m^3 for rats was reported to EPA (539a). Air concentrations of 40 and 12.9 mg/m^3 temephos were reported as single and repeated exposures that led to cholinesterase inhibition in rats (1).

Rabbits given 100 mg/kg/day temephos for 5 days experienced organophosphate poisoning (*sic*) as well as significant RBC acetylcholinesterase inhibition (Gaines et al., 1967). Rabbits given 10 mg/kg/day for 35 days experienced significant RBC acetylcholinesterase inhibition but no signs of organophosphate poisoning. Guinea pigs were apparently resistant to temephos and showed no signs of organophosphate poisoning when given 100 mg/kg for 5 days.

When rats were given single oral doses of temephos and malathion equivalent to one-eighth the LD_{50}, a fourfold potentiation of acute toxicity occurred (42). Further, when groups of rats were given drinking water that contained 5 or 30 ppm temephos for 7 days followed by single acute intraperitoneal doses of 400 mg/kg malathion, the degree of malathion-induced brain and tissue (submaxillary gland) cholinesterase inhibition was significantly enhanced (373).

Temephos is only very slightly irritating to the eye and skin and is not a skin sensitizer (539a).

Hens given single subcutaneous doses of 1000 mg/kg temephos developed immediate leg weakness that lasted for about 26 days and died; hens given 500 mg/kg also developed immediate leg weakness that lasted for about 15 days but survived (42). All hens given temephos in their diet at concentrations of 1000 or 2000 ppm died after 30–43 days. When hens were given a diet of 500 ppm (about 15.5 mg/kg/day) no deaths occurred and leg weakness developed, but only after 30 days; when given a diet of 250 ppm, no leg weakness occurred (42).

28.4.1.2 Chronic and Subchronic Toxicity Rats given 100 mg/kg temephos by gavage for 44 days showed “typical symptoms of organophosphate poisoning” (*sic*) after three doses and inhibition of RBC acetylcholinesterase (42). Gradual recovery from symptoms occurred while dosing progressed even though the degree of RBC acetylcholinesterase activity continued to decrease. Overt cholinergic toxicity was not evident in rats given 10 mg/kg/day, even though they also showed inhibition of RBC acetylcholinesterase. Neither overt toxicity nor RBC cholinesterase inhibition

occurred among rats given 1 mg/kg/day.

All ten rats fed a diet that contained 2000 ppm temephos (150 mg/kg/day) developed organophosphate poisoning and RBC cholinesterase inhibition, and eight died between days 5 and 10 (42). No rats fed diets that contained 2, 20, or 200 ppm temephos exhibited organophosphate poisoning, although rats given the 200 ppm diet exhibited a progressive inhibition of RBC acetylcholinesterase. RBC inhibition was not evident in rats given the 20- or 2-ppm diets.

Dogs given drinking water that contained 10 or 50 ppm temephos (0.6–0.8 or 3–4 mg/kg/day) for 129 days did not exhibit overt signs of cholinergic toxicity. However, RBC acetylcholinesterase activity in dogs given 3–4 mg/kg/day was significantly inhibited.

When rats were given diets that contained 2, 6, 18, or 350 ppm temephos (0.1, 0.3, 0.9, or 17.5 mg/kg/day) for 92 days, no adverse effects of any kind (clinical signs, opthalmology, food consumption, clinical chemistry and hematology, gross or microscopic changes) occurred in any group except decreased body weight gain in females and decreased liver to body weight ratio in males fed the 350-ppm diet (539a). RBC acetylcholinesterase was significantly inhibited in rats fed either the 18- or 350-ppm diets. Brain acetylcholinesterase activity was not significantly inhibited at any dose level. When rats were fed diets that contained 0, 6, 18, or 54 ppm temephos for 90 days, RBC acetylcholinesterase activity decreased in the 18- and 54-ppm group (539a).

28.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Oral absorption of temephos is limited. Thirty-six to 65% of a single oral dose given to rats in sesame oil was recovered unchanged in feces (543). There are no studies available on inhalation, dermal, or intravenous absorption.

Peak plasma concentrations of temephos occurred 5 to 8 hours after intubation of rats and guinea pigs with temephos (543). All but traces of absorbed temephos were eliminated in urine and feces in rats. The parent compound and small quantities of its sulfoxide metabolite were found primarily in adipose and gastrointestinal tissues. In feces and fat, temephos was mostly unchanged. Temephos appeared in rat urine as at least 13 urinary metabolites, including primarily 4,4'-thiodiphenol, 4,4'-sulfinyl diphenol, and 4,4'-sulfonyl dipheno ester conjugates. The elimination half-life was estimated at about 10 hours (543).

Although temephos clearly inhibits acetylcholinesterase, it is a much more effective inhibitor of liver carboxylesterases. When rats were given single oral doses of temephos, the dose giving 50% inhibition for three liver carboxylesterases was three to eighteen times smaller than that for RBC cholinesterase and eight to forty-five times smaller than that for brain cholinesterase (373). Carboxylesterase activity was still 30–80% of control by 10 days after dosing, suggesting its relatively slow recovery. This relationship was also apparent when rats were repeatedly exposed to temephos in drinking water. When rats were given drinking water that contained 0, 1, 3, or 5 ppm temephos for 8 weeks, RBC, brain and tissue (submaxillary gland) cholinesterase activity were unaffected, whereas liver carboxylesterases were significantly inhibited by week 2, even among 1-ppm treated rats.

28.4.1.4 Reproductive and Developmental When rats were given diets that contained 500 ppm temephos (25 mg/kg/day) throughout mating, gestation, parturition, and lactation, there was no effect on the number of litters produced, litter size, the viability of young, or the incidence of congenital deficits (42, 539a). However, the RBC acetylcholinesterase activity of dams and healthy 21-day-old offspring decreased. No adverse reproductive or developmental effects occurred among rats fed diets that contained 0, 25, and 125 ppm temephos (equivalent to 0, 1.25, and 6.25 mg/kg/day) for three generations (539a).

No maternal or developmental toxicity occurred in rabbits given 0, 3, 10, or 30 mg/kg/day or 12.5, 35, or 50 mg/kg/day temephos orally during days 6 through 18 of gestation, although rabbits given 50 mg/kg/day exhibited decreased body weights (539a).

28.4.1.5 Carcinogenesis EPA noted a chronic dog study (period of exposure not specified) in which significant inhibition of plasma and RBC cholinesterase occurred at dietary exposures equivalent to 12.5 mg/kg/day but not at 0.46 mg/kg/day (539a).

No evidence of carcinogenicity or other treatment-related effects occurred in rats fed a diet that contained 0, 10, 100, or 300 ppm temephos (equivalent to about 0.5, 5.0, or 15 mg/kg/day) for 2 years (539a).

28.4.1.6 Genetic and Related Cellular Effects Studies Weakly mutagenic effects of temephos were noted in one bacterial strain (EXTOXNET). Additional tests on rabbits and on other strains of bacteria have shown that the compound is nonmutagenic.

28.4.2 Human Experience Adverse effects were not reported among residents in the West Indies or among applicators when indoor and outdoor walls of residence and potable water were treated with temephos to control mosquitoes (1). Topical treatment with 34 to 57 g/person (about 486 to 814 mg/kg) of a 2% formulation of temephos in pyrax powder for lice control was considered both safe and effective (1).

Twenty-eight human volunteers were given daily doses of temephos in milk at an initial rate of 2 mg/day (equivalent to about 0.03 mg/kg/day) which was doubled every 3 or 4 days for a period of 4 weeks, reached the highest daily dose of 256 mg/man (about 3.7 mg/kg/day) for 5 days (544). Higher doses were impractical to administer because of an obnoxious taste. Separate volunteers were given a constant dose of 64 mg/man (about 0.9 mg/kg/day) temephos for 4 weeks. At no time were clinical symptoms reported or observed at any of the doses administered, nor was there any effect on plasma or RBC cholinesterase. The concentration of temephos in the men's urine was proportional to the dose, and temephos could still be detected at a greatly reduced concentration 3 weeks after dosing stopped.

28.5 Standards, Regulations, or Guidelines of Exposure

Temephos is undergoing reregistration by the EPA (78). The ACGIH TLV for temephos is 10 mg/m^3 (154). The OSHA PEL-TWA for temephos is 15 mg/m^3 total dust and 5 mg/m^3, respirable fraction. The NIOSH REL-TWA is 10 mg/m^3 (total dust) 5 mg/m^3, respirable. Other countries have Occupational Exposure Limits of 10 mg/m^3 (Australia, Belgium, France, The Netherlands, and Switzerland). 0.5 mg/m^3, Russia.

Organophosphorus Compounds

Jan E. Storm, Ph.D

29.0 TEPP

29.0.1 CAS Number:

[*107-49-3*]

29.0.2 Synonyms:

Diphosphoric acid tetraethyl ester; ethyl pyrophosphate; tetra- phosphoric acid tetraethyl ester; tetraethyl pyrophosphate; Nifost; Vapotone; Tetron; Killax; Moropal; Tetraethyl ester diphosphonic acid; *O*,*O*,*O*′,*O*′-tetraethyl pyrophosphate; diphosphoric acid tetraethyl ester; bis-*O*,*O*-diethylphosphoric anhydride; pyrophosphoric acid, tetraethyl ester; fosvex; hexamite; kilmite 40; lethalaire g-52; lirohex; mortopal; Nifos; tetraethyl diphosphate; tetrastigmine; tetron-100

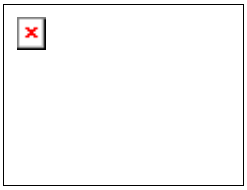
29.0.3 Trade Names:

Bladan®; Fosnex®; Grisol®; HETP®; Killex®; Kilmite®; Nifos T®; Pyfos®; Tetraspa®

29.0.4 Molecular Weight:

290.20

29.0.5 Molecular Formula:
$C_8H_{20}O_7P_2$
29.0.6 Molecular Structure:



29.1 Chemical and Physical Properties
TEPP is a clear to amber hydroscopic liquid that decomposes at 170–213°C and evolves ethylene. The commercial product is 40% TEPP.

Specific gravity	1.185 at 20°C
Boiling point	124°C at 1 torr
Vapor pressure	1.5×10^{-4} torr at 20°C (saturates in air at 0.20 ppm)
Solubility	miscible with water and most organic solvents except petroleum oils; hydrolyzes in water to form mono-, di- and triethyl orthophosphates; the resulting solutions are corrosive to metals

29.2 Production and Use
TEPP was introduced in 1943 as a nonsystemic aphicide and acaricide used to control aphids, spiders, mites, mealy bugs, leafhoppers, and thrips. It is commercially available as a 0.66–1.2% dust, an emulsifiable concentrate (10–40%), and as a solution in methyl chloride to be used as an aerosol (1, 155).
29.4 Toxic Effects
29.4.1.1 Acute Toxicity TEPP is an organophosphate compound that has extremely high oral toxicity and oral LD_{50}s of 1–2 mg/kg (38, 64a). A dermal LD_{50} for the male rat was 2.4 mg/kg (Gaines 1969). A 1-hour LC_{50} of 23.5 mg/m^3 and a 4-hour LC_{50} of 6.75 mg/m^3 were reported for rats (123). An intraperitoneal LD_{50} of 0.65 mg/kg was reported for rats, indicating that it is well absorbed orally; and an intravenous LD_{50} of 0.3 mg/kg was reported for rats (545). Similar results were obtained in mice—oral, dermal, intraperitoneal, and intravenous LD_{50}s in mice were 3, 8, 0.83, and 0.20 mg/kg, respectively (545). In all cases, the mechanism of death was peripheral inhibition of cholinesterase in the muscles, leading to respiratory paralysis, anoxia, and terminal convulsion.

29.4.2 Human Experience 29.4.2.2 Clinical Cases Many deaths have resulted from accidental and intentional contact with TEPP. In Japan, by 1959, TEPP had caused eight poisonings during spraying, eighteen by other accidents, and 101 by suicide attempts, ninety-nine of which were successful (1). In one case, one mouthful (*sic*) of TEPP was reported to have led to complete collapse in less than 5 minutes and death shortly afterward (1).

A pilot who spilled TEPP concentrate directly on his leg while adding it to the spray tank of his plane experienced serious poisoning (blurred vision, weakness, lightheadedness, followed by vomiting, unconsciousness, cyanosis, and frothing of foamy material from the nose and mouth) within one hour (1). He was successfully treated at a hospital and released after 50 hours. Another pilot who was covered with a spray solution containing TEPP when the hopper in his plane ruptured, collapsed almost immediately and died within 2 days despite aggressive treatment with atropine and pralidoxime (546). In another case, a 6-year-old boy died after aspilling TEPP concentrate over the

front of his pants from the groin to the knees (1).

Severe poisoning (characterized by excessive salivation, breathlessness, coughing, staggering, frequent urination, and defecation) occurred among cows when a pasture was sprayed with a 1% dust of TEPP during a thermal inversion. Two cows collapsed, convulsed, and died. The owners of the cows also experienced coughing and shortness of breath (547).

In studies to evaluate the effectiveness of TEPP in treating glaucoma, a 0.01–0.0125% solution produced definite miosis in 20–30 minutes that usually lasted 24 hours (548, 549). A 0.05% solution produced maximal miosis in 20–40 min, and some pupillary constriction remained for 2 days. In addition to miosis, ciliary spasm developed and lasted 12–18 h, but there was no significant change in ocular tension. A 0.1–0.2% solution produced maximal miosis in 7–20 minutes, and it lasted more than 2–3 weeks. The higher concentration also produced twitching of the eyelids, moderate spasms of accommodation for near vision, and aching of the eye and supraorbital area. There was no change in intraocular pressure. In several glaucoma patients, 0.05–0.1% TEPP effectively lowered tension, but in two cases it was actually raised (548–550).

A maintenance dose of 8–12 mg/day TEPP (about 0.1–0.2 mg/kg/day) given in two or three divided doses by mouth was effective in treating myasthenia gravis in atropinized patients (557). Intramuscular or intravascular administration of 1 mg TEPP or more (about 0.0143 mg/kg) resulted in rapid depression of plasma cholinesterase and RBC acetylcholinesterase. Approximately four times as large a dose was required to produce a similar effect when the compound was administered orally. (From a graph presented in the study, an intramuscular dose of about 0.5 mg (about 0.007 mg/kg) reduced plasma cholinesterase and RBC acetylcholinesterase to about 20% and 75% of control, respectively.) Thus, a no-effect level for RBC acetylcholinesterase inhibition following intramuscular administration is probably <0.007 mg/kg. Maximum depression of plasma cholinesterase occurred within 1 hour of dosing, and the maximum depression of RBC acetylcholinesterase occurred within 2 hours of dosing, regardless of the route of administration. Overt cholinergic symptoms (anorexia, vomiting, swearing, salivation, giddiness, uneasiness, headache, abdominal cramps, diarrhea, etc.) occurred after a single parenteral dose of 5 mg, after 3.6 mg for 2 days, or after 2.4 mg for 3 days. Similar results were obtained following oral dosing of 7.2 mg every 3 hours, three to five times. When symptoms appeared, they usually began suddenly about 30 minutes after the last dose of TEPP. In this same study, an average dose of 41 mg TEPP administered during a period of 5 hours or more was effective in reaching maximal or near maximal strength in eleven patients who had moderately severe and severe myasthenia gravis (550a). The average daily amount for maintaining strength was 16 mg orally in two or three divided doses. The difference that distinguished the dose of TEPP that produced a maximal increase in strength with a minimum of side effects, the dose that produced very little effect, and the dose that produced prohibitive side effects (including increased weakness) was very narrow (2–4 mg higher or lower than the optimum).

In another study of myasthenia gravis, patient's daily doses between 13 and 17 mg/day in two or three divided doses were effective (552). These authors also noted that the difference between the dose required to produce a maximal response and the dose that produced toxicity was remarkably small and ranged from 0.5 to 3 mg.

29.5 Standards, Regulations, or Guidelines of Exposure

The ACGIH TLV for TEPP is 0.05 mg/m^3 with a skin notation (154). The OSHA PEL-TWA for TEPP is 0.05 mg/m^3 with a skin notation. The NIOSH REL-TWA is 0.05 mg/m^3 with a skin notation.

Organophosphorus Compounds

Jan E. Storm, Ph.D

30.0 Terbufos
30.0.1 CAS Number:
[*13071-79-9*]
30.0.2 Synonyms:
(*S*-(((1,1-Dimethylethyl)thio)methyl)-*O*,*O*-diethyl phosphorodithioate; AC 92100; phosphorodithioic acid *S*-[(tert-butylthio)methyl] *O*,*O*-diethyl ester; Contraven; *S*-*tert*-butylthiomethyl *O*,*O*-diethyl phosphorodithioate; *O*,*O*-diethyl *S*-(((1,1-dimethylethyl)thio)methyl) phosphorodithoic acid; phosphorodithioic acid, *O*,*O*-diethyl *S*-[1,1-dimethylethyl)thio]methyl ester; ST 100
30.0.3 Trade Names:
Counter®; Counter 15G®; ENT 27920
30.0.4 Molecular Weight:
288.42
30.0.5 Molecular Formula:
$C_9H_{21}O_2PS_3$
30.0.6 Molecular Structure:

30.1 Chemical and Physical Properties
Terbufos is a clear, slightly brown liquid that hydrolyzes under alkaline conditions

Specific gravity	1.105 at 24°C
Melting point	–29.2°C
Boiling point	69°C at 0.1 mmHg
Vapor pressure	3.2×10^{-4} mmHg at 25°C
Solubility	Soluble in acetone, aromatic hydrocarbons, chlorinated hydrocarbons, alcohols

30.2 Production and Use
Terbufos is an organophosphate insecticide/nematicide that is applied as a granular formulation (15 and 20% active ingredient) by soil incorporation, during planting, or postemergence to terrestrial food and feed crops. Crops treated are corn, grain, sorghum, and sugar beets. Aerial/broadcast treatment is not registered (552a).
30.4 Toxic Effects
30.4.1.1 Acute Toxicity Terbufos is an organophosphate insecticide that has extremely high acute oral toxicity and oral LD_{50}s of 1.3–9.2 mg/kg for rats, mice, and dogs (552a). “Severe” signs of toxicity (tremors, shallow breathing, motionless crouching, and loss of righting reflex) occurred among deer mice given single oral doses of 1.69 or 2.48 mg/kg terbufos by gavage; mortality was 33% among mice given 1.69 mg/kg and 63% among mice given 2.48 mg/kg. Deaths occurred between 0.4 and 70 hours after dosing, and 90% of mice died between 2 and 9 hours after treatment.

The dermal LD_{50} for terbufos in rabbits is 0.8 to 1.1 mg/kg (552a). Dermal LD_{50}s of 123 mg/kg and 71 mg/kg were reported for rats for a formulated product in which terbufos is mixed with clay, and dermal LD_{50}s of 566 mg/kg and 238 mg/kg were reported for a formulated product in which terbufos is mixed with polymer granules (552a).

Rats inadvertently supplied with bedding contaminated with about 30 ppm terbufos developed cholinergic signs (muscle fasciculations, severe depression, exophthalmus, and ptyalism) that progressed rapidly to death (553). Exposures were most likely primarily dermal but could also have been via ingestion and inhalation. When terbufos was inadvertently mixed into cattle feed (so that

doses were about 7.5 mg/kg), all heifers exposed died (554). Cows that received about one-tenth this dose (0.75 mg/kg) developed signs typical of ogonophosphate poisoning (554). The cows most "severely affected" (*sic*) had whole blood cholinesterase activity that averaged 0.9% of controls, and, cows that were "moderately affected" had whole blood cholinesterase activity that averaged 20% of controls. Inhibition continued for at least 30 days following ingestion of contaminated feed.

Mortality and cholinesterase activity depression (plasma, RBC, or brain not specified) occurred in rats exposed to 0.0394 mg/m^3 (552a). No other details were provided. In another study, rats were exposed to 0, 0.01, 0.02, 0.05, or 0.1 mg/m^3 terbufos for 8 h/day, 5 days/week for two weeks. Significant reductions in RBC cholinesterase activities occurred at 0.05 mg/m^3 (552a). No adverse effects occurred when rats were exposed to about 0.01, 0.025, 0.05, or 0.10 mg/m^3 terbufos for 8 h/day 5 days/week for 3 weeks, although RBC and brain cholinesterase activity decreased at the highest dose (552a).

No signs of cholinergic toxicity or depression of RBC or brain cholinesterase activity occurred at any dose in dogs given 0, 0.00125, 0.005, or 0.015 mg/kg/day terbufos by oral capsule for 28 days (552a). Decreases in RBC and brain cholinesterase activity occurred in rats given dermal doses of 5, 10, or 25 mg/kg/day (equivalent to 1, 2.5, or 6.75 mg/kg/day active ingredient) for 6 h/day, 5 days/week for 4 weeks (552a). A dermal dose of 2 mg/kg/day had no effect.

In primary eye and primary dermal irritation studies in rabbits, all animals died within 24 hours after dosing with 0.5 ml or less of terbufos (552a). No dermal sensitization study has been performed due to the acute lethality of terbufos.

Terbufos was not neurotoxic when administered to hens in a single oral dose of 40 mg/kg in an acute delayed neurotoxicity study (552a). Nor did acute delayed neuropathy occur in hens treated orally or dermally with terbufos (128).

30.4.1.2 Chronic and Subchronic Toxicity Mesenteric and mandibular lymph node hyperplasia occurred in rats given 0.05 mg/kg/day terbufos, and liver weight and liver extramedullary hematopoiesis increased in rats given 0.025 or 0.05 mg/kg/day terbufos via their diet for 13 weeks (552a).

30.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms A metabolism study of rats indicated that 83% of a single administration of 0.8 mg/kg terbufos was excreted in the urine in the form of metabolites and 3.5% in the feces during 168 hours. No terbufos accumulated in tissues (552a).

30.4.1.4 Reproductive and Developmental No adverse reproductive effects occurred in rats given 0.0125 or 0.05 mg/kg/day terbufos for three generations (552a). When rats were given diets that contained 0, 0.5, 1, or 2.5 ppm terbufos for three generations, those fed 2.5 ppm (0.2 mg/kg/day) showed decreased pregnancy rate and male fertility and decreased body weight gain and lower pup weights during lactation (552a). No maternal or developmental effects occurred among rats fed 1 ppm (about 0.08–0.09 mg/kg/day).

Early fetal resorptions, the number of litters that had two or more resorptions, and postimplantation losses increased among rats given 0.2 mg/kg/day terbufos dose by gavage on gestation days 6 through 15 (552a). No adverse developmental effects occurred in rats given 0.05 or 0.1 mg/kg/day. A slight reduction in fetal body weight and an increase in resorptions occurred among rabbits given 0.5 mg/kg/day by gavage on gestation days 7 through 19 (552a). No adverse developmental effects occurred in rabbits given 0.05, 0.1, or 0.25 mg/kg/day.

30.4.1.5 Carcinogenesis No signs of cholinergic toxicity occurred at any level in dogs given 0, 0.015, 0.06, 0.09, or 0.12 mg/kg/day terbufos via capsule for 1 year (552a). However, initial higher doses of 0.24 and 0.48 mg/kg/day had been reduced after the first 6–8 weeks due to cholinergic-related

behavioral signs, reduced food consumption and weight gain, depressed hematology parameters, and gross changes of congestion, edema and necrosis in the gastrointestinal tract. RBC and brain cholinesterase activities were inhibited in dogs given 0.09 and 0.12 mg/kg/day.

No adverse cholinergic effects occurred in rats fed diets that contained 0.125, 0.5, or 1.0 ppm terbufos for 1 year (0.007–0.009, 0.028–0.036, and 0.055–0.071 mg/kg) (552a). Brain cholinesterase activity was reduced among rats given the 1-ppm diet. There was no evidence of neoplastic activity among rats given diets that delivered doses of 0, 0.0125, 0.05, or 0.1 mg/kg/day (which was raised to 0.2 mg/kg/day at week 6, to 0.4 mg/kg/day at week 12, and reduced back to 0.2 mg/kg/day at week 16) for 2 years (552a). Mortality and exopthalmia increased in rats given 0.05 mg/kg/day. RBC cholinesterase inhibition occurred at all doses, and brain cholinesterase inhibition occurred at the 0.05-mg/kg/day dose and higher.

When dietary doses of 0, 0.45, 0.9, or 1.8 mg/kg/day were administered to CD-1 mice for 18 months, mortality and reduction in weight gain increased at the highest dose (552a). There was no evidence of neoplastic activity.

30.4.1.6 Genetic and Related Cellular Effects Studies Terbufos was positive in a dominant lethal study using rats (552a). However, it was not mutagenic in a variety of other studies tested to cytotoxic levels. Terbufos was negative in the Ames reversion assay with *S. typhimurium* and *E. coli* strains and in the CHO/HGPRT assay (552a). Terbufos did not cause structural chromosomal aberrations in Chinese hamster ovary cells in culture or in an *in vitro* cytogenetics assay in rats, was negative in the rat hepatocyte primary culture/DNA repair test, and did not alter DNA repair in *S. typhimurium* and *E. coli* strains (552a).

30.4.2 Human Experience Among eleven farmers who applied a formulated terbufos product while planting corn, dermal exposure (assessed using gauze patches) was estimated at an average of 72 mg/h, and respiratory exposure (assessed using personal monitoring pumps) was estimated at an average of 11 mg/h (range 2.8–27.4 mg/h). Exposure duration averaged 7.4 hours. No alkyl phosphates were detected in urine, and no significant depression of RBC cholinesterase activity occurred. Assuming an 8 hour day, 100% absorption, and a 10-m^3/day inhalation rate, a respiratory dose of 11 mg/hr would be achieved by exposure to roughly 0.009 mg/m^3 terbufos. Thus, this study suggests a human no-observed-effect level □0.009 mg/m^3 (551).
30.5 Standards, Regulations, or Guidelines of Exposure
Terbufos is undergoing re-registration by the EPA. There is no ACGIH TLV, OSHA PEL-TWA, or NIOSH REL-TWA for terbufos.

Organophosphorus Compounds
Jan E. Storm, Ph.D

31.0 Trichlorfon
31.0.1 CAS Number:
[*52-68-6*]
31.0.2 Synonyms:
O,*O*-Dimethyl 1 (2,2,2-trichloro-1-hydroxyethyl)-phosphonate; DEP; Chlorofos; Metrifonate; DETF; Chlorophos; (2,2,2-trichloro-1-hydroxyethyl)-phosphonic acid dimethyl ester; *O*,*O*-dimethyl 1-hydroxy-2,2,2-trichloroethylphosphonate; Bayer L 13/59; Vermicide Bayer 2349; TCF; dimethoxy-2,2,2-trichloro-1-hydroxyethylphosphine oxide; *O*,*O*-dimethyl-(1-hydroxy-2,2,2-trichloro)ethyl phosphate; dimethyl 1-hydroxy-2,2,2-trichloroethyl phosphonate; *O*,*O*-dimethyl 1-oxy-2,2,2-trichloroethyl phosphonate; dimethyl trichlorohydroxyethyl phosphonate; 1-hydroxy-2,2,2-trichloroethylphosphonic acid dimethyl ester; methyl chlorophos; trichlorophon; trinex; aerol

1; agroforotox; anthon; bay 15922; bayer 15922; bilarcil; bovinox; britten; briton; cekufon; chlorak; chloroftalm; chlorophthalm; chloroxyphos; ciclosom; combot equine; Danex; depthon; dipterax; dipterex 50; diptevur; ditrifon; dylox-metasystox r; Dyrex; Dyvon; equino-acid; equino-aid; flibol e; fliegenteller; forotox; foschlor; foschlor 25; foschlor r; foschlor r-50; hypodermacid; leivasom; loisol; masoten; mazoten; metifonate; metriphonate; neguvon a; phoschlor; phoschlor r50; polfoschlor; ricifon; ritsifon; satox 20wsc; soldep; sotipox; trichlorphon fn; tugon fly bait; Tugon; volfartol; votexit; WEC 50; wotexit; dimethyl (2,2,2-trichloro-1-hydroxyethyl)phosphonate; Briten; dimethyl (2,2,2-trichlorohydroxyethyl) phosphonate; Foschlorine; Metrifonatum; OMS-0800

31.0.3 Trade Names:

Dylox®; Dipterex®; Proxol®; Neguvon®

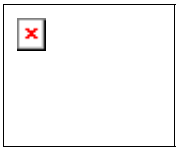
31.0.4 Molecular Weight:

257.44

31.0.5 Molecular Formula:

$C_4H_8Cl_3O_4P$

31.0.6 Molecular Structure:



31.1 Chemical and Physical Properties

Pure trichlorfon is a white crystalline solid

Specific gravity	1.73
Melting point	83–84°C
Boiling point	100°C
Vapor pressure	7.8×10^{-6} mmHg at 20°C
Solubility	readily soluble in dichloromethane, 2-propanol; soluble in toluene; nearly insoluble in *n*-hexane; slightly soluble in water (1–5 g/100 ml at 21°C)

31.2 Production and Use

Trichlorfon is used to control a wide variety of lepidopteran larvae, white grubs, mole crickets, sod webworms, leaf miners, stink bugs, ants, and other nuisance pests on outdoor turf and ornamentals; to indoor control flies, ants and roaches; for mound treatment for harvester ants; and to control cattle grubs and cattle lice. It is available as a soluble powder, granules, or bait. For turf, ornamental, or nursery use, it is applied via mechanical or hand-held sprayers, spreaders (for granular formulations), or irrigation systems; for indoor or outdoor perimeter use, it is applied as a soluble powder in water through hand-held sprayers or is applied as the solid; and for livestock, it is poured on from a cup or dipper (554a).

Trichlorfon (termed metrifonate when used therapeutically) has also been widely used as an antihelminthic to treat schistosomiasis (558) and has been extensively investigated as a treatment for Alzheimer's disease (556, 557).

31.4 Toxic Effects

31.4.1.1 Acute Toxicity Trichlorfon is a moderately toxic organophosphate compound that has oral LD_{50}s of 136–630 mg/kg for rats and 727–866 mg/kg for mice (62, 64a). The dermal LD_{50} for trichlorfon was more than 2000–2800 mg/kg (64a, 81). Thus trichlorfon is considerably less potent

on a body weight basis via dermal contact than via ingestion. Four-hour LC_{50}s of 533–1300 mg/m^3 have been reported for rats (123). Death occurs unusually quickly—within 5–15 minutes after dosing (81, 558a). If animals survive, recovery is equally quick and occurs within a few hours.

The single acute oral dose that causes 50% inhibition (ED_{50}) of brain, RBC, and plasma cholinesterase activities in 3-month-old rats was determined and compared to ED_{50}s for dichlorvos, the major *in vivo* nonenzymatic breakdown product of trichlorfon. The oral ED_{50} values for trichlorfon were 90 mg/kg for brain and 80 mg/kg for RBC and plasma cholinesterase, whereas the oral ED_{50} values for dichlorvos were 8 mg/kg for brain and 6 mg/kg for RBC and plasma cholinesterase (559). Thus, trichlorfon is one-tenth to one-fifteenth as potent a cholinesterase inhibitor as dichlorvos.

When rats were given single oral doses of 10, 30, and 100 mg/kg trichlorfon, the 100-mg/kg dose of trichlorfon caused salivation, tremor, diarrhea, ptosis, flat body, decreased body temperature, and decreased pentylenetetrazole seizure threshold, whereas the 30- or 10-mg/kg doses did not (560).

Trichlorfon is unusual among organophosphate pesticides in that several animal studies have demonstrated a beneficial effect of acute low doses of trichlorfon on certain behaviors in rats. For example, in old rats, improvements in spatial reference memory function in the water maze and in passive avoidance learning occurred after acute oral treatment with 10–30 mg/kg trichlorfon (561, 562). Performance in another behavioral task (Morris water escape) was optimally improved among young adult rats given 10–30 mg/kg trichlorfon or 0.03 mg/kg dichlorvos, the breakdown product of trichlorfon (563), and among rats given 3–30 mg/kg trichlorfon (564). Higher acute doses (80 mg/kg) were required to significantly increase the concentration of cortical acetylcholine and to improve “object recognition” in aged rats—a 30 mg/kg dose had no effect on these measures even though it caused significant acetylcholinesterase inhibition (565). Acute oral treatment with trichlorfon (5–15 mg/kg) has also ameliorated deficits in certain behaviors (water maze performance; passive avoidance tasks) caused by scopolamine or lesions of the basal forebrain (566).

Trichlorfon was moderately irritating to the eye and was a moderate contact allergen in the skin (554a).

31.4.1.2 Chronic and Subchronic Toxicity Trichlorfon does not have a cumulative effect. Repeated intraperitoneal doses of 50 mg/kg/day trichlorfon (about one-fourth of the i.p. LD_{50}) for a period of 60 days had no effect on mortality. But repeated doses of 100 mg/kg/day (about one-half LD_{50}) produced 40% mortality by 60 days, and repeated doses of 150 mg/kg produced 100% mortality by 60 days (558a).

Cholinergic toxicity was not observed among rats fed diets that contained 1, 5, 25, or 125 ppm (equivalent to doses of 0.088, 0.39, 2.4, or 11.3 mg/kg/day) for 1 to 13 weeks (81). When rats were given diets that contained 100, 500, or 2500 ppm trichlorfon (about 6–7, 31–35, and 165–189 mg/kg/day) for 13 weeks, cholinergic toxicity and inhibition of RBC and brain cholinesterase activities occurred in male rats given 2500 ppm, and RBC and brain cholinesterase inhibition occurred in females given 500 or 2500 ppm (63).

No signs of cholinergic or other toxicity were seen in dogs fed 42 mg/kg/day trichlorfon for 6 days/week for 3 months (1) or in dogs given diets that contained 50, 200, or 500 ppm trichlorphon for 12 weeks (84). The dietary level of 500 ppm (about 10.5 mg/kg/day) inhibited RBC cholinesterase activity (84).

No cholinergic toxicity occurred when trichlorfon was administered dermally to rabbits for 15 days (4 days/week for 3 weeks) at doses of 0, 100, 300, or 1000 mg/kg/day, although RBC cholinesterase

activity was inhibited at 300 mg/kg but not at 100 mg/kg/day (554a).

There is no evidence that trichlorfon causes delayed neuropathy. Hens that received acute subcutaneous doses of 100 or 300 mg/kg trichlorfon showed no visible sign of acute neurotoxicity. Brain, spinal cord, and plasma cholinesterase activities were significantly inhibited, but no significant reductions of neurotoxic esterase activity in these tissues were observed. Subcutaneous doses of 100 mg/kg trichlorfon every 3 days for a total of six doses caused little or no sign of overt neurotoxicity. No inhibition of spinal cord or brain NTE occurred. When trichlorfon was given to hens at doses of 0, 3, 9, or 18 mg/kg/day for 90 days, there were no overt indications of response characteristic of delayed neurotoxicity, although, histologically, a slight effect on nervous tissue, characterized as axonal degeneration was present in hens that received 18 mg/kg/day (554a).

31.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms Trichlorfon is rapidly and completely absorbed via oral exposure and is extremely rapidly metabolized and excreted. Once absorbed following a 133 mg/kg oral dose, trichlorfon was not detected, but dichlorvos (a nonenzymatic breakdown product of trichlorfon) was distributed primarily in blood, adipose tissue, muscle, and liver. Peak concentrations occurred 1,7,7, and 7 days after exposure, respectively. Dichlorvos was undetected at 20 days. Calculated half-lives in blood, adipose tissue, muscle, and liver were 7, 11, 10, and 12 days, respectively (388).

Trichlorfon and dichlorvos levels were followed in plasma and RBCs of seven individuals given single oral doses of 7.5–10 mg/kg trichlorfon repeated after 2 weeks for treating schistosomiasis (574). The relationship of dichlorvos to trichlorfon in plasma and RBCs was about 1%. A biphasic curve for the elimination of trichlorfon in Plasma developed; the first phase had a half-life of 0.4 to 0.6 hours, and the second phase had a half-life of about 3 hours. Clearance of trichlorfon was primarily due to formation of dichlorvos.

Regardless of whether rats were given single or repeated oral doses or single intravenous doses of trichlorfon, 80–90% of the dose was excreted within 24 hours. The major route of excretion was via the urine, followed by feces and expired air. About 1 to 2% of the dose was found in the tissues after 96 hours.

Several groups of investigators examined the pharmacokinetics of trichlorfon in humans in conjunction with assessing its efficacy as a treatment for schistosomiasis and Alzheimer's disease. These studies confirmed that trichlorfon (and its decomposition product dichlorvos) is very rapidly absorbed and cleared in humans. After acute oral treatment of healthy male volunteers with a 2, 5, 7.5, or 12 mg/kg dose of trichlorfon (metrifonate), the maximum blood concentration of trichlorfon was obtained between 12 minutes and 2 hours and the half-life in blood was about 2 hours (575, 576). The concentrations of dichlorvos, the nonenzymatic breakdown product of trichlorfon, closely followed those of trichlorphon at a constant ratio of about 1 to 100. The concentrations of trichlorfon were detectable up to 8 hours, but those of dichlorvos had fallen below the level of detection by then. Both plasma and RBC cholinesterases were readily inhibited and were still low after 24 hours—none of the volunteers complained of side effects (and the half-life of the breakdown product, dichlorvos, was about 3.8 hours).

Pharmacokinetic analysis of both trichlorfon and dichlorvos in blood on the first and sixth day of a 21-day treatment regimen indicated that, regardless of maintenance dose (0.25 to 1.0 mg/kg/day), the half-lives of elimination were the same (about 2 or 3 hours for metrifonate and dichlorvos, respectively). This confirms that there was little or no accumulation of either of these compounds from long-term administration (556). Blood concentrations of dichlorvos were approximately 2% of the parent (trichlorfon) compound concentrations.

The predominant metabolic pathway that involves cleavage of the P–C phosphonate bond that generates trichloroethanol and dimethyl phosphate which are then excreted in urine (576a). Quantitatively minor pathways of metabolism include demethylation (to dimethyl trichlorfon) and

(nonenzymatic) dehydrochlorination to dichlorvos which is rapidly metabolized to dichloroethanol and dimethyl phosphate which are then excreted in urine. Trichlorfon itself does not act significantly as a cholinesterase inhibitor, but induces cholinesterase inhibition through its hydrolytic degradation product, dichlorvos (559).

31.4.1.4 Reproductive and Developmental When rats were fed diets that contained 0, 300, 1000, or 3000 ppm for three generations, 3000 ppm (about 150 mg/kg/day) caused a marked decrease in the pregnancy rate and early deaths in pups, 1000 ppm (about 50 mg/kg/day) caused reduced numbers of pups per litter and weight of individual pups, and 300 ppm (about 15 mg/kg/day) had no detectable effect on reproduction. There was no indication of teratogenesis, even at dosages that were highly toxic (1). When rats were fed diets that contained 0, 150, 500, or 1750 ppm (about 0, 15, 50, and 175 mg/kg/day) for two generations, pulmonary and renal lesions in the F1 generation and adverse reproductive outcomes (dilated renal pelvises in F1 pups and decreased F1 pup weight on days 7 and 21) occurred at 1750 ppm (554a).

Decreases in brain and RBC cholinesterase activities and an increased incidence of abortion occurred among rabbits given 35 or 110 mg/kg/day trichlorfon by gavage on gestation days 6 through 18 (554a). Increased numbers of resorptions, decreased fetal body weights (males), and delayed ossification occurred among rabbits given 110 mg/kg/day. Decreased cholinesterase activity (*sic*) and reduced ossification of skulls, vertebrae, and sternebrae in fetuses occurred among rats fed diets that contained 2500 ppm trichlorfon (equivalent to 45 mg/kg/day) on gestation days 6 through 15 of gestation (554a). Dietary exposures of 500 or 1125 ppm (about 102 or 227 mg/kg/day) had no adverse effect.

Trichlorfon was teratogenic when given to pregnant CD rats by gavage at 480 mg/kg/day on gestation days 6 through 15, but not when given only on gestation days 8 or 10 alone. Signs of cholinesterase inhibition occurred in dams after each dose. Teratogenic responses (increased fetal death and stunted and malformed fetuses) also occurred in hamsters after administration of 300 or 400 mg/kg/day on gestation days 7 through 11, but not after 200 mg/kg/day. Embroyotoxicity, but not teratogenicity, occurred after administration of 400 mg/kg/day only on day 8 of gestation. In mice, there was a significant increase in the incidence of cleft palate following treatment with 600 mg/kg/day on gestation days 10 through 14 and on days 12 through 14 (567).

Congenital ataxia and tremor occurred in piglets of sows treated with trichlorfon between days 45 and 63 of pregnancy (1). Usually all of the piglets in any given litter were affected, and many died. Autopsy revealed marked cerebellar and spinal hypoplasia. Retrospective study showed that the smallest dose capable of causing this effect was 56 mg/kg. In another study, cerebellar hypoplasia occurred in piglets from sows treated with 60 mg/kg on day 55 or on days 55 and 70 of gestation (568). Similar cerebellar lesions were observed in guinea pigs treated with trichlorfon during prenatal development. Dose–response studies showed that 100 mg/kg trichlorfon given to guinea pigs on 3 consecutive days during days 40–50 of gestation resulted in offspring that had brain hypoplasia, ataxia, and tremors (569). When trichlorfon (125 mg/kg/day) or dichlorvos (15 mg/kg/day) was administered to guinea pigs between day 42 and 46 of gestation, offspring exhibited severe reductions in brain weight that was most pronounced in the cerebellum, medulla oblongata, thalamus/hypothalamus, and quadrigemina (570).

31.4.1.5 Carcinogenesis When trichlorfon was administered to monkeys via Tang orange drink at doses of 0, 0.2, 1.0, or 5.0 mg/kg/day for 6 days/week for 10 years, RBC and brain cholinesterase activities decreased in those given 0.2 mg/kg/d. Monkeys given 5.0 mg/kg/day exhibited decreased body weight, anemia, and transitory signs of cholinesterase inhibition (pupillary constriction, muscle fasciculation, and diarrhea; females only) (554a).

There were no effects on mortality or body weights nor was there any cholinergic toxicity in dogs given diets that contained 0, 50, 250, 500, or 1000 ppm (equivalent to 0, 1.25, 6.25, 12.5, or 25 mg/kg/day, respectively) for 1 year (554a). There was mild to moderate enlargement of the spleen

in dogs fed the 1000-ppm diet, as well as congestion of the spleen and lymphoid atrophy and foci of inflammatory liver cells. Dogs given the 500- or 1000-ppm diet exhibited decreases in RBC cholinesterase activity. When dogs were fed diets that contained 0, 50, 200, 800, or 3200 ppm for 4 years, dogs fed the 50-ppm diet were unaffected; dogs fed the 200-ppm diet had depressed RBC cholinesterase activity; dogs fed the 800- or 3200-ppm diet had depressed RBC cholinesterase activity, reduced food intake, retarded body weight gain, and increased mortality; and, dogs fed the 3200-ppm diet also exhibited tremors, cramps, and salivation (588).

When rats were fed diets that contained 0, 50, 100, 200, 250, 400, 500, or 1000 ppm for 17–24 months, no treatment-related effects occurred in those fed 50 to 250 ppm (588). Serum cholinesterase activity was depressed in rats fed 500 ppm trichlorfon, and serum, RBC, and tissue (submaxillary gland) cholinesterase activities were depressed in rats fed 1000 ppm trichlorfon. Histopathological results that suggested the occurrence of mammary tumors, the absence of primary follicles and primitive ova, and necrotizing arteritis in rats fed 400, 500, and 1000 ppm; and tubular and roblastomas, focal aspermatogenesis, decreased growth rats, and decreased survival in rats fed 1000-ppm were equivocal (345). However, in another study, when rats were fed diets that contained 0, 50, 250, 500, or 1000 ppm trichlorfon for 24 months, no treatment-related effects other, than whole blood cholinesterase depression at 1000 ppm occurred (588). There was no increase in incidence of either benign or malignant tumors, including mammary tumors. Nor was there any indication of cystic atrophy, tubular hyperplasia in the ovaries, or aspermatogenesis.

When rats were fed diets that contained 0, 100, 300, 1514 (males), or 1750 ppm (females) trichlorfon (equivalent to about 0, 4.4–5.8, 13.3–17.4, and 75–94 mg/kg/d) for 24 months, the females given 1750 ppm exhibited rough hair coats, granular kidneys, foci in lungs, decreased body weight gain, and anemia, but no evidence of oncogenicity (554a). The males given 1514 ppm exhibited paleness and hunched backs, thickened enlarged duodenum, thickened, granular nonglandular stomachs, decreased body weight gain, anemia, and an increase in the incidence of benign pheochromocytomas and mononuclear cell leukemia. The EPA Office of Pesticide Programs (OPP) Carcinogenicity Peer Review Committee, however, concluded that these lesions were not compound-related.

When rats were fed diets that contained 2500 ppm trichlorfon (equivalent to 129–159 mg/kg/day), they exhibited signs of cholinergic toxicity, decreased body weight and body weight gain, decreased RBC parameters (hematocrit, hemoglobin, RBC count and MCV), hypercholesterolemia, increased serum hepatic enzymatic (SAP, AST, ALT, GGT) activity, and decreased brain and RBC cholinesterase activity. Nonneoplastic lesions included duodenal hyperplasia, gastritis, pulmonary hyperplasia and inflammation, nasolacrimal inflammation, hepatocellular hyperplasia and vacuolation, chronic nephropathy, and dermal lesions. There was an increase in the incidence of alveolar/bronchiolar adenomas in males, renal tubular adenomas in males, and alveolar/bronchiolar carcinomas in females that were not statistically significant, but the EPA noted that they were outside the historical control range for these types of tumors. There was no compound-related increase in the incidence of either benign pheochromocytomas or mononuclear cell leukemia (554a).

Cholinergic signs and inhibition of brain and RBC cholinesterase activities occurred in all mice given diets that contained 0, 300, 900, or 2700 ppm trichlorfon (equivalent to 0, 45, 135, and 405 mg/kg/day) for 24 months (554a). Mortality in female mice was significantly related to dose. There was an increase in lung tumors in low- and mid-dose females, but not in high-dose females. Therefore, the EPA OPP Carcinogenicity Peer Review Committee concluded that the tumors were not dose-related and trichlorfon was not carcinogenic in this study.

31.4.1.6 Genetic and Related Cellular Effects Studies Trichlorfon is sometimes mutagenic in *in vitro* systems (554a). In gene mutation assays with *S. typhimurium*, trichlorfon was weakly mutagenic at toxic concentrations with or without activation (554a). Trichlorfon produced base-pair substitution mutations in *S. typhimurium*, although mutagenic activity decreased in the presence of S9 (594). Trichlorfon was not mutagenic with or without activation in one gene mutation assay with *S. cerevisiae* (554a).

In other bacterial or prokaryotic assays, trichlorfon was positive for DNA damage and repair in *S. typhimurium* but was negative in relative toxicity assays with *E. coli* and *B. subtilis* strains (554a). In a DNA damage and repair study conducted with *S. Cerevisiae*, trichlorfon was positive for mitotic recombination with and without S9 activation (554a). In a recombinant DNA study, trichlorfon did not inhibit the growth of *Bacillus subtilis* (554a).

The genotoxity of trichlorfon in mammalian cells has also been equivocal. Trichlorfon induced significant increases in mutation frequencies with or without activation in an *in vitro* cytogenetic study in mammalian cells (type not specified) (554a). Trichlorfon was inactive in inducing unscheduled DNA synthesis in rat hepatocytes up to levels of severe cytotoxicity (554a). At cytotoxic levels of 1000 mg/mL, trichlorfon was associated with a marginal but significant increase in sister chromatid exchange in Chinese hamster ovary cells (1). Trichlorfon was clastogenic in human lymphocytes in the absence of S9 activation (554a) and also reportedly induced sister chromatid exchange in human lymphocytes. In other studies, trichlorfon reportedly slightly increased the frequency of chromosomal abnormalities in cultured human lymphocytes (571).

Under physiological conditions, trichlorfon alkylates DNA (through its conversion to dichlorvos which is more easily demethylated), and an increased rate of chromosomal aberrations in bone marrow cells of Syrian hamsters and mice treated with trichlorfon has been observed. In mice that received a single dose of trichlorfon, liver DNA adducts increased maximally 6 hours after dosing, were substantially reduced 24 hours after dosing, and were undetectable by 48 hours after dosing (584a). Increases in sister chromatid exchanges occurred in the bone marrow of mice treated 24 hours earlier with 120 mg/kg, but not with 30 or 50 mg/kg trichlorfon (584). Some researchers have obtained positive effects in dominant lethal mutation tests with mice (595), but some have not (571). No chromosomal aberrations occurred in the bone marrow or spermatogonia of mice treated with acute doses of 100 mg/kg trichlorfon, and dominant lethal mutations did not significantly increase in mice given 5 ppm trichlorfon for 5 days/week for 7 weeks (571).

Significant and persistent increases (lasting at least 180 days after exposure) in aneuploidy in lymphocytes of individuals who attempted suicide by using trichlorfon (Ditriphon-50) were reported (572). Trichlorfon also produced aneuploidy in genetically engineered human lymphoblastoid cell lines (573).

31.4.2 Human Experience 31.4.2.2 Clinical Cases Trichlorfon has been associated with numerous cases of accidental or incidential poisonings (1, 572). Gallo and Lawryk (1) reviewed 379 cases of trichlorfon poisoning and found that in some cases (3%), acute poisonings were accompanied by "mental disturbance" (described as loss of memory and problem-solving ability, delirium, depression and anxiety, psychomotor stimulation, hallucinations, and paranoid delusions); and in other cases (21%), poisoning was accompanied by a delayed type polyneuropathy. It is not clear, however, whether these symptoms were due to trichlorfon itself or to some contaminant in the ingested material. Estimates of dosages associated with poisonings suggested that ingestion of 40 mg/kg causes light to moderate poisoning, ingestion of 80–700 mg/kg causes severe poisoning, and ingestion of 30,000–90,000 mg/kg causes death (1).

Trichlorfon-contaminated fish was implicated as the cause of a cluster of congenital abnormalities that occurred in a Hungarian village in 1989–1990 (584a). Eleven of fifteen live births, were affected by congenital abnormalities (four with Down's syndrome) and six were twins. Examination of this group along with two negative control groups (mothers and their children born in the same village in 1987–1988, and mothers and children born in 1989–1990 in a nearby village) and a positive control group (mothers and their children who had congenital abnormalities from the same village) indicated that all mothers of affected children had eaten "contaminated" fish during pregnancy, whereas only about one-third of mothers from all control groups combined had. Other potential causes for the cluster, such as known teratogens, familial inherited disorders, and consanguinity were excluded as contributing causes. The "contaminated" fish were obtained from a pond which had been heavily

treated with trichlorfon to eradicate parasites. The content of trichlorfon in fish was 0.15 to 0.26 mg/kg and, it was estimated was as high as 100 mg/kg.

In a poorly described study, air concentrations of trichlorfon (dipterex) and blood cholinesterase activity were monitored among employees who worked in a trichlorfon (dipterex) packing facility in China (577). Estimates of mean 8-hour time-weighted average air concentrations (aerosol or dust not specified) ranged from about 0.2 to 0.6 mg/m^3 estimated dermal exposure (mainly to face, neck, and hands a 44 cm^2 area) ranged from about 0.4 to 7.2 mg/cm^2, and blood cholinesterase activity decreased to about 23% of preexposure baseline levels after about 2-month's work. The occurrence of overt cholinergic effects was evidently not examined. Unfortunately, specific types of exposures were not thoroughly described, and it was not possible to distinguish between the relative contribution of inhalation and dermal exposures to an internal dose.

Trichlorfon has been widely used as an antihelminthic (1, 578). The formulations of trichlorfon that have been used for treating people infested by worms have frequently produced mild, rapidly reversible side effects (560). The dose ordinarily employed is 5 to 15 mg/kg given orally three times at intervals of 2 weeks. (555, 579). When used as an antihelminthic, a total dose as high as 37.7 mg/kg produced very mild poisoning, and dose of 10 mg/kg/day had no untoward effects. However, mild poisoning was reported among other persons when they received daily doses as low as 5 mg/kg/day for 12 days. A single dose at the rate of 10 mg/kg was tolerated (1).

Trichlorfon has been proposed as a treatment for Alzheimer's disease based on its ability to elevate brain levels of acetylcholine because of its relatively long lasting inhibition of acetylcholinesterase. Clinical trials in Alzheimer's disease patients suggest that maintaining RBC cholinesterase activity at levels that are 40–60% of predose baseline through daily dosing with trichlorfon can significantly improve “cognitive ability” (557, 580). Effective therapeutic doses were a 2 mg/kg/day loading dose for 2 weeks followed by a maintenance dose of 0.65 mg/kg/day. This regimen yielded significant RBC cholinesterase inhibition and “mild and transient” cholinergic adverse effects that were primarily gastrointestinal. Lower doses—a 0.5 mg/kg/day loading dose for 2 weeks followed by a 0.2 mg/kg/day maintenance dose—significantly inhibited RBC cholinesterase activity but did not affect other outcome measures.

In a 21-day study, Alzheimer's disease patients received loading doses of 1.5, 2.5, 4.0, or 4.0 mg/kg/day for 6 days followed by maintenance doses of 0.25, 0.40, 0.65, or 1.0 mg/kg/day, respectively, for 15 days (556). After 21 days of treatment, RBC acetylcholinesterase inhibition occurred at all doses. In another study designed to evaluate the safety and tolerability of relatively high loading doses followed by lower maintenance doses and to determine the maximum tolerated dose of trichlorfon, groups of probable Alzheimer's disease patients were administered either 2.5 mg/kg/day for 14 days followed by 4.0 mg/kg/day for 3 days, then 2.0 mg/kg/day for 14 days or 2.5 mg/kg/day for 14 days followed by 1.5 mg/kg/day for 35 days (581). RBC acetylcholinesterase inhibition occurred in all groups. Moderate to severe cholinergic effects (muscle cramps, abdominal discomfort, headache, muscle weakness, generalized moderate to severe muscle cramps, weakness, inability to resume daily activities, and coordination difficulties) occurred in six of eight patients given the higher doses (4.0 mg/kg/day for 3 days and 2.0 mg/kg/day for 14 days); mild to moderate cholinergic effects (gastrointestinal disturbances, muscle cramps, and lightheadedness/dizziness) occurred among patients given the lower maintenance dose (1.5 mg/kg/day).

In some cases, weekly rather than daily dosing has been used. When doses were 2.5, 5, 7.5 and 15 mg/kg/week, no side effects occurred at 2.5 mg/kg, but did occur in patients who received 15 mg/kg (582). Nausea, vomiting and diarrhea were most commonly reported. Sixteen patients had electroencephalographic (EEC) abnormalities. When a weekly dose of about 5 mg/kg was given for 3 or 4 weeks followed by a weekly dose of 2.1 mg/kg for up to 6 months, adverse effects were reported as “mild and transient” (583). When patients were given 2 mg/kg/day trichlorfon for 5 days and 0.95 mg/kg on day 6, followed by 2.9 mg/kg weekly, adverse effects were uncommon (583).

31.5 Standards, Regulations, or Guidelines of Exposure
Trichlorphon is undergoing reregistration by the EPA. There is no ACGIH TLV, OSHA PEL-TWA, or NIOSH REL-TWA for trichlorphon.

Organophosphorus Compounds
Jan E. Storm, Ph.D

Summary
Tables 95.1–95.3 summarize toxicity data for compounds listed in text.

Organophosphorus Compounds

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Toxicological Effects of the Physical Agents
David H. Sliney, Ph.D.

Introduction
The toxicological approach has been shown to have benefit when deriving human exposure limits, or threshold limit values (TLVs) for physical agents. However, some adjustments must necessarily be made to the approach followed by chemical toxicologists. Also, the philosophies relating to the control of exposure may be quite different. Concepts such as "routes of entry" must be modified. Target organs differ and dosimetric concepts vary from agent to agent.

There are over 700 chemical substances that have had TLVs assigned by the American Conference of Governmental Industrial Hygienists (ACGIH) (1–2). Many other chemicals have been studied. Toxicologists, industrial hygienists, and occupational physicians are generally well trained to recognize the hazards of different classes of chemicals, their route of entry, sampling techniques, and control measures. The toxicological literature is extensive, and the ACGIH Documentation for all these substances is both extensive and widely available (2). However, when one approaches the several physical agents, most toxicologists, industrial hygienists, and physicians appear to feel somewhat uneasy and less than fully informed. Noise is perhaps one exception, as most of these specialists have had some exposure to the subject. Mention magnetic fields, lasers, whole-body vibration, infrared, or other physical agents, and most health scientists must search for a book. Fortunately, there are only a few physical agents with which to be concerned. The ACGIH Physical Agents TLV Committee has identified only 16 physical agents for which TLVs could be established since that Committee was initiated in 1966. Hazard assessment, measurement and evaluation, and engineering controls for each physical agent may differ considerably. If one examines the physical agents TLVs, one is struck by the variation in the physical quantities and units to describe, measure, and assess the hazard. Indeed, rather different technologies apply to different agents. Specialists exist in each technology who are expert in assessing those hazards, but are frequently not expert in the hazards and terminology of other technologies. The detailed information relating to each physical agent is generally found in separate texts.

Industrial hygienists and occupational health professionals worldwide routinely make use of PELs, TLVs, MACs, and toxicological data for chemicals. Industrial hygienists are very familiar with the use and the special notations for different classes of chemical substances. However, when it comes to the evaluation and control of potential hazards from physical agents, the beginner is frequently astonished by the seeming complexity—with different terminologies for different human exposure limits, the different types of engineering technologies, the various restrictions, and the specialized mathematical formulas. Some occupational health professionals complain that even the TLVs and basic technical data for many physical agents are overly complex. They feel that too many specialized mathematical expressions are used and are not readily understood by the average health and safety professional. Others also question whether the exposure guidelines and controls could not be simplified or made more readable.

These concerns are understandable when one recognizes that physics, biophysics, and engineering disciplines are applied most heavily in studies of any physical agent; whereas chemistry, biochemistry, and biological disciplines are fundamental to the studies of the chemical agents. The different approaches in dealing with chemical agents also appear when one examines occupational exposure limits, such as the ACGIH TLV list. If one examines an entry in the chemical substances TLV list, a single line of print is normally sufficient to present the TLV for a single substances. With large groupings of the chemical substances, similar toxicological approaches, similar methods of analysis, and similar methods of controls can apply. Broad statements can be made about each grouping of chemical substances. By contrast, a listing for a physical agent may require several pages to present. A physical agent may act uniquely on one organ or tissues, and these vary with each physical agent. Different physical quantities and units often apply, and different spatial and time dependencies are typical for each agent. Entire books and lengthy standards have been written about each physical agent (3–17).

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Emission Limits and Exposure Limits
Two fundamental approaches can be taken to control the hazards of a physical agent: control the exposure or control the emission. Product safety standards exist for most physical agents that place the weight of responsibility upon the manufacturer to control emissions from the physical equipment. The product safety standards make use of *emission limits*. The alternative approach places the primary responsibility on the industrial hygienist or health physicist to make use of *human exposure limits* such as TLVs to aid in risk assessment in the workplace and control potentially hazardous exposure (Fig. 96.1). The manufacturer employs product safety measures (engineering controls) to limit emissions and warning labels and product information (administrative controls) to minimize risks. The occupational health specialist can use engineering controls, personal protective equipment, and administrative measures to minimize risk. If the manufacturer cannot completely eliminate hazardous emissions, then the occupational health specialist must evaluate the hazards for a particular operation and recommend appropriate control measures.

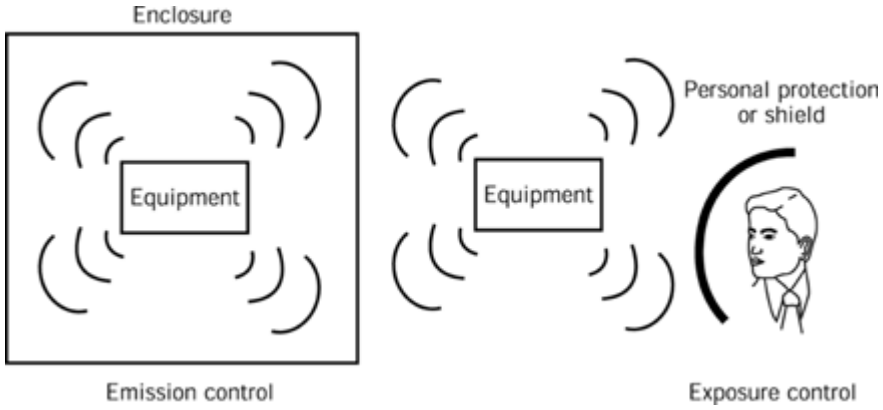

Figure 96.1. The two different approaches to reduce hazards from physical agents: at the source through emission controls or at the worker with exposure controls.

Depending upon the physical hazard and the field of technology, one approach to controlling hazards generally dominates. For example, in the control of hand/arm vibration and whole-body vibration, manufacturer product safety standards play the most important role, although vibration isolation devices such as specialized gloves may also play a role. Optical radiation hazards are frequently dealt with by the product safety approach through lamp safety standards and laser safety standards, but not all lamps and lasers can meet the safe category (e.g., “Class 1 laser product” or “Exempt” lamp), and user controls are required (18–20).

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Categories Of Physical Agents
When considering physical factors upon health, it is useful to first set out broad categories. The broadest categories are: mechanical, thermal, radiation, and static (or slowly varying) electric and

magnetic fields. Mechanical factors are vibration, noise, and ultrasound. Radiation includes radiant energy across the entire electromagnetic spectrum from power-frequencies of 50 and 60 cycles per second (hertz, Hz) to high-energy gamma rays. Table 96.1 summarizes these physical factors. Within each broad category are subcategories as shown in the table. The physical terminology, measurement methods, and controls vary significantly between each category and these can vary even within a broad category. Figure 96.2 explains the spectrum of frequencies.

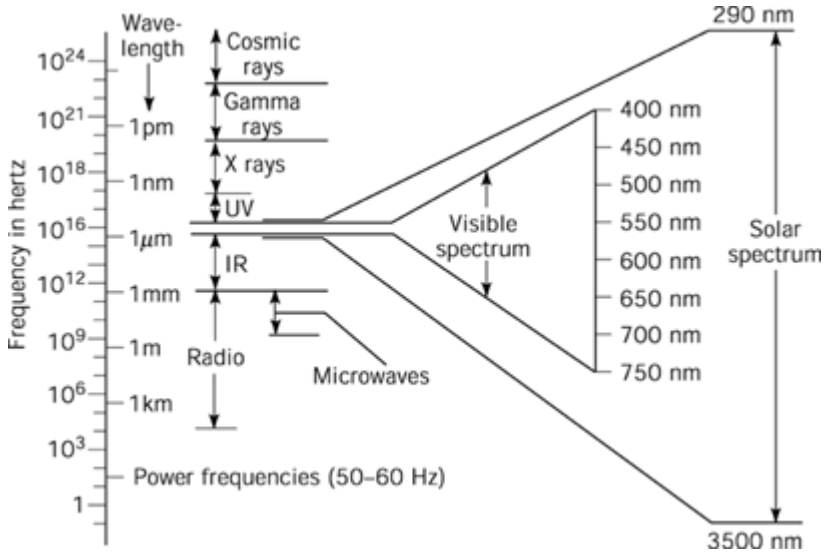

Figure 96.2. The electromagnetic spectrum. Dividing lines are approximate.

Table 96.1. Categories of Physical Agents of Concern

Category of Physical Factor	Dosimetric Concept	Terms and Units
Mechanical Ultrasound Audible noise Infrasound	Airborne power and energy: pressure levels in air	Sound pressure level (SPL) expressed as logarithmic (dB) levels referenced to 10 dyn/cm^2
Whole-body vibration Segmental (hand/arm) vibration	Energy or power conducted by mechanical structures	Transducer
Thermal Heat Cold	Measures of heat exchange of body with environment	Air temperature modified as WBGT air temp./humidity modified by wind
Electromagnetic radiation Ionizing	Absorbed dose 5/kg	Ionization in air (Sv) or absorbed dose (Gy)
Nonionizing Ultraviolet	Radiant power, energy per unit area transferred as electromagnetic waves in free space	W/cm^2 (irradiance or power density)

Visible (light) Infrared Radio frequency (includes microwaves)		J/cm^2 (irradiance exposure or energy density)
Static and slowly varying fields		
Electric fields	Electric field potential across two points in space	Volts/m
Magnetic fields	Magnetic flux concentration	Amperes/m and teslas (T)

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Extrapolation from Animal to Human

For some physical agents, animal research has not been the focus for research studies. Clinical and epidemiological data have been relied on heavily. The application of a toxicological approach to deriving human exposure limits has not generally been applied to all physical agents, but is aptly illustrated by examining the approach followed in deriving laser limits. Human exposure limits for laser radiation are based upon experimental ocular injury studies. The limits are derived by committees of ophthalmic and occupational health experts through a review of all available threshold data and an understanding of mechanisms of laser/tissue interaction. A major point of discussion in this derivation process relates to the level of uncertainty of the threshold of injury. An indication of the level of uncertainty relates to the slope of the transformed dose–response curve, or the "probit plot" of the data. The most important point on the probit plot is the exposure, which represents a 50% probability of injury: the ED_{50}. It is this value that is frequently referred to as the "threshold," even though some experimental damage points exist below this "threshold." The slope is related to the reciprocal of one standard deviation of the normal distribution of experimental data, and thus it reflects not only natural biological variation, but also the impact of experimental errors. The class of damage mechanism will also alter the steepness of the probit plot. When the steepness is less, it may indicate problems in conducting the experiment. The techniques of probit analysis come from toxicology, and certain inherent assumptions are carried over to laser safety studies.

An analysis of any number of example data sets reveals that the slope in most experiments could not be explained by biological variation alone. This type of critical analysis is essential in deriving exposure limits. For example, if the slope is not very steep, as with some retinal injury studies, the probit curve may suggest that at one-tenth the ED_{50} energy value, there might be a 0.1% risk of injury—a risk generally not acceptable in the laser safety community. Yet, from fundamental biophysical principles, this result could be shown clearly to be flawed. If the ED_{50} energy corresponds to a retinal temperature elevation of 15°, an energy of 10% of the ED_{50} must correspond to 1.5° (10% of the ED_{50} temperature elevation), which could not produce photocoagulation. This aptly illustrates that any derivation of human exposure limits for laser-induced injury requires one to estimate the true biological variation and separate this from the added experimental errors, which reduces the probit slope.

Analysis of reported experimental data indicates that the thermal and thermoacoustic damage mechanisms apparently have an intrinsic slope of approximately 1.15 to 1.2. However, experimental threshold data from retinal studies give slopes that are often much greater (e.g., 1.5–1.7), which is really not surprising. The enormous difficulty of seeing a minimally visible lesion and focusing the laser beam to produce the nearly diffraction-limited image leads to this greater spread of data and shallower slopes. If a probit curve is applied to the derivation of human exposure limits, it should have a slope of 1.2 or less with the ED_{50} point shifted to a lower value.

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Mechanisms of Action
The interaction of physical energy with biological tissues varies greatly, and this variation accounts for some of the differences in the quantities and units required to assess the potential hazards from the different agents. The interaction can be systemic as in the case of heat and cold stress or organ-specific as in the cases of optical energy focused on the retina of the eye or airborne mechanical energy damaging structures within the car. Cellular response can be very important in the case of ionizing radiation and some photochemical effects from ultraviolet radiation.

To study biological effects and potential hazards of any physical agent, one must examine the possible means of coupling energy into tissue and the mechanisms of interaction with biological tissue. There are many parallels that may be drawn between the different physical agents. In all cases, researchers must examine how power and energy in the environment reaches sensitive biological tissues, the interaction mechanisms at cellular, tissue, and organ level, the biological response as a function of time physical parameters (wavelength, frequency, exposure duration), the time course of biological responses, injury thresholds, the natural means that are employed by biological tissues or organisms to defend against damage from overexposure, and possible subsequent biological repair.

The sensory organs—notably the eyes and ears—and skin are the most typical “routes of entry” of the physical energy which may cause harm. The most sensitive structures vulnerable to damage by physical energy are the sensory structures of the inner car (hair cells) and the sensory cells of the retina of the eye. The means to specify the action of this energy can vary. It may be possible actually to measure, or at least calculate, the power or energy concentration at these target cells. The external levels of acoustic or optical power and energy that result in these internal concentrations depend upon the transmission of the energy by the outer structures of the eye (cornea, aqueous, lens, and vitreous) or the ear (outer ear and transfer structures as the tiny bones of the middle ear). For mechanical energy (acoustic and vibration), one may determine the impedance of energy-transfer structures at different acoustic frequencies; for optical energy, one may determine the spectral transmission at different wavelengths of the ocular media.

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Dosimetric Concepts
Several physical factors may be relevant to specify dose. Unfortunately, since the biological effects for each physical agent varies, the relevant dosimetric quantities and units vary. For electromagnetic radiation, the same dosimetric concepts may actually have different names because of different

conventions in sister fields of engineering or physics. For example, the incident power in watts per surface area (e.g., W/cm^2 or W/m^2) is termed "irradiance" in the optical spectrum (100 nm to 1 mm in wavelength) and power density in the radio-frequency (RF) region. To add further confusion, geometrical factors sometimes play a role. For example, slightly different radiometric concepts are used in the optical spectrum that have the same units: "fluence rate" has the same units as "irradiance," but includes power equally from all angles without a cosine correction and includes backscatter through the surface area. Unfortunately, not all scientists working in one discipline are rigorous in their use of these physical quantities and develop slightly different conventions, leading to confusion in conducting a review of the literature.

Each physical agent is frequently evaluated by specialists of that one agent, who study the biological effects and potential hazards and have differing conventions for examining damage at the cellular or organ level and expressing their results. In occupational health, one typically finds some specialists who routinely apply the exposure limits and are familiar with the special technology and techniques of hazard evaluation and control. This has led to the criticism that the limits are indeed too complicated or difficult to apply if they require an expert to apply. Furthermore, the presentation of the exposure limits are often succinct (as in the ACGIH TLV booklet), and a generalist feels that insufficient information is provided. The documentation for any ACGIH TLV contains a description of the biological effects of the agent, the relevant research studies and the rationale for the derivation of the TLV. Further clarification about the measurement and applications can also be included, but the TLV booklet presentation will be flawed if it does not provide the necessary caveats in the application of the limits and provide sufficient information for knowledgeable practitioners having training in that agent to apply the TLV.

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Selected Industries and the Physical Agents Commonly Found

Construction	heat and cold stress, noise, and perhaps vibration and solar ultraviolet radiation.
Meat packing	cold stress
	Laser company or physical/chemical research facility lasers
Metallurgy	heat-stress, UV, laser, RF, or cold stress.

Common airborne sampling procedures and basic instrumentation may cover a large number of chemical substances, but there are many different types of instruments and sampling procedures (specifying exposure geometry, etc.) used for physical agents. For lasers one might need five different instruments to cover all of the conditions covered by the TLV (e.g, pulsed, continuous-wave, ultraviolet, visible or infrared, etc.).

Radio-frequency may apply to many different frequency bands of a single physical agent over a wide spectrum where measurement techniques differ. One can imagine many separate TLVs for small increments of the spectrum; hence the length of the TLV cannot be short without leading to ambiguity and confusion.

Toxicological Effects of the Physical Agents

Conclusions

Occupational health specialists require knowledge of the potential hazards, existing exposure limits, and control technology. Expertise in the physical agents is widespread, but diffused, since different technologies apply to different physical agents. Providing understandable guidance for control of hazards to health from physical agents is not an easy task. Currently available exposure limits and emission limits are generally scientifically well stated, sound and complete, and hopefully not misleading. For example, most of the wording in the ACGIH physical-agent TLVs has been carefully crafted over decades of review and from experience with incidents of misinterpretation, confusion, etc. Hence, the call to "simplify" the TLVs without recognizing these factors should be carefully studied. Perhaps the extensive efforts put into the seemingly lengthy and highly technical physical agent TLVs and related standards explain why they have been used in international standards and have been adopted by other countries. An expert committee of European scientists recommended the adoption of a number of physical agent ACGIH TLVs in the European Community a few years ago.

Toxicological Effects of the Physical Agents

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Cold Stress and Strain
Harry Mahar, Ph.D., CIH

1 Introduction

The human body has the thermoregulatory capacity to maintain its body temperature within about 1° C of normal (i.e., 37°C) under a variety of external environmental temperatures. When the body's heat loss to the environment is greater than its ability to maintain its internal homeostatic temperature, the body undergoes cold strain in response to the external cold temperature stress. Prolonged exposure to any temperature less than normal body temperature to which the body's thermoregulatory capacity cannot accommodate may result in cold-related injuries to tissues or cause other systemic changes, including hypothermia and death. Those injuries may involve local tissue damage that results when the tissue actually freezes (e.g., frostbite) or that can result from nonfreezing conditions in tissue sufficient to cause temporary or permanent vascular damage (e.g., chilblain, immersion foot). Heat loss sufficient to overcome the body's thermoregulatory mechanisms can produce a critical drop in the body's deep-core temperature and eventually hypothermia and death.

Exposure to cold stress may also produce physiological or metabolic changes or shifts in endocrine systems, affect judgment or behavior, or exacerbate existing medical conditions (e.g., cardiovascular disease). For acute exposures, the body's response to cold stress is a function of the rate of heat loss, the temperature to which the individual is exposed, and the duration of exposure. For chronic exposures which produce subtle endocrine and metabolic shifts, the diurnal or seasonal (e.g., circannual) periodicity of that exposure may be more important than the environmental temperature to which the person is exposed. In assessing the impacts of exposures to cold stress, one should differentiate between normal changes that result as the body accommodates to that stress (homeostatic response mechanisms) and actual damage or disruption that result when the body's homeostatic response mechanisms are exceeded.

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2 Prevalence
Most regions of the globe have environmental temperature fluctuations, seasonally or diurnally, that are sufficiently extreme to produce cold-related injury in unprotected persons. High-latitude areas (e.g., circumpolar regions) of the world in particular experience prolonged and severe periods of deep freezing temperatures, although sufficiently cold temperatures will occur in midlatitude and subtropical climates to produce cold-stress-related exposure risks.

Cold-related injuries are not exclusively freezing injuries, and in fact can occur at environmental air temperatures of ~10°C, whereas continuous immersion in water at temperatures only a few degrees below normal body temperature eventually will produce hypothermia. Morbidity and mortality statistics suggest that cold-related injuries are geographically widespread and appear more dependent on other co-factors than on the actual environmental temperature. Those statistics also suggest that cold stress does not appear to be a substantial occupational risk but rather more of a public health issue. From 1979 through 1992, the annual, age-adjusted death rate in the United States for hypothermia was 0.3 per 100,000, with approximately half of all hypothermia deaths occurring among persons aged 65 years or greater (1). In a survey of 428 cases of civilian accidental hypothermia in the United States, a majority of the cases occurred in urban settings, with 16% occurring in Florida (2). During 1991–1995 in Alaska, 327 persons were hospitalized for cold-related injuries, 46% of which were for hypothermia and 42% for frostbite of the foot (3). In 20% of all the cases, the individual sustained the injury while working. Occupations in which cold stress is an occupational risk include those industries involving outdoor work in cold or cold and wet environments (e.g., commercial fishing, recreational industries, underwater diving, construction and maintenance, military operations, transportation) or work in artificially cold environments (e.g., cold storage/freezer operations). In the nonoccupational setting, individuals pursuing outdoor sport and recreational activities in cold climates are at risk, in one survey accounting for over 50% of all clinical cases of frostbite injuries reported (4). From a public health perspective, cold stress appears to contribute to increased morbidity and mortality from a number of existing medical conditions such as ischemic heart disease and respiratory disease (5). Cold stress affects the elderly, infirm, or indigent (1) or those with personality disorders or substance-abuse problems more frequently or more severely than the average adult population (3, 4).

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3 Physiological Response to Cold Stress
In homeothermic organisms, the body's temperature, specifically the temperature of the deeper core, is in dynamic equilibrium with the external environment, where internal heat production is balanced against heat loss to the environment. This balance is sustained by the integration of heat production from normal metabolic function (M) and from energy produced during work (W) with the heat exchange due to evaporation (E), convection (C), conductance (K), and radiation (R) and can be expressed in basic thermodynamic principles as:

$$S = M + W \pm E + C + K + R$$

where S represents heat storage in the body and can be a positive (heat gain) or negative (heat loss) term. Both convection (C) and evaporation (E) may have a respiratory component (C_{resp}, E_{resp}) that reflects heat transfer via respiration. These values can be either positive or negative depending upon

the environmental conditions. In normal circumstances, heat is transferred from the human body to the surrounding environment, and the body's core temperature is maintained within about 1°C of the normal body temperature (~38°C) without undue physiologic strain. In humans exposed to environmental conditions colder than body temperature, heat loss will occur, typically via radiation or evaporation. Although a number of factors are involved, a generic representation of heat loss in air or in water is provided in Fig. 97.1.

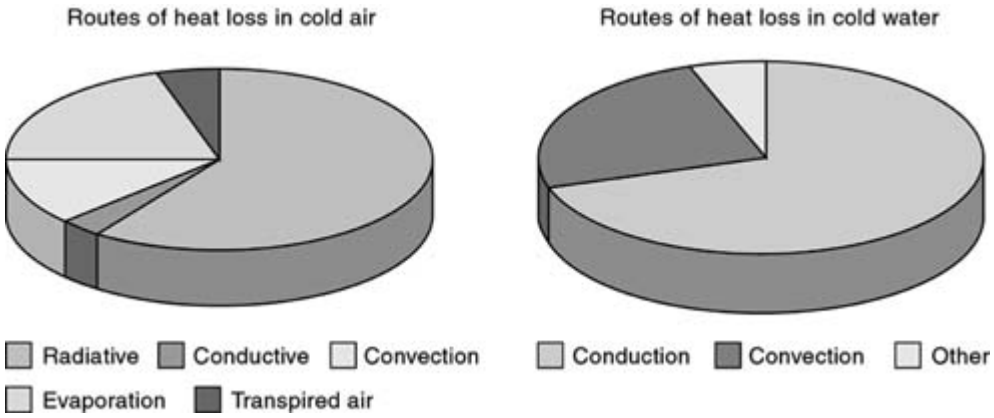

Figure 97.1. Typical routes of heat loss for humans in cold air or in cold water. Adapted from Herington and Morse (7), Toner and McArdle (10), and Danzl et al. (11).

Environmental conditions and the amount of insulating clothing worn will have a significant effect on those heat transfer values, and conductive or convective heat loss mechanisms may predominate under certain circumstances, particularly cold and wet conditions. Movement of cooler air across exposed body surfaces will increase convective heat loss, and forms the basis for the concept of wind chill (6). Clothing provides insulation between the body and the environment, reducing convective and conductive heat losses, but wet clothing provides considerably less insulation than dry, increasing the rate of heat loss up to five fold via those mechanisms (7). Because water has a higher thermal capacity than air, heat transfer from a warm body immersed in cooler water may be from 25 to 70 times greater than in air at comparable temperatures (7, 8). Thermal strain during exposure to cold air is less than immersion in water at comparable temperatures because of the differences in cooling rates (9), but the consequences of continuous exposure in air can be as severe.

An immediate thermoregulatory control mechanism is modulated through the autonomic nervous system, while a delayed control mechanism is modulated by the endocrine system. The hypothalmus acts as the body's temperature control center, regulating both the immediate and delayed control mechanisms based on input from temperature receptors found predominantly in the skin but present in other organs as well.

3.1 Immediate Thermoregulatory Control

Heat loss from the human body to the surrounding environment is a two-phase process. It first involves transfer of heat from the central core to the body's surface, and then from the surface to the surrounding environment. Although some of that heat loss is retarded by the insulating capacity of the tissue, the majority of the heat is transferred by means of the circulatory system. The normal physiologic response to cold stress is (*1*) to retard heat transferred by the circulatory system by constriction of the peripheral blood vessels to reduce blood flow and (*2*) to replace any heat lost to the environment by increasing metabolic heat production, as is indicated conceptually in Fig. 97.2.

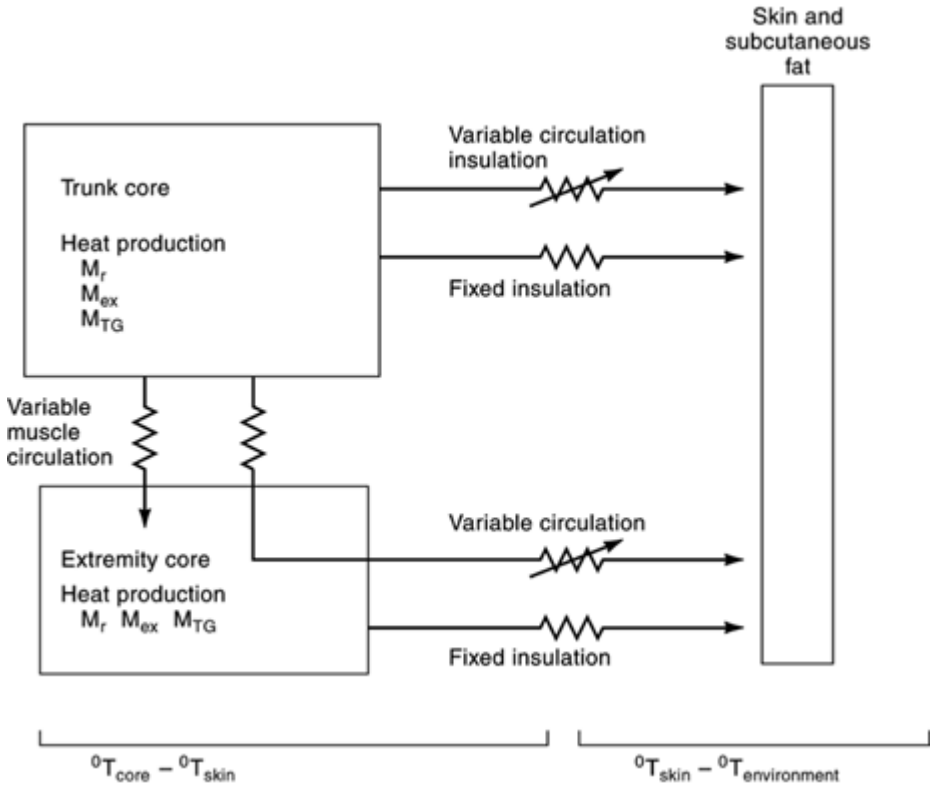

Figure 97.2. Physiologic components of heat transfer. Adapted from Toner and McArdle (10) and Bullard and Rapp (12).

Metabolic heat production may arise from the resting metabolism (M_r), exercise metabolism (M_{ex}), or from thermogenesis (M_{tg}). Transfer of heat between body compartments becomes a function of circulatory output, which is variable, conductive heat transfer from the site of metabolism through the overlying tissue to the surface, and the temperature differential between the compartments and the surrounding air or water ($[T_{core} - T_{skin}]$, $[T_{skin} - T_{environment}]$). Subcutaneous and deep body fat can be major factors in determining the rate of internal and external heat transfer, since thermal resistivities (insulation capacity) of fat are two to five times higher than for skin or muscle (13, 14). The benefits of body fat in maintaining core temperature during immersion in cold water (9, 15–17) and in cold air (18, 19) have been demonstrated in a number of independent studies.

Vasoconstriction of the peripheral blood vessels, particularly in the extremities, provides the primary line of defense against heat loss to the environment. When regional blood flow is reduced, skin temperature drops and begins to approach the temperature of the surrounding environment, thereby increasing the insulating capacity of the skin. This drop in skin temperature is not uniform throughout the body, with greater temperature reductions noted in the extremities and less in the torso areas (21, 22). Heat loss from the body is affected by the change in regional blood flow and the presence of subcutaneous fat, particularly when this vasoconstriction restricts blood flow to tissues underlying these insulating fat layers. In the extremities, a second vasomotor response to cold occurs, cold-induced vasodilation, which alternates with vasoconstriction. This cycling between vasoconstriction and vasodilation, termed the *hunting reaction* (23), provides periodic re-warming of those tissues (thus delaying the onset of freezing injuries) but at the expense of overall body temperature reduction (due to transient increased blood flow at the surface). There appears to be general agreement that as the core temperature is reduced below about 32–35°C, cold-induced vasodilation is reduced and eventually eliminated (10).

Other factors that affect the rate of convective heat transfer from a body immersed in cold water or air include the surface area-to-mass ratio of the body; the temperature differential of the body and

surrounding fluid; and the stability of the boundary layer at the skin-water (or air) interface. In general, as the surface area-to-mass ratio increases, the greater the observed heat transfer (9). The thin boundary layer of water or air at the surface of the skin acts as insulation, because as that layer is heated above ambient, heat conduction through this warmer boundary layer is reduced. Any disruption to this boundary layer increases heat loss, whether that disruption results from air or water currents past the skin surface or is induced by body movement during exercise (24, 25). This suggests that for a body immersed in cold water, any movement (e.g., swimming) removes this insulating boundary layer and exacerbates heat loss (10, 26). The heat produced during the physical movement, (i.e., metabolic heat from exercise) is rapidly lost causing a net loss of body heat to the environment.

Increases in metabolic heat production can allow the body to compensate for any heat lost to the environment and attempt to maintain core temperature. This metabolic capacity is determined by a number of factors, including body size, composition (e.g., muscle mass), nutritional state, endocrine system status, age, and race. Heat production can arise from the resting or basal metabolism (M_r), or metabolic heat from exercise (M_{ex}) or shivering thermogenesis (M_{tg}), as noted in Fig. 97.2, all of which can be expressed in terms of maximum aerobic power or oxygen uptake, V_{O2max} (27, 28). For short-term exposures to cold stress, the resting or basal metabolic rate does not change significantly; so heat production is primarily from muscle contraction during exercise (M_{ex}) or involuntary shivering (M_{tg}). In human infants and some other mammalian species, there may be a nonshivering thermogenesis associated with the aerobic metabolism of brown adipose tissue, but that does not appear to occur in human adults (10, 29). The resting metabolic rate may change over time (e.g., seasonally) as a result of delayed thermoregulatory mechanisms mediated by the endocrine system (30–32).

The increase in metabolic heat production from muscle contraction during exercise and/or shivering varies with the severity of the cold stress as the body attempts to replace the heat lost to the environment. Shivering may contribute up to ~50% of an individual's V_{O2max} during immersion in cold water (28) and somewhat less in cold air (33). While exercise or shivering increases heat production, the increased blood flow to the muscles also facilitates heat loss; so there may be a net loss of body heat in cold water. In contrast, exercising while exposed to cold air provides an effective means of maintaining thermal balance, since convective and conductive heat losses are less than in water. For an unclothed person at rest immersed in cold water or air, there is a critical environmental temperature below which an increase in energy metabolism (i.e., M_{tg}) is noted as the body attempts to replace heat lost to its surroundings. This critical temperature of the surrounding air or water can be correlated to the insulating capacity of the skin and subcutaneous fat deposits (expressed as skinfold thickness). As the body core temperature drops below 35°C, tissue metabolic rates decline with decreasing body temperature (34), accelerating the drop in body core temperature and the onset of hypothermia. Because of this decline in metabolic rate, 35°C is generally considered that body core temperature threshold below which the cold-stressed individual cannot recover without outside intervention.

The increased cardiac output needed to sustain this oxygen transport to the muscles in support of higher metabolic rates results from an increase in stroke volume rather than an increase in heart rate (35). The substrate source to fuel this increased metabolic activity appears to be an increase in carbohydrate and lipid oxidation, rather than protein oxidation (36, 37). Substrate mobilization and utilization appear to be the limiting factors in sustaining prolonged increases in exercise or shivering thermogenesis (37), along with the lactate threshold of exercising muscles (38). Therefore, muscle fatigue appears to be the most significant factor in hypothermia incidents where prolonged exposure to even mildly cold conditions was involved (39). It has been demonstrated that fit subjects also have more efficient thermoregulatory abilities against cold stress than unfit subjects because of an improved sensitivity of the thermoregulatory system (40).

3.2 Delayed Thermoregulatory Control

Two major hormonal mechanisms affect human cold tolerance. During cold exposures there is an immediate release of catecholamines (e.g., norepinephrine, dopamine), which activate the sympathetic nervous system to reduce heat loss via peripheral vasoconstriction and shift substrate utilization toward fatty acid metabolism for heat production. The hypothalamic–pituitary–thyroid axis provides the second hormonal control mechanism for regulating physiologic response to cold stress, with thyroid hormones (particularly triiodothyronine, or T_3) being the most influential (30). Whereas the catecholamines appear to act during the acute stages of cold exposure, the thyroid hormones are the primary mechanism for adapting to chronic cold exposures, such as those resulting from seasonal temperature changes or from the relocation of individuals from temperate to polar climates. These thyroid hormones stimulate a general increase in metabolic rate by increasing the activity of the enzyme sodium–potassium adenosine triphosphatase (Na–K ATPase), thereby decreasing the efficiency of mitochondrial oxidative phosphorylation (30, 41). This stimulation of T_3 kinetics (and its precursors) is noted initially within 2 wk of chronic cold exposure and eventually equilibrates within a 4–6-mo time period. This phenomenon has been characterized as the Polar T_3 Syndrome (42, 43).

Studies have shown an increase in energy requirement (up to 40%) for persons relocating from a midlatitude, temperate climate to a colder, high-latitude, polar climate (44). Some of this increase can be accounted for by an increase in resting metabolic rate or by a reduction in the efficiency of muscle activity at a predetermined workload (45) brought about by the stimulation of Na–K ATPase. These changes have been correlated with thyroid hormone levels, particularly T_3 in skeletal muscles, and are similar to other conditions involving thyroid hormone excess (46). This delayed hormonal response to cold stress has been demonstrated in populations exposed to chronic cold environments as well as in occupational groups intermittently exposed to cold conditions during normal work shifts (47) or in experimental subjects exposed to repeated short-duration cold exposures (48, 49). Changes in thyroid hormone levels resulting from prolonged habitation in Antarctica have been correlated with increased total serum cholesterol and high-density lipoprotein (HDL) cholesterol, a response consistent with other medical conditions of thyroid hormone imbalance (50). Changes in thyroid hormone levels have also been correlated with increased depressive symptoms and reductions in cognitive performance characteristic of Winter-Over Syndrome found in persons spending the austral winter in research stations in Antarctica (51).

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4 Adaptation

Humans can adapt to continuous or intermittent cold stress through a variety of mechanisms, usually related to the individual characteristics of the subjects (e.g., diet, fitness level, body fat) and the duration and severity of the cold stress. Physiologically, these adaptations can be characterized as (*1*) metabolic, where there is an alteration in metabolic heat production; (*2*) insulative, where there are improvements in heat conservation through more effective peripheral vasoconstriction; or (*3*) hypothermic, where a lower core body temperature than normal is tolerated before shivering occurs.

These physiological adaptations have been demonstrated in aboriginal peoples residing in high-latitude environments (e.g., Eskimos, Lapps) or in areas with significant diurnal temperature variations (e.g., Australian Aborigines, Kalahari Bushmen) (52–56). These types of adaptations have also been demonstrated in individuals intermittently exposed to cold stress in the occupational setting or in experimentally manipulated environments.

Longitudinal studies carried out in breath-hold divers in Korea subjected to repeated underwater dives in cold (~10°C) water have demonstrated all three adaptations—metabolic, insulative, and hypothermic (57–60). During the winter months, these divers developed an approximately 35% increase in basal metabolic rate over nondiving controls, apparently due to increased uptake of thyroid hormone in tissues (61). Studies of fishermen who immerse their hands repeatedly in cold water have demonstrated an insulative response locally in the cold-exposed hands. These fishermen developed a more rapid cycling of the vasoconstriction and vasodilation response in the cold-exposed hands and were able to maintain motor function in the hands in the cold water without a drop in body temperature that one might expect with increased peripheral vasodilation (62, 63). This insulative-type adaptation has also been hypothesized to occur in individuals working in Antarctica for an austral winter season who were able to sustain significant experimental cold challenges (e.g., standard cold air tests) without a concomitant drop in body core temperature (64). It is not clear whether these responses were due to insulative adaptations or reflected a change in energy balance resulting from delayed thermoregulatory controls mediated through the endocrine system.

Note that the type of cold adaptation that develops (i.e., metabolic, insulative, or hypothermic) is closely related to the cold stress to which the individual is exposed and the characteristics of the subjects (e.g., diet, age, physical fitness level, body fat content). As a result, different individuals exposed to the same environmental conditions may develop different adaptation approaches to accommodate to that stress.

Short exposures to severe cold may elicit different adaptive responses than prolonged exposures to moderate cold (65). Deacclimatization occurs over time, usually over a comparable time scale as was needed to produce the adaptation initially, but it may take several years to disappear completely, as was demonstrated in Korean breath-hold divers (57, 66). These adaptation responses to cold stress appear to confer a survival advantage to some aboriginal populations and to provide a modest benefit to certain cold-stressed groups.

Because anthropometric differences (body size, surface-to-mass ratio, fat composition) between individuals account for most of the variability in response noted in populations exposed to cold stress, it is difficult to define the magnitude of the contribution of adaptation processes to maintaining thermal balance. However, these adaptations provide only small improvements in body heat conservation compared to other heat-conserving alternatives such as the use of protective clothing; so their benefit in protecting the individual from cold stress should not be overstated. Short-term acclimatization to cold stress does not appear to convey as significant a physiological advantage as the acclimatization to heat stress that is observed in individuals exposed repeatedly to heat-stress conditions.

The delineation between the physiological changes indicative of normal adaptive response to cold stress (where the individual is accommodating the stress without long-term injury or detriment) and the physiological changes indicative of actual injury may be difficult to establish clearly in some instances. It is not uncommon for an individual's skin or core temperature to be lowered during exposure to cold stress without the individual sustaining any long-term damage or significant physiological strain. For example, individuals wintering in Antarctica and who have had an opportunity for adaptation may demonstrate a reduction in average body core temperature of more than a degree Centigrade with no long-term detrimental sequelae. On the other hand, a one-degree reduction in body core temperature in an individual exposed to an acute cold stress may indicate an excessive rate of heat loss in that individual and possible impending hypothermia.

5 Cold-Related Injuries

Direct tissue injuries resulting from acute exposures to cold stress can be categorized into several groupings, the most common being freezing cold injuries (where the affected tissues are frozen) and nonfreezing cold injuries (where the affected tissues never freeze but sustain damage from the cold stress). Examples of freezing cold injuries include frostbite and its less severe precursor, frostnip. Nonfreezing cold injuries include cold urticaria, chilbain and its more severe form pernio, trenchfoot, and immersion foot. Typically, freezing cold injuries occur when the environment is sufficiently cold and dry for the exposed tissue actually to freeze, whereas nonfreezing injuries occur in cold (but not freezing) and wet or moist/humid conditions, often as immersion in cold water. Nonfreezing cold injuries are time/temperature dependent—the warmer it is, the longer the time required to produce damage. Some nonfreezing injuries can occur at environmental temperatures as high as 16°C (60°F), but may take many hours or days to develop. Freezing cold injuries are usually determined by the rate of heat loss, and may manifest themselves within seconds or minutes.

Hypothermia is a condition associated with a lowering of body core temperature below which normal thermoregulatory and physiological functions are disrupted. The condition is not associated with specific tissue damage *per se*, as is frostbite or pernio, and can occur in association with either freezing or nonfreezing injury scenarios. Hypothermia may be produced in either cold/wet or cold/dry conditions, and may occur in what are considered warm conditions. For example, individuals can be immersed in water only a few degrees below normal body temperature and lose heat to the environment, eventually becoming hypothermic.

In chronic cold stress, shifts in thyroid hormone production and uptake have been demonstrated and are considered part of the normal adaptation process. Decreases in immune function, sperm function, and testicular cancer have been associated with cold stress. There are other sequelae from cold stress that do not demonstrate frank pathology but nonetheless might be considered injuries. Decrements in performance and work capacity, cognitive function, and mood disturbances are examples.

5.1 Nonfreezing Cold Injuries

5.1.1 Chilblain Chilblain is a recurrent localized erythema and swelling caused by exposure to cold (67, 68). The condition typically occurs on the hands and feet and occasionally on the ears and face in children. The affected area becomes red and swollen, with blistering and ulceration in the more severe cases, and is accompanied by a burning and itching sensation. The injury appears to result from repeated vasodilation and constriction with localized histamine release in the affected tissues (7, 69). It is produced by exposure to cold [anywhere from just above freezing up to 16°C (60°F)] and damp conditions, usually over long periods of time (i.e., many hours). Such environmental conditions frequently exist within rubberized boots and footwear, where the humidity can be high. Seasonally recurring chilblains on the hands (e.g., “milkers' chilblains” in dairy farmers) can occur, often aggravated by sunlight (70). Persons with poor peripheral circulation are predisposed to chilblain and may exhibit the condition after exposure to only moderately cold temperatures. Chronic chilblain occurs repeatedly in cold weather and disappears in warm weather, and can persist is some individuals for many years. Other predisposing conditions include Raynaud's syndrome and collagen-vascular diseases such as systemic lupus erythematosus (7, 71).

5.1.2 Pernio Pernio is a more severe form of chilblains, where the affected skin areas become necrotic and may slough off, leaving painful lesions that are slow to heal. The depth of the injury is dependent on the duration of exposure. As with chilblain, persons with certain existing conditions (e.g., Raynaud's syndrome, lupus erythematosus, and other skin lesions) are more susceptible. Persons with anorexia nervosa, with its attendant altered thermoregulation and hyperactive peripheral vascular response to cold, may also be at increased risk (72). It is difficult to establish precisely the environmental conditions of temperature, humidity, and duration of exposure that lead to the development of chilblains or perniosis, since many sufferers have existing conditions predisposing them to problems. However, exposure to moderately cold (but not freezing) temperatures, coupled with humid or wet microenvironments for hours may be sufficient to produce the condition. Recurrent pernio can be particularly painful to individuals upon re-exposure to cold conditions.

5.1.3 Trenchfoot and Immersion Foot Trenchfoot and immersion foot are comparable injuries, the former caused by exposure to cold/moist environments and the latter caused by immersion in cold water. Both can occur at temperatures from just above freezing to about 10°C (50°F), particularly if the individual is immobile or is wearing constricting footwear, with an exposure time in excess of 12 h (longer for the warmer temperatures). Pathology is indistinguishable between the two conditions, and is a result of ischemia and anoxia from prolonged vasoconstriction of the blood vessels. Injury shows a clear time–temperature relationship. Such nonfreezing injuries are cumulative and include vascular damage, tissue atrophy, peripheral neuropathy, blistering and ulceration of tissue, and possibly gangrene (7, 67, 69, 73–75). Peripheral nerve damage seems to favor large myelinated fibers (76, 77) and the distal portions of the nerve at the nerve fiber–receptor junction (78). Persistent pain, particularly on re-exposure to cold, is common in persons recovering from trenchfoot injury. Prior trenchfoot sufferers may develop Raynaud's syndrome, an abnormal maintenance of vasoconstriction in the fingers and toes (67). Individuals with poor peripheral circulation appear predisposed to developing trenchfoot, with one study suggesting up to 60% of the normal population base to be at risk (79).

5.2 Freezing Cold Injuries—Frostbite and Frostnip

Frostbite, and its less severe precursor frostnip, develops when tissues freeze, and can evolve slowly over several hours or rapidly (within minutes). Such freezing occurs when the body is unable to maintain sufficient warmth in the affected tissues because the rate of heat loss exceeds the capacity of the body to reheat the area through vasodilation. Freezing cold injuries can be subdivided into superficial (limited to the skin and adjacent subcutaneous tissues) and deep frostbite. Tissue damage is due to the direct effects of ice crystal formation in the tissues, the effects of vascular stasis and accompanying tissue anoxia, and the loss of integrity of the vascular system (7, 67). As the tissue freezes, ice crystals form in the extracellular spaces, dehydrating the adjacent cells and disrupting the cell membranes. During rapid freezing, ice crystals may form intracellularly, producing more extensive tissue damage. As blood flow in the cooling tissues is reduced by vasoconstriction and lowered temperature, oxygen tension is lowered, and diffusion rates into surrounding tissues decrease, combining to produce anoxia in the more distant tissues. Tissue freezing causes endothelial cell damage in the microvasculature, with destruction of the vessel walls, as well as plugging of the lumen of the vascular tree and capillary beds with cellular debris and fibrin, so that tissue healing after thawing is difficult because of the vascular destruction (67, 80, 81). Cell types differ in their susceptibility to frostbite, with nerve, muscle, and bone tissues more sensitive than skin.

The rate of heat loss in the tissue exposed to cold stress is an important determinant in cold injury (82). For exposed skin, air movement across the skin surface increases heat loss above that lost by the temperature differential alone. This concept of “wind chill factor,” originally derived from empirical measurements (6), can be used to predict the onset of frostbite in skin exposed to cold, dry air under various wind speed conditions. Ophthalmic injuries have occurred, particularly freezing of the cornea, in individuals who force their eyes open in high windchill conditions (e.g., snowmobiling, cross-country skiing) (80). Exposed skin in contact with cold metal objects may freeze very quickly because of the high conductive heat loss, although those types of injuries tend to be superficial rather than deep frostbite injuries. Evaporative heat loss during skin exposure to supercooled liquids may cause almost instantaneous frostbite.

Certain host factors may predispose individuals to frostbite injuries. Drugs that impair thermoregulation or vasodilation, alcohol, diabetes mellitus, peripheral vascular disease, and previous cold injury predispose individuals to frostbite injury (7, 83). Attenuated or abolished cold-induced vasodilation (i.e., “hunting reaction”) or persistent vasoconstriction of peripheral blood vessels evident in Raynaud's syndrome or cold-induced white finger disease make individuals susceptible to frostbite injuries (84–86). Dermatologic conditions that increase heat loss through the skin may increase the individual's risk of developing frostbite (11).

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6 Hypothermia
Hypothermia is defined as a drop in body core temperature to 35°C (95°F) or lower. It occurs when the body continually loses heat to the environment and is unable to maintain normothermic core body temperature through available mechanisms of heat production (e.g., basal metabolism, exercise, shivering) and heat conservation. When the body's core temperature drops below about 35°C, it becomes difficult or impossible for the individual to recover on his own, and outside intervention is required for survival. Environmental conditions that increase the rate of heat loss (e.g., high wind chill; cold and wet conditions; water immersion) are particularly dangerous, as are situations where the individual is unable to sustain metabolic heat production (e.g., muscle fatigue, malnutrition, forced inactivity). Typical routes of heat loss by the body have been described earlier (refer to Fig. 97.1). Environmental temperatures do not need to be below freezing to cause hypothermia; in fact, cool temperatures coupled with rain and moderate wind conditions create significant hypothermic risks.

As the body begins to cool and lose water from cold diuresis, the circulating blood volume decreases along with a concomitant increase in blood viscosity and peripheral resistance. Cardiac arrhythmias develop, leading eventually to ventricular fibrillation and asystole. Respiratory rate gradually decreases with progressive cooling, along with tidal volume proportional to the drop in metabolic demand. At a core temperature of about 32°C, the respiratory rate becomes insufficient to remove CO_2, and respiratory acidosis occurs (11, 67). As the body cools there is a decrease in cerebral metabolism and a general depression of central nervous system (CNS) function. Cerebral blood flow is reduced 6–7% for every 1°C reduction in body temperature between 35°C and 25°C (7). Temperature-dependent enzyme systems present in the brain may be more sensitive to temperature than in other organs, where colder temperatures seem to be better tolerated. On initial chilling of the body, a significant volume of urine is voided (i.e., cold diuresis), an apparent response to the hypervolemia induced by vasoconstriction (87). Renal circulation is decreased as the core temperature decreases, with about 50% of the normal flow when the body is cooled to 28–30°C. Many of these physiologic responses to hypothermia are so predictable that intentionally induced hypothermia is routinely used in certain surgical procedures to manipulate organ and system functions to the patient's advantage.

Mild hypothermia may occur frequently in individuals, often insidiously. Because normal body temperatures are restored eventually, with no long-term sequelae developing, these hypothermic incidents often are ignored. Underwater divers, in particular, are at risk of this insidious hypothermia when making repetitive dives in water only a few degrees below normal body temperature because body heat can be transferred to the surrounding water so rapidly. In addition, if water is only a few degrees below body temperature (e.g., ~28°C), normal heat conservation responses may not be triggered to respond to the cold stress, but the body will gradually cool to a little below 35°C without noticeable discomfort or shivering (88). Individuals progress through the sequential stages of hypothermia during cold-water immersion as they do during exposure to cold air but tend to pass through those stages more rapidly because of the increased rate of heat transfer from the body to the environment. Cold-induced diuresis is increased more than threefold during cold-water immersion compared to thermally neutral water and appears greater than produced during cold air exposure, apparently due to the affects of “hydrostatic squeeze” in submerged tissues (89).

Without monitoring the individual directly, it is difficult to predict when hypothermia will occur in a person exposed to specific cold conditions, since host factors, activity level, environmental conditions, and clothing all influence its progression. Body morphology, particularly subcutaneous fat deposits, is a prime determinant in defining the rate of heat loss to the environment. Conditions that influence metabolic heat production (such as endocrine diseases, age, and nutritional status), or

thermoregulation (such as anorexia nervosa or diabetes mellitus), affect one's susceptibility to hypothermia. Conditions that influence heat loss, such as certain dermatological diseases (e.g., psoriasis, eczema) or burns will affect susceptibility. Certain drugs and alcohol can increase heat loss or impair thermoregulation. Environmental conditions that increase the rate of heat loss to the environment, such as wind speed or water immersion, will exacerbate the hypothermic situation. Conversely, insulating clothing that retards heat loss to the environment will reduce the risk of hypothermia under cold or freezing conditions. Table 97.1 summarizes the clinical presentations of hypothermia.

Table 97.1. Clinical Signs of Progressive Hypothermia

Core Temperature (°C)	(°F)	Clinical Signs
37	98.6	Normal body temperature (±0.6°C)
35	95.0	Maximum shivering occurs (M_{tg}; see text)
34	93.2	Victim conscious, progressive disorientation; rewarming may require intervention, cerebral blood flow decreases (6–7% per °C reduction)
33	91.4	Ataxia, disorientation
32	89.6	Respiratory rate decreases to ~75% of normal; respiratory acidosis occurs
31	87.8	Involuntary shivering may cease
30	86	Cardiac arrhythmia develop; renal circulation reduced to ~50% of normal; cardiac output reduced
29	85.2	Progressive loss of consciousness; pulse and blood pressure difficult to obtain
28	82.4	Ventricular fibrillation probable with rough handling; cerebral blood flow ~50% of normal
27	80.6	Voluntary motion ceases; reflexes absent
26	78.8	Victim seldom conscious; major acid–base disturbances
25	77	Ventricular fibrillation may occur spontaneously; cerebral blood flow ~30% of normal
24	75.2	Pulmonary edema probable; significant hypotension
22	71.6	Maximum risk of ventricular fibrillation; oxygen consumption reduced 75%
20	68	Lowest temperature for resumption of cardiac electromechanical activity
18	64.4	Asystole
16	60.8	Coldest adult hypothermia victim to recover
9	48.2	Coldest therapeutic hypothermia patient to recover

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7 Other Effects of Cold stress

Exposure to cold stress, either as a short-term, acute exposure, or as a result of chronic exposure, including seasonal weather changes, may cause other conditions than those already mentioned. Decrements in performance or work capacity, cognitive function, endocrine function, immunological responses, and respiratory system changes, along with potential carcinogenic or reproductive impacts and general malaise, have been associated with acute or chronic exposure to cold stress.

7.1 Manual Performance/Work Capacity

Performance of manual tasks, particularly those requiring dexterity, has been shown to deteriorate the longer the individual is exposed to cold stress or the more severe the cold exposure. As regions of the body cool in response to cold stress, muscle tissues also cool, and with that cooling comes a decrease in maximal aerobic power, as measured by V_{O2max}. For example, a reduction in muscle temperature from 39.3°C to 35.1°C produced a 15% decrease in V_{O2max} (90). Aerobic power is a function of the rate of ATP splitting, whose velocity constant is temperature dependent (91), so as the muscle mass cools, the rate of ATP splitting is reduced. In addition, a reduced body temperature also reduces cardiac output, thereby limiting available oxygen to the muscle tissues (36, 90, 92). In cold-water immersion studies (at 10°C), forearm grip strength dropped approximately 1.8% per minute after 5 min of exposure (93). The ability to perform complex manual tasks is also affected by cold. Fine motor control may be lost when skin temperatures of the hand reach 12–16°C, and tactile sensitivity lost at about 8°C (94). However, the rate of cooling, particularly to the deeper tissues of the hand and arm, rather than actual skin temperature, may be a better predictor of such performance degradation (95, 96). The impacts of cold stress on manual performance depend on the tasks to be performed, with greatest impact on those tasks requiring fine motor skills, rapid finger movement, or joint flexibility.

7.2 Cognitive Function

Exposure to cold stress, especially when sufficient to cause mild or severe hypothermia, has been associated with reductions in cognitive functions, including short-term memory, quantitative or discrimination skills, and judgment or decision-making. This decrement in cognitive functions becomes particularly important when individuals are becoming hypothermic and fail to recognize it or are unable to take the proper steps to remedy the situation before the situation becomes extreme.

The effects of cold stress on cognitive functions include decrements in performance of tasks requiring vigilance, memory (particularly short-term memory), and rapid and accurate judgments under time constraints. Negative effects on memory and recall (97) and on more complex mental performance (98) have been associated with reductions in body core temperature of 2–4°C. Decrements in reaction time, tracking efficiency (e.g., visual-motor coordination), and time estimation have also been associated with cold stress (98). Cognitive impairment, as measured by standardized delayed matching-to-sample (DMTS) tasks, has been associated with acute cold stress and attributed to the effect of cold on short-term, or working memory (99).

A variety of physiological stresses, (87) including cold exposure, disrupt the sustained release of central nervous system catecholamines (i.e., norepinephrine and dopamine), which are needed for maintaining neurotransmitter release. It has been hypothesized that the inability of these neurons to sustain normal levels of release during acute cold exposures could be responsible for the observed deficits in cognitive function and working memory (100). The administration of supplemental tyrosine, a necessary precursor for catecholamine biosynthesis, appeared to allow for the continued biosynthesis of those neurotransmitters during cold exposure, preventing a cold-induced memory deficit as measured by the DMTS tasks. It is unclear whether the effects of less extreme cold stress—that is, exposure to moderate or short-duration cold exposures that are not sufficient to cause a reduction in body core temperature or a significant release of catecholamines—cause a measurable effect on these higher-order cognitive functions (101). Preliminary reports suggest the possible

effects of chronic cold exposures (e.g., seasonal residence in Antarctica) on cognitive function, memory, and mood and the role thyroid hormones may play in the process. Within the first several months of Antarctic residence, memory declined by about 13% in individuals but could be restored in those taking thyroxine supplements, whereas the placebo group's memory levels remained depressed throughout the remainder of the Antarctic winter (102).

7.3 Endocrine Function

The endocrine system plays a role in the physiological response to cold stress, providing immediate thermoregulatory control via the sympathetic nervous system and a delayed thermoregulatory response via the hypothalamic–pituitary–thyroid axis. The immediate release of catechloamines during acute cold exposure, primarily norepinephrine and dopamine, affect peripheral vasoconstriction and shift substrate utilization toward fatty acid metabolism for heat production. During prolonged exposure to cold environments (e.g., seasonal changes), the thyroid hormones, particularly triiodothyronine or T_3, stimulate an increase in the basal metabolic rate to accommodate long-term adaptation to the cold stress. This hypothermic cold adaptation begins to develop within several weeks of cold exposure, even though only the hands and face may be directly exposed to the outdoor temperature (48). Both the short-term catecholamine release and the delayed T_3 increase are normal physiological responses to cold stress and are not considered detrimental. However, the asymptomatic compensatory increase in thyroid hormone levels is suggestive of a partially corrected subclinical hypothyroidism condition (50), which may be indicative of subgroups within the general population potentially sensitive to cold stress. Altered baseline thyroid hormone levels, particularly T_3 levels, appear to be associated with resident populations in high Arctic latitudes when compared to reference populations in warmer climates (103) and may indicate a genetic adaptation to the circumpolar environment (104).

7.4 Respiratory System Reactions

Heat loss through respiratory gas exchange can be a significant contributor to body heat loss (~30%), particularly during periods of high ventilation rates. Inhalation of cold air can lead to a number of acute and chronic respiratory problems. Bronchospasms and brochorrhea (excess fluid in the airways) have been experienced in underwater divers breathing cold (0–7°C) compressed breathing gas in thermoneutral water, with the symptoms resolving if the gas was warmed (i.e., 23–32°C) and humidified (105). Exercise- and cold-induced asthma produces airway narrowing and increased airway resistance. The immediate airway response (within 5–15 min poststimulus) is thought to be due to rapid removal of heat and moisture from the respiratory tract, while a late-phase response (4–10 h poststimulus) in some individuals seems to be triggered by chemical mediators, possibly histamine (106, 107). Exposure to cold air (–23°C) increases the number of inflammatory cells in the lower broncho-alveolar airways in healthy subjects and has been implicated in the development of a chronic asthmalike bronchoconstriction noted in healthy subjects exercising in cold conditions (108). The initial onset of high-altitude pulmonary edema (HAPE) and other respiratory conditions brought on by heavy exertion and high ventilatory rates in cold air (e.g., “frosting” of the lungs) may be a result of cold-induced bronchorrhea. Chronic effects, such as “Eskimo lung,” similar to chronic obstructive pulmonary disease (COPD), occurs in individuals chronically subjected to hard physical exertion in severe cold. Although the disease may have a complex etiology, the increase in pulmonary arterial pressure and pulmonary hypertension produced from recurrent episodes of heavy exertion in cold conditions seems to establish the disease (106).

7.5 Immunological Responses

Studies of seasonal or temporary (up to one year) residents in Antarctica have suggested that changes to cell-mediated and humoral immunity may occur. It is not clear whether these changes are a result of cold or isolation stresses or the relative absence of other environmental immunological triggers, but the diminished immune function occurs within the first month of arrival in Antarctica (109, 110). However, year-long periods of isolation in Antarctic research stations have not resulted in enhanced susceptibility to respiratory infections (111, 112). Acute cold exposures have an immunostimulating effect that may be related to circulating norepinephrine levels (113).

7.6 Carcinogenesis

Cold stress has not been linked to carcinogenicity except in the case of testicular cancer. The normal extra-abdominal position of the testes makes it difficult for the body to maintain appropriate

temperatures within the scrotal sac during environmental temperature fluctuations without the benefit of protective clothing. Such testicular temperature variations have been associated with a reduction in spermatogenesis, sperm count and motility, and an increase in abnormal sperm morphology (114, 115). Several retrospective epidemiological studies have suggested an association between high and low environmental temperatures and an increase in testicular neoplasms (116, 117). However, there is an absence of data linking actual testicular tissue temperature to these adverse outcomes, and the association between environmental cold stress and testicular cancer remains statistical in nature.

7.7 General Health Complaints

Intermittent exposure to moderate cold stresses (e.g.,–5 to 15°C) in the work environment has been associated with a number of general health complaints and the exacerbation of existing conditions that may be influenced by cold exposures. Work in refrigerated food processing facilities, for example, has been associated with general discomfort, respiratory problems, rheumatic complaints, and back and joint pain (118, 119). Rapid-onset Raynaud's syndrome or cold-induced white finger has been linked to the repetitive vasoconstriction response to cold exposure, and is exacerbated in the presence of hand vibration or high grip forces (86, 118). In a number of situations involving moderate cold exposures, there is a high prevalence of nonspecific symptoms or health complaints and reports of general thermal discomfort that are not correlated reliably with specific environmental conditions (e.g., air temperature, air movement, surface temperatures). Although these effects have not been established unequivocally, they occur with such regularity to suggest a possible risk to health or worker performance.

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8 Combined Effects with Other Physical Stresses

Prolonged cold exposure has been associated with higher prevalence rates of several musculoskeletal disorders, in particular vibration-induced white fingers and nonspecific cumulative trauma disorders often evident in refrigerated meat and poultry processing facilities. Vibration-induced white finger, or secondary Raynaud's phenomenon, also is common in forestry occupations in cold climates and appears to be associated with not only vibration but also grip forces exerted on the vibrating implement (120). It is thought that the repeated vasoconstriction in the extremities associated with cold exposures exacerbates the development of vibration-induced white finger, an acknowledged occupational disease of multifactorial origin.

The prevalence of noise-induced hearing loss appears to increase when accompanied by cold exposure, and the time-to-onset of the disease may be more rapid (118, 120).

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9 Control of Cold Stress

In evaluating whether exposure to cold stress in a particular situation is detrimental and should be discontinued, one must focus on the particular end point of concern. Most current regulations or standards have been established to influence survival (e.g., hypothermia) or to prevent the development of adverse physiological effects (e.g., frostbite, chilblain). Conversely, certain guidelines or standardized industry practices have been developed to maintain or enhance performance of manual tasks or to maintain or improve subjective comfort levels. This distinction between discomfort versus frank physiological damage must be kept in mind when comparing

particular industrial standards or regulations—if the end points of concern are not comparable, then any comparison of permissible exposures to cold stress will be inappropriate. One must also keep in mind whether particular indices of cold exposures are normal physiological responses to the stress. For example, it is normal for the body's core temperature to fluctuate within certain temperature ranges as the body accommodates to the heat lost to the surrounding environment. There are minimal physiological impacts so long as that thermoregulatory capacity is not exceeded. However, if an exposure standard is based on the assumption of maintaining thermoneutrality in a given exposure situation (i.e., no net reduction in body temperature), then one is ignoring the capacity of the body to accommodate to that cold stress. At some point, perceived comfort and work performance may be impacted, but without the individual experiencing adverse health impacts.

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10 Exposure Standards

Regulations or standards defining acceptable cold-stress situations rely on one or a combination of approaches to control cold stress. Those traditional approaches include behavior (e.g., modifying work rates, adjusting clothing ensembles), use of insulating clothing to reduce heat loss, limiting the time of exposure to the cold environment, and by providing localized or general heating within the area. A summary of the prevalent national or international exposure guidelines are provided below.

10.1 ACGIH Threshold Limit Value

The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) (121) for cold stress is a series of exposure limits intended to (*1*) prevent body core temperature from falling below 36°C (i.e., hypothermia) and (*2*) protect against cold injuries to the extremities. Whole body and extremity cooling is based on the wind chill index (WCI), a derivation of the concept of the wind chill (6), and is intended to protect exposed skin from freezing by limiting exposure times. A modification of that index (not included in the TLV), the "apparent temperature" (122), incorporates additional meteorological parameters beyond temperature and wind speed that influence heat loss to the environment (e.g., relative humidity, solar radiation). The TLV also addresses conductive heat loss through cold objects. The TLV focuses on prevention of hypothermia and freezing cold injuries, but does not address directly nonfreezing cold injuries or chronic impacts of cold stress.

10.2 ISO TR 11079

The International Standards Organization (ISO) Technical Report 11079 utilizes the IREQ index (i.e., "insulation required") to maintain body heat balance based on clothing, metabolic heat load, and environmental conditions (111). Under the prescribed conditions, if the IREQ cannot be met to maintain "comfort" (i.e., thermoneutral) or "just acceptable" (i.e., minimal), then maximum exposure times to the cold stress can be established to maintain thermoneutrality. The IREQ provides a useful approach to whole body cooling in indoor and outdoor environments, but does not address extremity cooling to any significant degree. A family of related ISO standards define how metabolic heat production, ergonomics, and physiological strain are quantified (124–127).

10.3 British Standard 7915

The British Standards Institute (BSI) has developed guidance for managing cold stress and discomfort in indoor work environments (air temperature <12°C) (128). Assessment methods include the wind chill index, the IREQ index, and other models for predicting heat loss to the environment and the perception of thermal stress.

10.4 DIN 33 403-5

The German Standards Institute (also known as DIN) utilize the IREQ index to develop a standard for indoor work environments (from –50°C to 15°C, in five ranges). Based on these environmental parameters, insulating clothing requirements are defined, along with ergonomic recommendations for reducing cold strain.

Existing standards or guidelines tend to focus on acute, whole-body exposures and do not emphasize contact with cold surfaces, chronic effects of cold exposure (e.g., endocrine system disruptions), or concomitant exposures with other stressors. In addition, there are few physiological indices of impending damage that are defined well enough to benefit from routine physiological monitoring of the individual, as is done in heat stress environments. Given the individual variability in response to cold stress, such monitoring would be effective in minimizing the prevalence of cold stress in the occupational environment.

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Heat Stress
Thomas Adams, Ph.D.

1 Introduction
This chapter's goal is to provide useful, interesting, and up-to-date information about the way people respond to acute and chronic heat stress. It also presents some groundwork about biological control systems, how heat is produced and stored in the body, and how it is exchanged with the environment. This background is necessary to understand the many complex and interactive phenomena associated with heat stress and with the challenges of heat strain.
1.1 Heat is a Unique Stressor
It is important to recognize the uniqueness of heat as a form of energy to understand issues of heat stress and strain and to see its special role in human welfare. No other potentially endangering energy, for example, is produced by the body itself, none other is so essential for life, and none other is the thermodynamic destiny in entropy for all other forms of energy.

No form of energy other than heat so directly affects life processes. Humans normally function in only a narrow range of deep body temperature (1, 2). Not more than a degree Fahrenheit, or so, deviation in brain temperature, sometimes not even that much, shows its effects in altered perceptions and behavior. We tread a narrow thermodynamic path from infancy to interment; hypothermia and cold injury are on one side, and heat strain and hyperthermia are on the other. Many personal and environmental circumstances unrelentingly persist in trying to unbalance us thermally. The path has about the same width for humans as for most other mammals. We all seek about the same degree of stability between about the same thermal limits. Body temperature for most mammals is about 99 ± 2.5°F (37 ± 1.5°C), even though it changes temporarily for an individual by as much as 5°F (2.8°C) because of loads from exercise and thermal exposure.

It is not always easy to spot the sources of heat danger or to gauge their effects. Heat-induced disabilities come from net heat gain from the environment and also from that produced by metabolic activity, which alone can be crippling and lethal. Danger levels for most energy and molecular environmental stressors are predictable for everyone, but they are not for heat. It is not hard, for example, to define a “threshold limit value” and safe exposure levels for gamma and ultraviolet radiations, sound intensity, and exposures to concentrations of specific chemicals. A toxic level for one person is just about as endangering as it is for someone else. It is quite different for heat.

The effects of heat stress must be seen in a different way. One level of environmental heat exposure and rate of heat production from work or exercise may be comfortably, safely and easily tolerated by one person, yet be uncomfortable, disabling, and potentially lethal for another, even though they work side by side at comparable tasks. Solving the complex problems of human thermal safety requires more than just measuring the intensity of contributing environmental factors. It requires additional analyses of a person's internal and external thermal environments and body heat distribution and also of many unique personal characteristics (3, 4).
1.2 Evaluating Heat Stress and Strain
Situations that challenge human thermoregulation must be surveyed at two levels. One is a need to look at the conditions of heat stress, the other must evaluate the level of heat strain. Heat stress and strain are functionally related, of course, but one does not predict the other.

Heat stress is quantified by measurements of a person's internal and external thermal environments. For example, measurements of air temperature, ambient relative humidity, air velocity, infrared radiant heat sources and sinks, emissivities and temperatures of clothing and nearby objects, heat production from work or exercise, conductive and convective thermal energy transfer coefficients of skin and clothing surfaces, thermal insulation of clothing and tissue, water vapor permeability of clothing, and related factors provide important, defining characteristics of heat stress. They do not, however, give any information about a person's competency for remaining thermally stable and safe under these conditions. Measures of heat stress provide no information about someone's level of heat strain. Personal danger comes directly from the level of heat strain and only secondarily from the intensity of heat stress.

Each person's level of heat strain is unique, and it also changes from moment to moment, even for the same, unchanging level of heat stress. Heat strain is defined by a person's total body heat content, deep body temperature, cardiovascular and peripheral vascular competencies and reserves, systemic arterial blood pressure, brain blood flow, ability to sweat, lean body mass, whole body hydration, circulating blood volume, hematocrit, blood viscosity, body fluid distribution and storage, whole body osmolarity, medication status and history, physical fitness, and other related personal factors. Because these are as precisely defined for each of us as are our fingerprints, no two people bear the same burden of heat strain, even when similarly exposed to the same level of heat stress (5–9).

Distinguishing between factors of heat stress and human heat strain is essential. It is naive, dangerous, and potentially lethal to consider that measuring only factors of heat stress, no matter how completely and precisely, or using one's own thermal comfort is any reliable gauge for another person's level of heat strain (10–12). Evaluating human heat strain is a complex but interesting detective story. Lessons learned are applicable to issues of the workplace, and they are also pertinent to each of us personally, to our family members, and to all life forms on the planet.

1.3 The Role of Heat in Life Processes

Heat is essential for life. It is a prime catalyst for biochemical reactions that support it. Each life form survives on its own, sometimes narrowly defined, thermal environmental niche. The range of thermal adaptation for all forms of life, however, is large (2a, 13). Some organisms survive in nearly freezing ocean water; others tolerate extreme temperatures near hot vents in the ocean floor. Some live only in polar regions; others inhabit exclusively equatorial zones. None other than humans, though, has extended its range of tolerable thermal environments so broadly. Though we are bare-skinned, comparatively puny, and generally vulnerable primates, we have, nonetheless, drawn from psychosocial and intellectual reserves to survive everywhere on the planet and extraterrestrially, as well. Stripped of these adaptive strategies, though, our species would not survive for long outside a narrow, paraequatorial zone. Most of us would not even make it there. It is astonishing that our ancestors prospered.

Humans share with other mammals and with birds, too, the ability to regulate physiological responses through complex, precise, and rapidly responding neurophysiological reflexes to support a nearly constant internal body temperature (14). We are the so-called “warm-blooded” animals (homeotherms). Other species do not do this. They are the so-called “cold-blooded” animals (poikilotherms). Yet, they depend on a narrow range of body temperature, too, but achieve it in a different way. Mammals and birds regulate physiological responses to achieve thermal stability, but other animals depend on adjusting physical activity and selecting appropriate habitats. Neither group uses exclusive strategies. Both share many adaptive and response techniques.

It does not take much close inspection before the distinctions between “cold-blooded” and “warm-blooded” animals blur. Under some conditions, as in states of torpor and hibernation, “warm-blooded” animals abandon tight thermoregulation and become thermally labile. Some “cold-blooded” animals, like species of deep-sea fishes, also use metabolic and cardiovascular strategies to regulate body temperature above that of their environment. Although they are in general use, the designations of homeothermy and poikilothermy are crude at best.

There is another nomenclature that discriminates better. “Endotherms” are those animals that regulate body temperature at a nearly constant level. Mammals and birds are in this category. Other animals, so-called “heterotherms,” keep a nearly stable body temperature when they are active. Many flying insects are in this group. So-called “ectotherms” depend more on environmental sources of heat to keep body temperature elevated, as do many reptiles and lizards (13a).

Not surprisingly, heat stress has challenged our species ever since we appeared. It has been documented before the Christian Era, has biblical references, and has determined the fates of armies and civilizations throughout history (15). It is alleged to have killed as many as 11,000 people in a heat wave in China in the eighteenth century and more recently contributed to the disability and deaths of more than a thousand people in the southwestern United States in 1980 (16). Hardly a year goes by that new records are not set for heat's dangers.

Although elderly and socially isolated people who have preexisting medical disorders are most vulnerable to heat strain (17), no one escapes the pressures of heat stress. It challenges physical abilities and also performance quality as well (18–21). It influences many daily activities, including such subtle skills and judgments as those involved in vigilance when operating a motor vehicle (22).

The name of the survival game for humans is to keep total body heat content and deep body temperature between narrow limits while facing a wide range of environmental thermal loads and deficits and producing considerable heat by physical activity (23–26). Seeing how we do this requires knowing some basics of physiological regulation and biological control systems. The next section introduces them.

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2 Physiological Regulation and Control—The Basics
More than a century ago, biologists and physicians began to describe physiological processes in terms of controlled, dependent variables (27). A couple of centuries before that, however, the mechanics of self-limiting societal events were known and discussed. The word, “control,” in fact, came into English about this time to imply that one thing working against another establishes stability in their relationship (“control” = “contra”, indicating “against”, and “role” implying function).

The idea that dynamic interplay between or among opposing forces provides stability was recognized in human affairs long before this important principle was ever applied to life processes. When it was, though, it brought an important new way of conceptualizing, investigating, and describing them. In the middle of the nineteenth century, biologists who considered life events in terms of established equilibria and controlled functions introduced the concept of “homeostasis.” Homeostasis (“homeo”—same; “stasis”—state) implies a static balance of fixed forces or events (Fig. 98.1A). They almost got it right. Biological process are established by control systems, but they are not homeostatic.

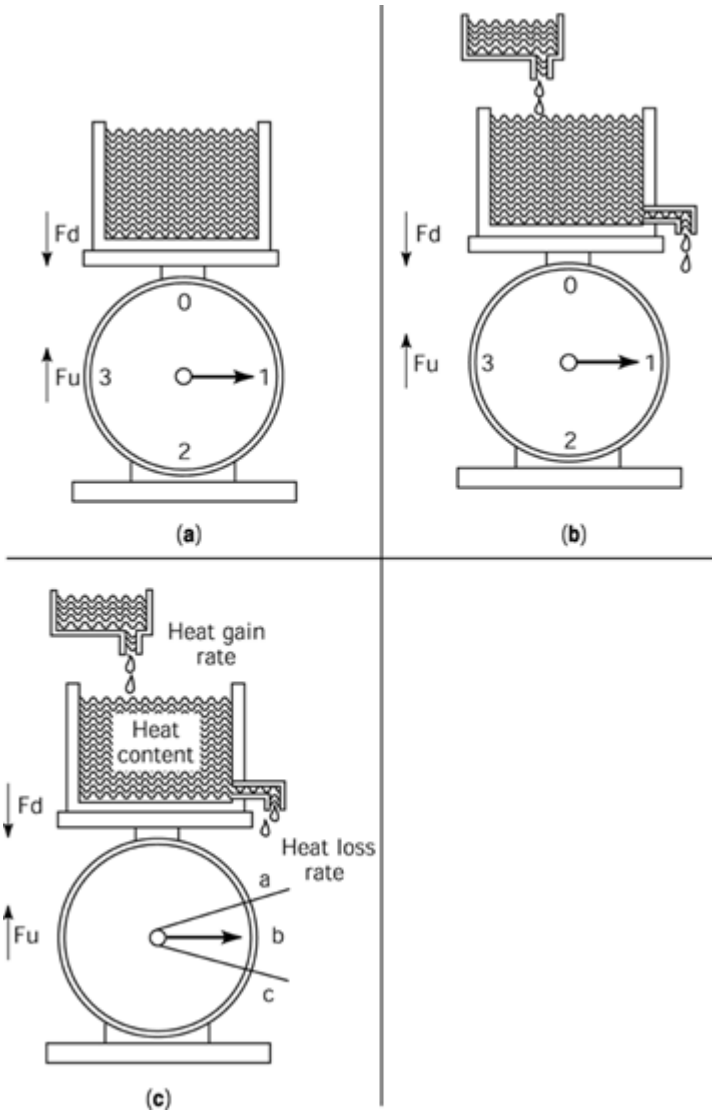

Figure 98.1. A. When a container of water holds a constant mass, its downward gravitational force (Fd) is matched by an upward force (Fu) from a spring in the scale. This system remains in homeostatic equilibrium because two, opposing, equal, and unchanging forces are in balance. B. Adding water at the same rate it leaks from a container establishes a balance between two dynamic phenomena, and the system remains in a steady state. C. A thermal steady state is established when heat is gained at the same rate that it is lost. Transient inequities are tolerated as long as body heat content remains in a normothermic range (b). Hyperthermia (c) develops when heat gain exceeds heat loss. Hypothermia (a) results from the opposite circumstance.

Although the idea of homeostasis was important in directing biologists' thoughts at the time, it is inappropriate for describing life processes. None is homeostatic in the sense that an equilibrium is ever achieved for it. All life processes are steady states. A steady state is a dynamic balance of rate processes (Fig. 98.1B). Stability of blood pressure, acid–base status, body weight, posture, body temperature (Fig. 98.1C), and all other physiological phenomena are steady states (28–30). There are differences in input and output rates among physiologically controlled processes, but all are balanced, dynamic events (30), as are those in psychological processes, too (31–33).

The gain and loss rates for body functions are ever changing, but in normal, good health they are juggled to yield a steady state. Bone mass, for example, changes more slowly than the partial pressure of oxygen in blood, but each is a controlled steady state—one changes over months and years; the other changes breath to breath. It is common for us to seek medical help when one or more of our controlled biological steady states go awry. We expect physicians, in a sense, to serve as

biological control system engineers to diagnose malfunctions in our physiological control systems and to set them right therapeutically (34–36).

2.1 General Control System Principles

Even a first-order understanding of how control systems function is important for interpreting the phenomenon of body temperature regulation and seeing how it responds under heat stress. There is a simple way to envision the basic relationships among elements in a controlled system. The familiar process for keeping room temperature in an acceptable range is an easy to understand example (Fig. 98.2).

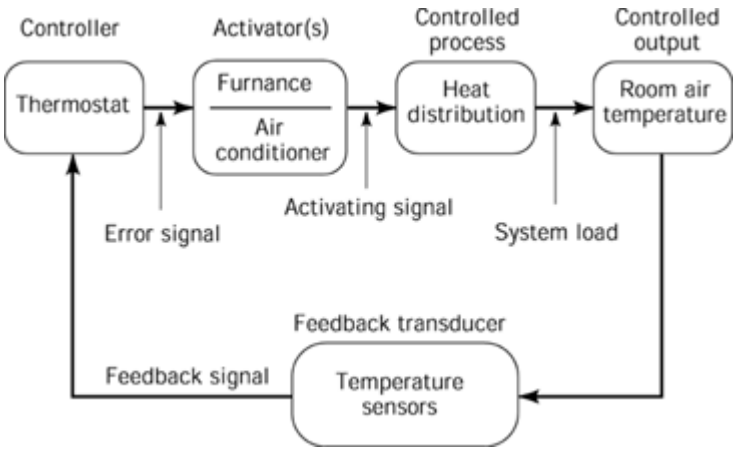

Figure 98.2. A model depicting interactions among control system elements for regulating room temperature. All components share information sequentially, so the control loop is "closed." Were any one disconnected, the control loop would be "open," and the system would not regulate.

A change in outside air temperature presents a "system load" (Fig. 98.2) to the stability of room temperature and causes it to rise or fall. Temperature sensors (usually in a wall-mounted unit) provide electrically encoded information ("feedback signal") about room temperature to a thermostat ("controller"). If room air temperature is outside a control zone limit, an "error signal" triggers either a furnace or an air conditioner ("activators") to bring heat into, or remove it, from the room. These controlled actions affect room temperature in the direction opposite to the feedback signal that triggered the response. The controlled process described in Figure 98.2, for example, would cause room temperature to go up, if the system load caused it to fall initially, and vice versa. This feature of the control system shows that it has "negative feedback." Negative feedback is an essential characteristic for any control system that regulates a dependent variable within a control zone limit.

There is a difference between the concepts of "control" and "regulation" in the context of interactive systems. A "control system" is one that has the basic five elements that sequentially share information (Fig. 98.2). If the control system operates with negative feedback, it achieves regulation. Some control systems, however, operate with "positive feedback." They do not regulate. Instead, they force the "controlled output" function to a limit, but they are still control systems. Coughing, sneezing, vomiting, ejaculation, parturition, urination, and defecation are examples. A diagram, like the one in Figure 98.2, would describe how these neurophysiologically controlled processes operate, but its analysis would reveal that the control system operates with positive feedback to empty a body cavity, not to regulate by its contents at some level negative feedback. The tickle at the back of the throat, for example, leads to contractions of nearby muscles and reflex salivation. These responses enhance the irritation and make the throat tighten all the more. The initial stimulus produces a response that increases the stimulus strength that, in turn, elevates the response. The end result is a cough to dislodge the irritant. Then, the control system remains silent.

2.2 The Control System for Body Temperature

How body temperature is regulated (Fig. 98.3) is less familiar than the process for stabilizing room temperature (Fig. 98.2), yet each system shares the same basic control system elements and each

functions similarly as do all other regulating control systems (30).

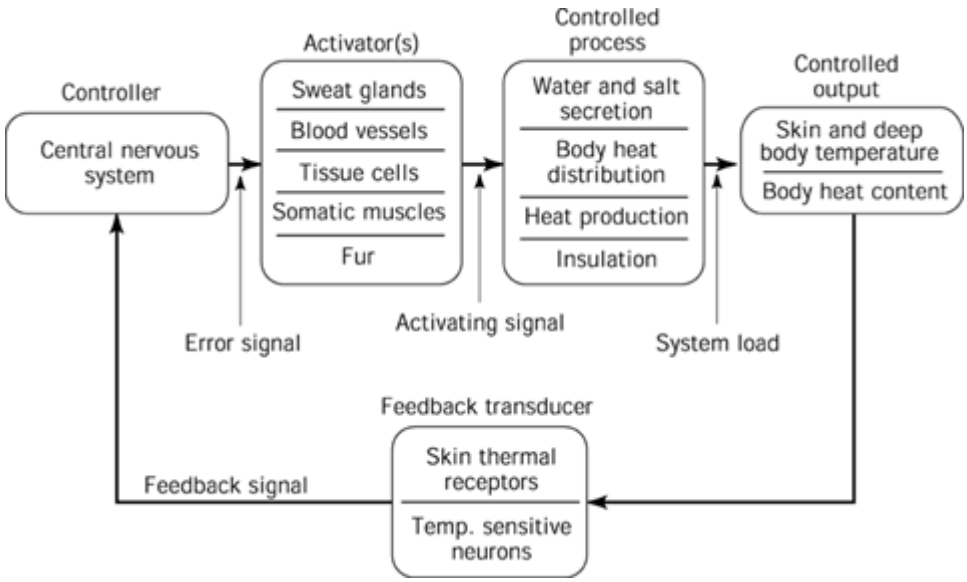

Figure 98.3. Deep body temperature and total body heat content are regulated within controlled limits through a closed-loop, negative-feedback control system that recruits many organ systems and physiological functions. This diagram shows only basic relationships and greatly oversimplifies the many complex ones required for thermoregulation.

Whole body exposures to thermally stressing environments and exercise impose system loads (Fig. 98.3) that affect the body's heat content and temperature. The body's thermal status is monitored and transduced by millions of thermal receptors that are widely distributed throughout the skin. The skin, the body's largest organ, covers about twenty square feet (1.86 m^2). The neurophysiological feedback transduction process encodes absolute levels of skin temperature, but more exquisitely, their rate of change, into frequency-modulated action potentials. Each action potential lasts only a few milliseconds, but there is a constant stream of them conducted afferently on sensory nerves. Thermal sensory receptors respond to little more than a rate of change in skin temperature of only about a few thousandths of a degree Fahrenheit (or Celsius) per second. The action potentials themselves are conducted at rates as fast as hundreds of miles per hour from the thermally stimulated skin site into the central nervous system.

Body temperature is protected by the responses of many thermal receptors in a large area of skin, and the control system (Fig. 98.3) is updated almost on a millisecond interval. Normally, this marvelous process continues uninterruptedly without conscious control and without error for a lifetime, even in the face of continuously changing, sometimes life-challenging thermal loads (36).

Skin thermal receptors provide feedback signals (Fig. 98.3) through synaptic connections with other nerve cells at millions of sites in the spinal cord, midbrain, cerebral cortex, and elsewhere, but most influentially in a small section of the hypothalamus, especially its anterior portion. The anterior hypothalamus is an unpaired structure that in humans lies just behind and at the level of the eyes and midway between the ears. It is no larger than about the size of a pea in an adult. This small mass of brain tissue plays a most important role for all homeotherms in controlling body temperature. It serves a highly complex controller function (Fig. 98.3), but it is also sensitive itself to temperature, although it has no thermal receptors, nor does any other part of the central nervous system.

Temperature affects nerve cells in the central nervous system by altering their transfer functions for processing action potentials. It changes the ratio between the rate at which they receive input information and the rate at which they send it to other nerve cells, tissues, and organs. Responses to

thermal stimuli at the skin, along with the temperature level of the brain itself, determine together how thermoregulation is achieved.

If body thermal stability is challenged by a cold environment, for example, frequency-modulated action potentials are generated as “error signals” (Fig. 98.3) by cells in the central nervous system to reduce convective heat transfer inside the body. This is done by reducing blood flow to the skin and to other peripheral tissues by vasoconstricting their arteriolar blood supplies. Appropriate “activating signals” (Fig. 98.3) also trigger reflex contractions in somatic muscle to produce heat by shivering and reorient fur and feather shafts so that they trap more air, thereby increasing thermal insulation. The net protective effect is to increase metabolic heat production and reduce body heat loss. In most cases, this preserves body heat content.

If a person's thermal stability is challenged by a warm environment or exercise, “error signals” (Fig. 98.3) cause peripheral blood vessels to dilate which increases convective heat transfer to the skin and heat loss from it. Sweat glands are also activated to bring water to the skin surface where heat is lost when it evaporates. Heat defenses in other homeotherms involve salivation and respiratory reflexes that increase airflow over wetted nasal, pharyngeal, and buccal surfaces. The net protective effects of reflex responses to heat stress are to deliver heat at a faster rate to the skin and increase its rate of dissipation. In most circumstances, this reduces body heat content.

For responses to either heat or cold stress, body temperature regulation is protected through a complex, nonlinear, closed-loop control system that has negative feedback (Fig. 98.3). Although there are differences among species in the physiological tools that they use for thermal stability, they all use about the same basic control system.

2.3 Characteristics of Controlled Processes

2.3.1 Time Functions Whether it is the stabilization of room temperature (Fig. 98.2) by a simple control system or body temperature by a highly complex and sophisticated one (Fig. 98.3), both are steady states (Fig. 98.1) earned through the controlled interaction of dynamic processes. Understanding their time-varying qualities gives important additional insight into their functions (Fig. 98.4).

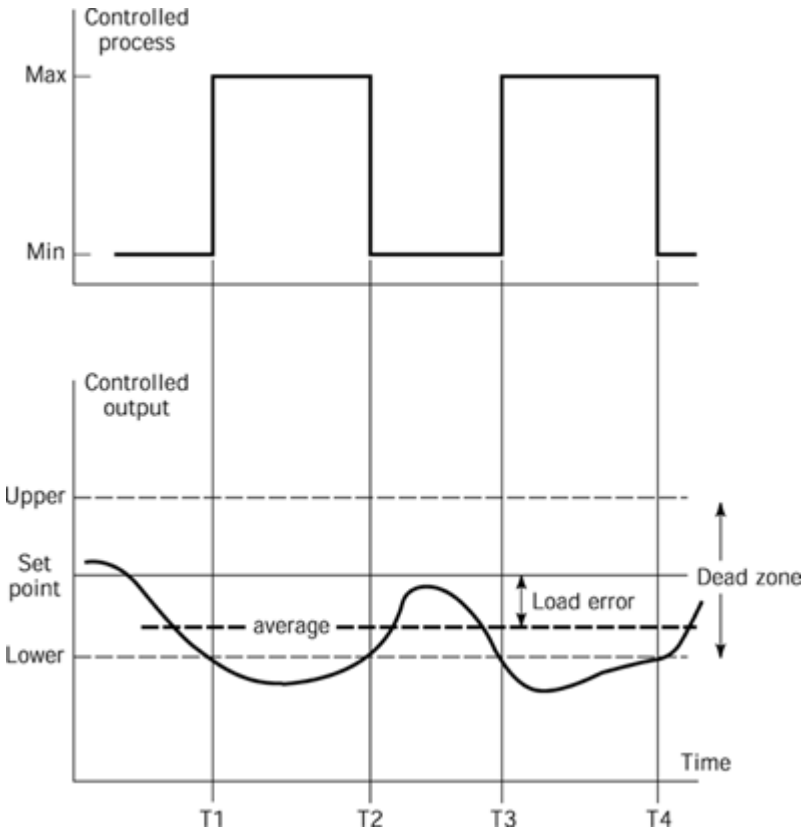

Figure 98.4. The controlled process for an “on-off” control system remains at a low level, as long as the controlled output remains in a “normal” range (the “dead zone”), whose center is its optimum value (the “set point”). When the controlled output drifts outside the dead zone (T1 and T3), the controlled process turns on. Once the controlled variable is again in a “normal” range, the controlled process turns off (T2 and T4). For a closed-loop control system with negative feedback, these interactions lead to regulation of the controlled output.

Air temperature in most homes is controlled by a relatively simple, closed-loop, negative-feedback control system (Fig. 98.2) that turns a furnace or an air conditioner on and off (“Controlled Process;” Fig. 98.4) to keep room temperature in an acceptable range near the optimum temperature set by the owner. The preferred temperature is shown typically by the manually adjusted red arrow on the thermostat. No control system, though, operates with infinite precision. Some variation in whatever is being regulated is to be expected. Were the thermostat set at 75°F (“set point”), for example, few people would complain if the furnace did not turn on until room temperature fell to 73°F. Similarly, room temperature might rise to 78°F before the air conditioner turned on. Typical of all control systems, there is a “dead zone” around an optimum setting (the “set point”) in which the controlled process is silent (Fig. 98.4). Only when the controlled variable drifts outside the dead zone are appropriate controlled processes started.

2.3.2 Load Error There is another expectation for the normal operation of a control system, whether it is one that controls room temperature, body temperature, or some other physical or physiological variable. When a control system operates under a load (“system load”; Fig. 98.2), the controlled variable does not vary around the system's set point (Fig. 98.4), but typically cycles to one side of it in the direction of the load. The system shows a “load error.” The average room temperature for a home on a cold day in the winter, for example, might be 74°F, even though the thermostat is set at 75°F. On a hot day in the summer, the average room temperature might be 76°F with no change in thermostatic setting. The larger the “system load” (Fig. 98.2), the larger the “load error” (Fig. 98.4), and vice versa.

Physiologically regulated processes also show load errors. Total body heat content, for example, will be lower for people who successfully respond to a cold stress, than it will be when they respond to a heat stress. Psychological processes show similar characteristics. Who has not felt a “little out of sorts” and “not feel like themselves” when under emotional stress? The imposition of challenging personal circumstances and events takes them a little further away from the “normal” personality “set point” that they usually try to maintain. Similarly, when things are going especially well, it is not unusual to feel a little better than we do on most other days.

2.3.3 Gain “Gain” defines how a change in the output of a control system varies in relationship to a change in its input. This is commonly seen as the ratio between a change in the system's “controlled output” (Fig. 98.3) and a change in its “feedback signal.” Gain adjustments are usually made at the level of the system's controller. There is high gain in the control system when there is a larger output than usual for the same level of input. There is low gain when there is a smaller output than usual for the same input.

Even in general physical examinations, physicians typically assess patients' gain for many of their physiological control systems. Seeing the change and rate of change of the eye's pupil in response to a bright light (input), for example, is one way to determine how the central nervous system (controller) is processing action potentials to control the iridial muscle (output). Sluggish or incomplete responses indicate low gain. A quickly developing pinpoint pupil shows high gain, compared to a normal rate and amount of pupillary constriction. Police make similar tests of reflex gain, sometimes even at the roadside, to evaluate suspected drug and alcohol effects on postural, pupillary, speech and other physiologically controlled processes.

Tapping a tendon or a muscle with a reflex hammer (input) to elicit a “tendon (or knee) jerk

reflex" (output) also reveals important information about central and peripheral nervous system control functions. A weak, slow, or incomplete movement of the leg suggests slowed, low gain reflex muscle control. A greater than expected, exaggerated kick of the leg shows high gain for the associated control system on that day, assuming that the stimulus was the same for each test.

Drugs like barbiturates and alcohol, that depress central nervous system action, reduce reflex gain. Lethal overdoses reduce it so far that respiratory, neurophysiological, and cardiovascular control system functions cease. Drugs, like caffeine, cocaine, and nicotine, that enhance central neural functions increase reflex gain. Central nervous system gain changes are also due to tumors, diseases like multiple sclerosis, infections of the brain or spinal cord, injuries, and any number of other events. They all show reflex gain changes in clinical tests that are easy and routine procedures, yet which reveal valuable information.

2.3.4 What is a "Normal" Value for a Regulated Variable? Understanding features of the "dead zone" is important in evaluating a control system's operation. There is no other rational way to distinguish between normalcy and pathology in the way it works. In the same way that it is impractical to define a "normal" room temperature, it is impossible to define a "normal" systemic arterial blood pressure, body weight, height, body temperature, behavior, personality, or other dependent variable. It is possible, however, to delimit an acceptable range of values for a controlled process in terms of its dead zone. A working definition for "normal" then depends on maintaining the control system's output in a dead zone (Fig. 98.4), but not necessarily at a specific set point. For this reason, laboratory analyses of body fluids, like blood and urine, show ranges of "normal" values for concentrations of sodium, potassium, chloride, and other ions, as well as for cholesterol, glucose, albumin, creatinine, and other molecules.

Police analyze dead zones more than set points when they evaluate driving behavior. Imagine, for example, the view from a hovering helicopter monitoring a car's position as it moves down the road. Not only will the vehicle's speed be noted, but so will its position on the highway. Little attention will be given to whether the car follows precise set points (optimum speed and movement down the exact middle of the traffic lane), but deviations from dead zones (going too slow or too fast or deviating from the left and right limits of the traffic lane) certainly will attract attention. Experienced officers take into account the effects of load error on speed and road position as the car goes around curves and up and down hills. Citations will document deviations of a driver's controlled behavior from acceptable dead zones of vehicle speed and position, but not from their set points. The narrower these dead zones, of course, the tighter the traffic regulation required in that community.

2.3.5 Thermoregulatory Control The many simultaneously operating biological control systems that regulate body temperature are much more complicated, of course, than the simple "on-off" one that stabilizes room temperature (Figs. 98.2 and 98.4). They incorporate features of proportional control, in which appropriate physiological responses (Fig. 98.3) respond to deviation of body heat content and deep body temperature from a control system's lower or upper dead-zone limits (Fig. 98.4). They also show features of differential control, in which body responses are proportional to the rate of change of skin and deep body temperatures, as well as those of integrational control, which provides summing operations. Most other controlled physiological, biochemical, and biological processes have these features, too.

Understanding how deep body temperature remains stable in a regulated thermal dead zone, while total body heat content may vary widely, requires insight into the body's thermal capacitance. This information is presented in the next section.

Heat Stress
Thomas Adams, Ph.D.

3 The Importance of Thermal Capacitance

Were there a change in the liquid volume of a rigid-walled container (Fig. 98.5A), its level would also change in direct proportion. If the container had flexible sides, though, like those of a rubber bag, its liquid level would no longer accurately reflect the liquid volume (Fig. 98.5B). Only when the container reached its upper limit of compliance, would its change in volume be reflected in a corresponding change in liquid level. Body heat content and temperature also change independently because there is a sizeable mass of body tissue that transiently stores, then releases heat, but does not change deep body temperature. The measurement of deep body temperature does not indicate how much heat is stored in the body until it has reached an upper limit of its thermal compliance.

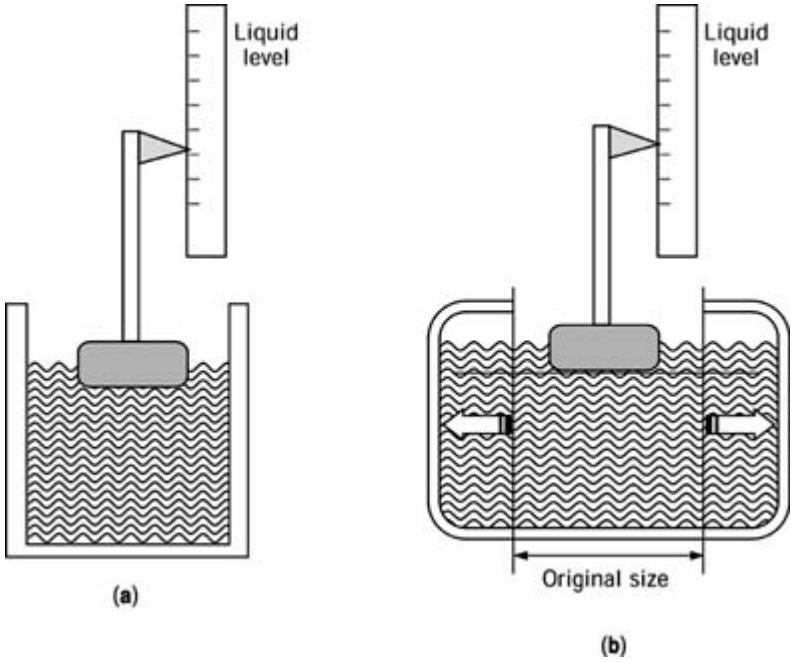

Figure 98.5. Liquid level and volume are directly related one-to-one for a rigid-walled container (A). Liquid level does not vary as a function of volume for a container that has flexible sides (B), at least within the limit of its compliance.

Humans and other animals take great advantage of the body's thermal capacitance to offset and delay the impacts of heat and cold stresses. It is necessary to keep the liver, gastrointestinal tract, heart and lungs, brain, and other internal organs at a nearly constant temperature, but skin, muscles, body fat, tendons, and other peripheral tissues can change their heat content and temperature without serious effect. The central nervous system, especially the brain, however, is particularly vulnerable to the effects of hypothermia and hyperthermia. Variations of not more than a degree Fahrenheit often produce altered reflex expression and changes in levels of consciousness. Some are reliable early warning indicators of impending heat strain. The hallucinations and convulsions that sometimes accompany a fever and the lethargy common to hypothermia testify to the need for keeping brain temperature in a range of about 96 to 101°F (35.5 to 38.3°C). The body depends, however, on allowing about 50% of its total mass to change temperature with little change in deep body temperature and no untoward effects during heat and cold stresses.

The body mass whose temperature must be kept stable is called the “thermal core.” The mass allowed to change its heat content is called the “thermal shell.” This metaphor is appropriate because the body mass of the thermal shell includes the peripheral tissues of the arms and legs. During a successful response to cold stress, a person's deep body temperature remains controlled in a thermal dead zone (Fig. 98.4), but total body heat content is low because the thermal shell is expanded. Because of a load error, however, even core temperature is predictably close to the lower limit of the thermal dead zone. During a successful response to heat stress, deep body temperature also remains

well enough regulated, although it will show a load error that holds it close to the upper limit of the thermal dead zone. The thermal shell in a heat stress, however, will no longer exist, because of heat stored in peripheral tissues. Its temperature is now close to, or even above, the level of deep body temperature.

The observant traveler recognizes well how people in different climates and at different times of year take good advantage of the buffering capacities of the body's thermal compliance. It is an informal, but common, observation that people in the summer use air conditioning to keep room temperature lower than they would when the weather turns cold. Similarly, a warmer room temperature is preferred for many homes in the winter than that adjusted in the summer. Experience has shown that heat strain is delayed if heat stress is faced with a heat depleted and expanded thermal shell. Sweating, peripheral vasodilation, and the discomfort of being hot are postponed until the thermal shell becomes heat-saturated as body heat content increases. Similarly, shivering, peripheral vasoconstriction, and the discomfort of being cold are held at bay until the heat stored in tissues of the body's thermal shell is depleted. Loading it with heat before a cold exposure has a real advantage. Entering a cold stress with a full store of body heat and beginning a heat stress with body heat stores depleted are both good strategies.

A careful analysis of heat stress and strain requires distinguishing between those exposures and exercise phenomena that affect the heat content of the thermal shell and those that threaten the stability of the thermal core. Not all heat-induced disability involves hyperthermia, an increase in deep body temperature. The majority of thermal discomfort and disabilities produced by human heat stress result from first- and second-order physiological phenomena related to body heat storage and expansion of the thermal shell. Stages of hyperthermia that lead to heatstroke, however, are exclusively related to temperature elevations of the thermal core. They occur almost without exception only when the thermal shell has become heat-saturated. Even an elementary understanding of the complexities of human thermoregulation requires knowledge of biophysical heat transfer principles. It is important, too, to see how they are linked to anatomy and physiological phenomena. The next section is a primer for this information.

Heat Stress
Thomas Adams, Ph.D.

4 How Heat is Exchanged
For good or for bad, most people know the dynamics of their savings accounts (Fig. 98.6A). Wealth, indicated by its amount of stored money, is not constant, but varies from transaction to transaction as a function of the rate at which money is deposited and earned from interest and the rate at which it is depleted by withdrawals and service charges. Wealth at any moment is their net effect. There is financial stability only when these processes are in a steady state. Mechanisms for establishing body heat content (Fig. 98.6B), as indicated by body temperature, have similar dynamics. At any moment, the system depends on the net effects at which heat is constantly gained and constantly lost. When these fluxes are balanced, the body is in a thermal steady state, as described by

$$\Delta H = q_{m} \pm q_{cd} \pm q_{cv} \pm q_{rd} \pm q_{cnd} - q_{ev} \qquad (1)$$

where

DH = change in total body heat content (kcal; kJ)
q_{m} = heat gain by metabolism (Btu/h; watts)
q_{cd} = heat exchange by thermal conduction (Btu/h; watts)

q_{cv} = heat exchange by thermal convection (Btu/h; watts)

q_{rd} = heat exchange by infrared thermal radiation (Btu/h; watts)

q_{ev} = heat loss by evaporation (Btu/h; watts)

q_{cnd} = heat gain by condensation (Btu/h; watts)

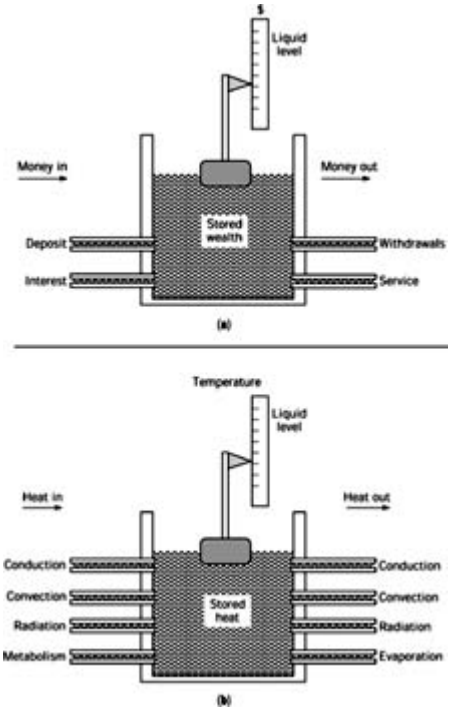

Figure 98.6. A. Savings accounts are financial steady states whose balances at any moment are a function of the dynamics of money deposited and earned as interest against that withdrawn and spent in service charges. B. Body temperature at any moment reflects the net balance of rates of heat gains and losses and the amount of stored heat. Whether heat is gained or lost by either thermal conduction, convection, or radiation depends on the direction of the associated gradients. Heat is always gained by metabolism and always lost by evaporation.

Heat Stress
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5 Evaluating Heat Stress

It is a complicated task to keep deep body temperature in a thermoregulatory dead zone (Fig. 98.4) during thermal stress, even with the buffering effects of the body's thermal shell. There are many factors and effects (Eq. (1)) that have to be balanced. Because the stressors wear many different faces, it is unreasonable to expect that any single environmental measure will adequately represent their net effect. The single measure of air temperature, for example, is woefully inadequate as an indicator of thermal stress, whether it is of cold or of heat. Generally, the more factors that are accurately measured in the environment and in metabolic heat production, the greater the precision in defining thermal stress. No matter how expansive and inclusive the strategies for quantifying thermal stress, however, they do not provide a reliable indicator of heat strain. But, it is still valuable to document thermal stress as completely as possible.

5.1 The Heat Index

It is common personal experience that ambient relative humidity has an effect on thermal comfort. High levels of humidity weaken the water vapor partial pressure gradient between the skin surface and the air, thereby restricting evaporative processes. Humid days also increase the heat transfer properties of the skin which affect thermal perceptions (43). It often seems hotter than the thermometer shows when ambient humidity is high. A so-called "effective temperature" for the relationship between air temperature and humidity is expressed in the evaluation of the "Heat Index" (Table 98.4).

Table 98.4. The Heat Index[a]

	Measured air temperature (°F)									
RH	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**
0	64	69	73	78	83	87	91	95	99	103
10	65	70	75	80	85	90	95	100	105	111
20	66	72	77	82	87	93	99	105	112	120
30	67	73	78	84	90	96	104	113	123	135
40	68	74	79	86	93	101	110	123	137	151
50	69	75	81	88	96	107	120	135	150	
60	70	76	82	90	100	114	132	149		
70	70	77	85	93	106	124	144			
80	71	78	86	97	113	136				
90	71	79	88	102	122					
100	72	80	91	108						

[a] Numbers in the table indicate "effective air temperature" corresponding to the combined effects of measured air temperature (top) and ambient relative humidity (RH, left side).

An "effective temperature" is useful as a first-order indicator of the effect of humidity on how hot a particular exposure feels, but its value as an indicator of heat stress stops there. It includes no evaluation of the effect of either convective or radiative heat exchange rates, and it does not consider the rates of heat gain by physical activity (Table 98.1).

5.2 Wet-Bulb, Globe Temperature (WBGT)

Any index of heat stress is improved by measuring as many environmental factors as practicable. "Heat index" data fall short of this mark. The calculation of so-called, "wet-bulb, globe temperature" (WBGT) is an improvement (74, 75). It includes information about air temperature ("dry-bulb"), the temperature of a thermal sensor from whose surface water is freely evaporating ("wet-bulb"), and that of another thermal sensor affected by the net effect of radiant heat exchange ("globe" temperature). The algebraic sum of these assessments provides a more complete statement of heat stress than any one of them alone.

WBGT is calculated for people working outdoors when there is solar radiant heat as

$$\mathrm{WBGT} = 0.7 \cdot (\mathrm{NWB}) + 0.2 \cdot (\mathrm{GT}) + (\mathrm{DB}) \tag{9}$$

where

WBGT = wet-bulb globe temperature (°C)

NWB = natural wet-bulb temperature (°C)
GT = globe temperature (°C)
DB = dry-bulb temperature (°C)

WBGT is calculated for people working indoors or outdoors with no solar or other radiant heating as

$$\mathrm{WBGT} = 0.7 \cdot (\mathrm{NWB}) + 0.3 \cdot (\mathrm{GT}) \qquad (10)$$

WBGT has received wide acceptance as a heat stress indicator. It does not, however, reflect the effects of all heat stress factors. It includes no assessment, for example, of metabolic heat production, commonly a major contributor to the imposed heat load for those who work or exercise. Supplemental evaluation is necessary to interpret WBGT limitations in these circumstances (74). Because work and exercise are not typically sustained activities, there is value in evaluating their effects with WBGT calculations on a time-weighted basis (Table 98.5), particularly if special clothing is involved (76). Also, WBGT does not directly measure air velocity, an important factor in setting both thermal energy transfer coefficients for convective heat exchange at the skin surface and mass transfer coefficients for evaporation of water in sweat (77), although suggestions are available to compensate for their effects (Table 98.6).

Table 98.5. WBGT Criterion Values for Work Rates

Hourly Activity		Light Work		Mod. Work		Heavy Work	
%Work	%Rest	°F	°C	°F	°C	°F	°C
100	—	86.0	30.0	80.1	26.7	77.0	25.0
75	25	87.1	30.6	82.4	28.0	78.6	25.9
50	50	88.5	31.4	84.9	29.4	82.2	27.9
25	75	90.0	32.2	88.0	31.1	86.0	30.0

Table 98.6. WBGT Adjustments for Clothing

Type of Clothing	"Clo" Value[a]	Add to WBGT
Summer work uniform	0.6	0.0
Cotton overalls	1.0	–2.0
Winter work uniform	1.4	–4

[a] 1 "Clo" (insulation value of clothing) is 5.55 kcal(m^2·h) of heat exchange by radiation and convection for each degree Celsius for the temperature difference between the skin and the average of dry-bulb temperature and an average radiant temperature.

Whatever its limitations, WBGT offers a practical guideline for protecting against heat strain and hyperthermia. It has been shown, for example, that intense physical activity, even for healthy, young males should be avoided when the WBGT is greater than 77°F (25°C), if internal temperature is to be protected from rising more than about 0.6°C (78). Data from additional physiological studies (79, 80) will undoubtedly improve its predictive precision, as will the development of appropriate

mathematical models (41, 81).

5.3 The Heat Stress Index (HSI)

In the 1950s, physicists and physiologists developed the Heat Stress Index (HSI) to represent the net effects of environmental factors, metabolic heat production, and physical limitations for sweating under a thermal load (82). Its calculation uses information about dry-bulb temperature, wet-bulb temperature, globe temperature, air velocity, and a person's work rate. From this information base, HSI calculations yield many important pieces of information. It presents, for example, a dimensionless number from zero to one hundred, the "heat stress index," that reports the level of heat strain (Table 98.7). It also calculates an estimated "safe exposure time" for a person, and it presents information for partitional calorimetric analysis of the major avenues of heat exchange and heat production in the defined heat stress (Table 98.8; 83).

Table 98.7. The "Heat Stress Index" (HSI)

HSI	Level of Heat Strain
100	⇐Maximum tolerated
90	Very severe
80	
70	
60	Severe
50	
40	
30	Mild
20	
10	
0	None

Table 98.8. Sample HSI Calculations[a]

	Before[b]		After[c]	
Measurements	**English**	**SI**	**English**	**SI**
Dry-bulb temp.[d]	88.0	31.1	85.0	29.4
Wet-bulb temp.[d]	75.0	23.9	60.0	15.6
Globe temp.[d]	91.0	32.8	88.0	31.1
Air velocity[e]	50.0	0.25	400	2.0
Work rate[f]	700	205	700	205
Calculations				
HSI	107.6	109.0	19.8	19.9
	5.34	4.46	Undefined	Undefined

"Safe" exposure time[g]				
Thermal radiation[f]	–18.6	–5.1	12.0	3.8
% thermal radiation	–2.9	–2.8	2.5	2.7
Convection[f]	–47.6	–13.8	–236.7	–69.2
% convection	–7.5	–7.4	–49.8	–49.6
% metabolism	110.4	110.2	147.8	146.8
Relative humidity (%)	54.8	54.9	20.2	20.5
Required evap. heat loss[f]	633.8	186.0	475.3	139.6
Maximum evap. by sweating[f]	589.0	170.7	2400	702.9

[a] Redrawn from Ref. 83. Slight differences between corresponding values are due to rounding.
[b] *Before*: Just mild work (about 200 watts) near hot machinery on a hot day, even when relative humidity is not too high (about 55%) presents an intolerable heat stress (HSI > 100) when mass and energy transfer coefficients are low because air convection is low in still air. Even with maximum sweating, there is limited evaporative heat loss (186 watts required; 171 watts achievable).
[c] *After:* Just increasing air flow and ventilation with an exhaust fan greatly improves this work situation, even though the work rate is unchanged. The increased flow of dryer air greatly boosts the efficacy of sweating and increases convective heat loss from the skin surface.
[d] °F; °C
[e] ft/min; m/s
[f] Btu/h; watts
[g] hour and minutes

Advantages of HSI calculations are that they are based on many measurements of the environment, and they include an evaluation of a person's rate of metabolic heat production and sweating limitations. It is significant that HSI evaluates data for convective heat transfer (air velocity), infrared radiative heat exchange (globe temperature), metabolic heat production and evaporative heat loss (dry-bulb and wet-bulb temperatures). Its calculations show the effects of the rates of heat transfer by convection, radiation, and evaporation, and they also consider a person's capacity for sweating. No other heat stress index includes so many assessments or provides such a wide range of valuable information.

Despite its comparative completeness and general utility, judgments about heat strain based on a computed HSI require considerable insight and caution, as do calculations of any other indicators of heat stress. HSI calculations, for example, do not consider any of the personal characteristics of age, lean body mass, clothing, medication history and status, level of heat acclimatization, or other related factors defining the individual's ability to withstand a heat stress successfully. For this reason, the HSI's calculated "safe exposure time" must be used most carefully. HSI calculations are also quite inappropriate for heat stressed people wearing water vapor barrier clothing, encapsulated suits, or other body enclosures that restrict the free movement of dry air across the skin surface. Within these limits, however, HSI calculations have considerable value for interpreting heat stress.

Although the HSI calculations have been available for several decades, they are not in as much general use as their utility and value would predict. One reason is the substantial time and energy for making the calculations themselves. Although relationships are expressed in sets of simple, easy-to-solve, interactive algebraic equations (82, 83), it is a cumbersome, error-prone, and time-consuming process to calculate them with paper and pencil.

It is more useful to make these calculations with a small, inexpensive, portable, battery-operated, programmable calculator/computer, like the Hewlett-Packard HP48G and HP48GX models in which appropriate algorithms have been stored (83a, 84). With this easy-to-use technology, sample

problems (Table 98.8) can be solved iteratively, quickly, easily, and accurately. For example, it takes only a moment or two to determine, the consequences of changing one or more environmental or personal independent variables. There is no more straightforward, interesting, and practical way to learn about the environmental and physiological interactions of a heat stress. HSI and WBGT programs can be downloaded from a desktop computer (83b, 84a), obtained by infrared data transmission, or keyed into the HP48G or HP48GX in just a few minutes.

Listed here, are the equations by which the HSI is computed:

$$\mathrm{HSI} = 100 * (E_{\mathrm{REQ}}/E_{\mathrm{MAX}})$$

$$\mathrm{XPT} = 250 * (E_{\mathrm{REQ}} - E_{\mathrm{MAX}})$$

$$\mathrm{RD} = 15 * (\mathrm{MRT} - 95) = 15 * (T_{\mathrm{GT}} + 0.13(V^{0.5}) * (T_{\mathrm{GT}} - T_{\mathrm{DB}})) - 95$$

$$\%\mathrm{RD} = 100 * (\mathrm{RD}/E_{\mathrm{REQ}})$$

$$\mathrm{CV} = 0.65 * (V^{0.6}) * (T_{\mathrm{DB}} - 95)$$

$$\%\mathrm{CV} = 100 * (\mathrm{CV}/E_{\mathrm{REQ}})$$

$$\%\mathrm{MET} = 100 * (W/E_{\mathrm{REQ}})$$

[TEXnical Error]

$$E_{\mathrm{REQ}} = W \pm \mathrm{RD} \pm \mathrm{CV}$$

$$E_{\mathrm{REQ}} = W + 15 * (T_{\mathrm{GT}} + [0.13 * (V^{0.5})] * (T_{\mathrm{GT}} - T_{\mathrm{DB}}) - 95) + 0.65 * (V^{0.6}) * T_{\mathrm{DB}} - 95)$$

[TEXnical Error]

[TEXnical Error]

$$p_{\mathrm{WB}} = 1000 * \{\mathrm{antilog}[28.59 - 8.2 * (\log(T_{\mathrm{WBC}} + 273)] + 0.00248 * (T_{\mathrm{WBC}} + 273) - 3142/(T_{\mathrm{WBC}} + 273)\} \quad (1)$$

$$p_{\mathrm{DB}} = 1000 * \{\mathrm{antilog}[28.59 - 8.2 * (\log(T_{\mathrm{DB}} + 273)] + 0.00248 * (T_{\mathrm{DB}}) + 273) - 3142/(T_{\mathrm{DB}} + 273)\} \quad (1)$$

$$\mathrm{MRT} = T_{\mathrm{GT}} + 0.13 * (V^{0.5}) * (T_{\mathrm{GT}} - T_{\mathrm{DB}}$$

[TEXnical Error]

Definitions of Symbols:

CV = convective heat exchange (Btu/h or watts)
E_{MAX} = maximum evaporative heat loss (Btu/h or watts)
E_{REQ} = required evaporative heat loss (Btu/h or watts)
HSI = heat stress index (dimensionless)
MRT = mean radiant temperature (°F or °C)
p_{DB} = pressure of saturated water vapor at TDB (mbars)
p_{H2O} = water vapor pressure (mbars)
p_{V} = water vapor pressure (torr)
p_{WB} = pressure of saturated water vapor at TWB (mbars)
RD = radiant heat exchange rate (Btu/h or watts)
RH = relative humidity (%)
T_{DB} = dry-bulb temperature (°F or °C)
T_{GT} = globe temperature (°F or °C)
T_{WB} = wet-bulb temperature (°F or °C)
T_{WBC} = wet-bulb temperature (°F or °C)
V = air velocity (ft/min or m/s)
W = metabolic heat production rate (Btu/h or watts)
XPT = "safe" exposure time (h.min)
%RD = % E_{REQ} of infrared radiant heat transfer
%CV = % E_{REQ} for convective heat transfer
%MET = % E_{REQ} of metabolic heat production

All things considered, there is great value and interest in evaluating environmental and personal factors to define heat stress. Results give useful insight into which are primarily important for a specific exposure. Recognizing heat strain, however, requires a different kind of analysis and a different kind of insight, as described in the next section.

Heat Stress
Thomas Adams, Ph.D.

6 Evaluating Heat Strain
Disabling heat strain does not present itself precipitously, although some of its early signs and symptoms might. Its development is typically slow, but its encroachment is insidious, and the unwary can be incapacitated before they know it. There is great value in knowing how to recognize the early warning signs and symptoms of heat strain, understand what causes them, and know what

to do about them with appropriately corrective actions (11, 85, 86).

Even relatively mild thermal strain affects human performance (18–22, 87). Besides being a hazard itself, heat strain also predisposes one to other, often fatal, disorders. For example, the incidence of coronary and cerebral thrombosis was higher for a large population in the days after a heat wave (88). This greater number of vascular disorders is attributed to increases in blood viscosity, lowered platelet volume, low blood pressure, and other direct consequences of heat strain.

Although much heat strain itself is survivable, it is dangerous to tolerate it any longer than necessary. It is foolhardy to ignore its early warning signs and symptoms. Sometimes, though, the preliminary indicators of impending heat strain are hard to recognize. Signs and symptoms in early stages mimic those of many other disorders and are easily discounted as consequences of heat stress. The slow evolution of heat strain, however, has an advantage. Correctly interpreting the indicators of heat strain in its early phases and doing something appropriate to discontinue them, guarantees that they do not worsen. Few other human disorders are so well predicted (6, 89) and lend themselves as well to preventive actions (90, 91).

6.1 Personal Monitoring and Predictive Models

Because heat strain is shown in early physiological responses to heat stress, there is reason to argue for direct thermal and cardiovascular measurements of people who have to work in heat stress, particularly for those who are deemed especially vulnerable to its effects. It is hardly practical, however, to expect people to wear rectal or skin temperature probes on the job. Although they may not be as reliable as direct measurements of deep body temperature (92), periodic, infrared measurements of tympanic membrane temperature, especially when used with telemetric techniques, offer some promise for showing early stages of heat strain (93). It may also be a more reliable indicator of deep body temperature than rectal temperature for people who have heatstroke (94). In some environments, tympanic membrane temperature proved as reliable as rectal temperature measurements, although oral temperature measurements were not (93). The technique for measuring tympanic membrane temperature is painless, quick, and generally compatible with social and work settings. With experience, it could provide valuable, first-estimate information about heat strain.

In a similar way that more is known about heat stress when many different environmental measurements are made, so it is in assessing heat strain. The more information there is about a person's physiological responses, the greater the likelihood that the heat strain level will be understood. There is clearly a place for personal monitors to evaluate time-weighted measures of heart rate and skin surface measures that evaluate deep body temperature (95), those that use microprocessor technology for data acquisition (96), and those that employ radiotelemetric reporting (97) of heat stress and strain indicators. There is also a practical need to continue developing numerical models (81, 98) and computer models (99) for human thermal response.

Most cases of heat strain do not come unannounced. They send their own, sometimes loud signals. The next few sections describe how to recognize, interpret, and act on these important messages.

6.2 The First Stage: “Heat Syncope” and “Exercise-Induced Heat Exhaustion”

The least serious of the heat-induced disabilities typically occurs during the first warm days of spring, or while someone is shopping and the weather is hot and humid for the first time in the season. People who are overweight and in poor physical condition are most vulnerable. A feeling of well-being is slowly clouded by growing fatigue, dizziness, nausea, and even collapse. Body temperature is typically in a normal range (normo-thermia—Fig. 98.1C; “dead zone”—Fig. 98.4), as are levels of whole body hydration and osmolarity. It takes considerable insight, even for a trained physician, to see the contributing causes of heat strain under these circumstances. The condition is called “heat syncope.” Because it commonly occurs with the combined effects of heat stress and exercise, it is also called, “exercise-induced heat exhaustion.”

The etiology of heat syncope resides in cardiovascular, not just thermoregulatory responses. Systemic arterial blood pressure is regulated through a control system (Fig. 98.13) similar to that which controls body temperature and heat content (Fig. 98.3) and has similar dynamics (Fig. 98.4).

Keeping systemic arterial pressure within the limits of a normal dead zone is essential for adequate blood perfusion of all organs, especially the brain, to retain full consciousness. It is easier for most quadrupeds to maintain brain blood flow than for us bipedal humans. For them, the head and brain remain at about the same height as the heart during most activities. For us, however, the head and brain are considerably higher than the heart level most of the time. This makes them harder to perfuse and especially vulnerable to the effects of lowered systemic arterial pressure.

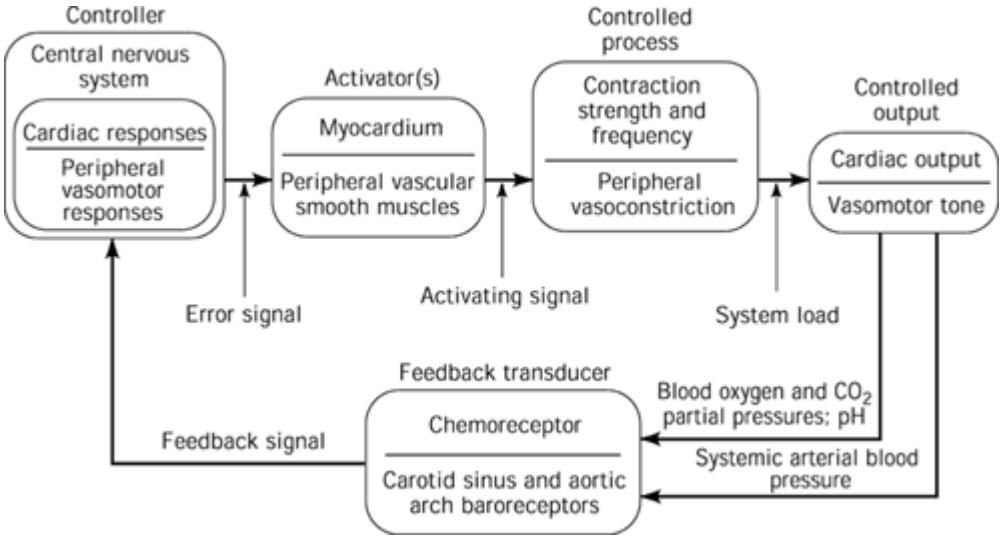

Figure 98.13. Systemic arterial blood pressure is regulated within narrow dead-zone limits by a closed-loop, negative-feedback control system that includes the myocardium and peripheral vascular smooth muscle as activators. This control system has effects coupled with that for body temperature regulation (Fig. 98.3). Reflex vasodilation produced by the simultaneous effects of exercise and heat strain causes systemic arterial pressure to fall, sometimes creating a substantial cardiovascular system load.

Unless there are compensatory control system responses (Fig. 98.13), when systemic arterial pressure falls, brain blood flow falls, and full consciousness is compromised. This happens when psychogenic stimuli cause a drop in systemic arterial pressure, for example, when someone receives astonishingly bad news or sees a particularly distressing sight. It happens also when circulating blood volume is depleted by hemorrhage. It is a common occurrence when the baroreceptor reflex is slow to respond to a change in body posture. Most people have experienced the effects of orthostatic (or "postural") hypotension. It produces a transient dizziness and lightheadedness after standing up quickly, especially if someone is recovering from the flu or has had a recent period of bed rest. Brain blood flow may also be diminished during heat strain, most commonly when there is concomitant exercise, as seen in "exercise-induced heat exhaustion."

It is a normal, control-system-activated, reflex response (Fig. 98.3) in heat strain to increase forced convective heat transfer in the body by increasing the volume of blood circulating to the skin to improve heat loss to the environment. The initiating physiological mechanism is to relax smooth muscle tone in cutaneous vascular beds, allowing their arterioles to increase in cross-sectional area, thereby decreasing peripheral vascular resistance and facilitating increased skin perfusion, with blood returning to the general circulation through deep veins (100). In normal circumstances, the consequent drop in systemic arterial blood pressure is readily countered by appropriate, controlled increases in cardiac output (Fig. 98.13).

Through similarly controlled cardiovascular responses, systemic blood pressure is well-regulated in the face of reflex vasodilation of contracting muscles during work or exercise. Their increased blood perfusion is necessary to provide needed oxygen at an increased rate and also to remove heat, as well as molecules and dissolved blood gases, that are metabolic by-products from the exercise. Reflex

cutaneous vasodilation driven by thermoregulatory reflexes, however, compromises blood supplies to exercising muscle (101). When large volumes of blood flood the skin, this also reduces circulating blood volume and inhibits venous return. It also leads to storage of water in peripheral tissues ("heat edema") (102). The effect is worsened if, at the same time, plasma volume is reduced because of water and electrolytes lost by prolonged sweating (41).

Exercise-induced heat exhaustion occurs when there are simultaneous demands on the cardiovascular control system from heat strain and exercise. Circulating blood volume may be on the low side of normal if someone is in poor physical condition, not heat acclimatized, and inadequately hydrated. Such a great fall in peripheral vascular resistance from the combined stresses of exercise and heat stress may not be adequately compensated for, so that brain blood flow is reduced. So is brain function, at least until the person collapses. Then, when the person is horizontal, the head is at the same level of the heart, its blood perfusion increases, full consciousness returns, and the person feels well, until collapse occurs again when trying to stand.

Feeling faint, light-headed, dizzy with blurred vision; experiencing tinnitus, tingling, or numbness of the face, hands and fingers, nausea, and a developing "funny taste" in the mouth are all predictable symptoms of heat syncope and exercise-induced heat exhaustion. Typical signs are low blood pressure, an elevated heart rate, redness and flushing of the face, diaphoresis, and postural instability. Both the signs and symptoms are of cardiovascular origin and are not necessarily coupled with hyperthermia.

Most people in general good health quickly and fully recover without complications from the usually short-term episodes of heat syncope and exercise-induced heat exhaustion. Feeling faint or even passing out on a particularly hot day is disconcerting, but it is not necessarily dangerous in itself. Diminished consciousness for any reason is of concern when someone is operating machinery, driving a car, or is in a compromised situation like crossing a street or working around moving machinery. Long-term exposure to heat stress, though, places many people at special risk (88).

6.3 The Second Stage: Dehydration and Loss of Body Electrolytes

Humans, other mammals, and birds depend on heat loss by evaporation for thermal balance (Eq. (1)). When ambient temperature is greater than skin temperature, this is the only way to lose heat (Eq. (2)). Most mammals do this by increasing ventilation of the respiratory dead space during panting when the thermal shell has stored heat from a bout of exercise, even when the air temperature is cool. Except for dripping saliva, panting animals retrieve molecules and electrolytes in saliva when they next swallow. They lose only water vapor and heat during panting. Humans, however, benefit from using a much larger surface area (virtually the entire skin surface) as an evaporative site but lose both water and electrolytes by sweating. Recovering these electrolytes and the lost water is essential.

For most people in general good health who do not sweat heavily on the job throughout the day, the water and electrolytes, primarily sodium chloride, lost in sweat are readily regained with a normal diet. Others need to consider electrolyte replacement fluids, in addition to drinking just plain water. Someone's physician is the most reliable consultant for determining these strategies. Failure to replace lost water leads to progressive, whole body dehydration. Water is drawn from body fluid compartments, leading to a reduced circulating blood volume. This makes it difficult to keep systemic arterial blood pressure within control system dead-zone limits and to distribute heat in the body by convection. Dehydration also increases blood viscosity and raises hematocrit, requiring greater cardiac work.

Water and electrolytes lost in sweat must be replaced so that the body eventually returns to its normal range of hydration and osmolality. Because sweat is hypotonic, prolonged sweating leads to hypovolemia and also to an increase in osmolarity. Just drinking plain water after prolonged, heavy sweating, however, can make body fluids hyposmotic. Failure to provide osmotic balance leads to muscle cramps, usually in the large muscles of the extremities and in the abdominal wall, (103), gastrointestinal disturbances, nausea, vomiting, and in extreme cases, susceptibility to toxins,

dementia, and death.

By many accounts, dehydration is an important, if not the predominant contributor to heat-induced illness in people, especially during exercise. Mild hyperthermia results from as little as a 1% body fluid loss. There is considerable impairment of work capacity when 5% has been depleted. Although humans depend solely on sweating for evaporative water loss in heat stress, we are not as good as most other animals in developing thirst and replacing lost body water in the early stages of dehydration. By the time someone senses thirst, dehydration is already established by perhaps as much as 2% of body weight (104). Even in responding to thirst, we do not replenish lost body water as effectively as many other species. We stop drinking water before we are fully hydrated again.

6.4 The Last Stage: Heatstroke

Heatstroke, also called "sun stroke," is life threatening but rare among the general population in the United States. Although only several hundred people die from heatstroke each year in this country (50), heat strain is a contributing cause of death for many thousands of others who lack normal cardiovascular and cerebrovascular reserves (105).

People who have diabetes mellitus may be predisposed to heat-induced illness and heatstroke for several reasons (40). They may be more susceptible to postural hypotension because of weakened baroreceptor reflexes. They may also have peripheral neuropathies and autonomic nervous system problems that affect peripheral vascular responses to heat and reduce sweating capacity.

6.4.1 Environmentally Induced ("Classical") Heatstroke When heatstroke develops from exposure to high ambient temperature, often with high rates of infrared radiant heating, it is called, "environmentally induced heat stroke," or "classical heatstroke." It predictably affects the elderly, the chronically ill or disabled, and those who use medication or drugs that affect thermoregulation, sudomotor, and cardiovascular functions. Typically, the affected person is sedentary or inactive, but overheated because of intolerable environmental conditions. People recovering from head injuries often have limited reserves for combating heat stress and are especially susceptible to heat strain, including heatstroke (106), as are those who have amyotrophic lateral sclerosis or cystic fibrosis (107) and those who have persistent, disabling mental illness (108).

6.4.2 Exercise-Induced Heatstroke When heatstroke results from high rates of metabolic heat production, for example, during prolonged periods of heavy exercise, it is called, "exercise-induced heat stroke," or "exertional heatstroke." It predictably affects those who are in good physical condition, often young, and who are exercising or working in the heat for extended periods. Exercise-induced heat stroke, however, can occur in virtually any set of environmental circumstances (109). It often presents itself with unique complications from strenuous muscle activity, such as rhabdomyolysis (89), intravascular coagulation (110), severe hyperkalemia (111), hypoglycemia, an increase in endogenous opioids (112), increased catecholamines (113), and major organ damage (114).

Exercise-induced heat stroke is most common among young, healthy adults. It is, in fact, the third leading cause of death among high school athletes in this country (102). It is a hazard to those in the military who are undergoing physical training (109) and is a danger to anyone involved in prolonged, high levels of exercise, especially in hot, humid environments (114).

6.4.3 Heatstroke Signs and Symptoms Even at high levels of heat strain, the skin is normally moist and cool because of sweat evaporation. In contrast, for those who have heat stroke, the skin is hot and dry, and deep body temperature is 105°F (40.6°C), or higher because the person's attempts to thermoregulate have been overwhelmed and sweating has ceased (115). As the person becomes progressively more hyperthermic, cardiac output increases to pump ever larger volumes of blood through maximally vasodilated vascular beds.

People in heat stroke may be dizzy, confused, nauseated, have a headache, be disoriented, or even delirious, in a manic state, have seizures (about 60%), or be comatose (about 85%) (40). They will

typically have polypnea, rapid and weak pulse, and will be hypotensive. Virtually all will have previously gone through earlier stages of heat strain, showing many of its early warning signs (40). Rectal temperature measurements may not be reliable indicators of deep body temperature in conditions of heatstroke and when body heat content is changing rapidly (94).

Many people who have heatstroke and sustained increases in cardiac output may develop multiple electrocardiographic anomalies (116) and abnormal heart rhythms because of hyperthermic damage to myocardial cells. Some will have demonstrable myocardial damage (117), some will die of heart failure (15), and some will experience pulmonary edema (118).

6.4.4 Heatstroke Sequelae Renal failure is common in about 30% of those who have heatstroke (15, 119). For those who have exercise-induced heatstroke, it is predictably secondary to the myoglobinuria and hyperuricemia associated with rhabdomyolysis and their high levels of muscle activity. It may also come from direct thermal damage to the kidney and its reduced perfusion when high rates of blood flow are directed to the skin. Hemorrhaging and disseminated intravascular coagulation in tissues throughout the body come from the direct thermal damage of blood vessel endothelial walls, especially in smaller vessels (120). Heatstroke endangers all tissues and organs, especially the liver (121, 122), and often causes death days after the heatstroke episode is ended (114).

Just because someone recovering from heatstroke regains consciousness and returns to a normal range of deep body temperature does not mean that the danger is ended. Possible damage to major organs may present a hazard for hours and days later. Heatstroke must be treated as a medical emergency. All who suffer its effects need prompt cooling, medical attention, and hospitalization.

The severity of injury from heatstroke and the likelihood of death clearly depend on how hot a person becomes and also on how long the hyperthermia has lasted. Some people survive damage-free after suffering heroically high body temperatures, but only for short periods. The highest recorded deep body temperature with complete recovery is a remarkable 115.7°F (46.5°C) (123). Although heat-induced hemolysis and erythrocyte damage occurs *in vitro* at temperatures as high as 118°F (48°C), there is some thermal damage at only 108°F (42°C) to blood samples held at that temperature for 24 to 48 hours (124). A good case can be made for vigorously treating people with heatstroke and lowering their deep body temperatures quickly (125). As a guideline, reducing deep body temperature to at least 102°F within an hour is a good safeguard against extending thermal damage in heatstroke (115).

There is a wide range of injuries from heatstroke, and some have no disabilities at all (126). Others have central (127) and peripheral nervous system damage (128), including that of the cerebellum, leaving them with permanent problems with balance and walking. Others may have personality changes to the point of dementia (16a).

6.5 Failure of Predictors

Considerable time and effort have been invested in establishing quantitative indices for human heat stress, and many laboratory and clinical studies provide mountains of indicators for heat strain. This is all valuable information. At first glance, it looks like we know a lot about the way people respond to this environmental stressor. We do, but we do not know everything. Limitations of our insights often come to light in reports of how well people function in the heat, despite violations of many of the rules.

Most indicators of heat strain, for example, put at high risk those people of older age, with excess body weight, histories of prior alcohol use, and who work and sweat heavily in the heat for long periods of time. But not all are at risk. Forty-three men, 18- to 59-years-old, were studied during 54 man-days of shearing sheep, pressing wool bales, and performing related heavy manual labor (129). Air temperature ranged from 66 to 105°F (19 to 41°C), WBGT indexes from 60.8 to 84°F (16 to 29°C), and just fewer than half the exposures exceeded threshold limit values for work rates of about 1365 Btu/h (400 watts). Despite problems of overweight, drinking more than 7 ounces (207 grams)

of alcohol the previous night, and sweating as much as 21.8 pounds (9.9 kg) during a 10-hour workday, none suffered disabling heat strain. Inexplicably, those who had consumed alcohol the evening before had lower rectal temperatures and were more productive than others. And surprisingly, those who were more overweight reported that they felt cooler during the workday. Age was not a factor in individual responses to the strain and heat and work. Much of the success of people in this group is attributable to their experience on the job and to their successful rehydration during the work period.

Although this carefully reported situation (129) is only one story, it is unlikely to be the only one. Its description emphasizes the need to focus on personal issues when evaluating heat strain, not relying just on formal heat stress indicators to predict who will do well in a work setting. The report also points to the important factors of personal, on the job experience and great individual variations in setting thermoregulatory competencies.

6.6 Early Warning Signs and Symptoms of Heat Strain

Heat disabilities are preventable. The best way to interrupt their predictably inevitable progression is to take appropriate actions as soon as their early warning signs and symptoms appear. Sometimes just lessening the intensity of an activity, interrupting a period of exercise, or taking a short break on the job is enough. Depleting body heat stores by resting for awhile in a cool, shaded and well-ventilated area is a good idea, too. Most people will know when they are dangerously overheated. Their disabling signs and symptoms will demand attention. It is the wiser and safer person who takes corrective actions long before that. The best time to take protective measures is when early warning signs and symptoms of heat strain first appear.

6.6.1 Visible Sweating

The rate at which atrichial sweat glands deliver their secretions to the skin surface is precisely controlled (Fig. 98.3). The process often goes without notice because the liquid water in sweat usually converts to an invisible vapor at just the rate required to supplement the other avenues of heat loss (Eqs. (1) and (3)) required for thermal balance. The neurophysiological control system that regulates sweating does so proportionally to drives from the status of deep body temperature, skin temperature, and total body heat content. As they increase, sweat glands proportionately increase their rate of secretion, sometimes bringing sweat to the skin surface at a rate faster than its water can evaporate. Then, it appears as a liquid on the skin surface. This signals danger.

Sweating does not cool. The water in sweat must evaporate at the skin surface. If sweat soaks into clothing or drips on the floor, it cools these surfaces when it evaporates, but not the body. It is a poor investment for the loss of body water and electrolytes when sweat is produced, but does not evaporate from the body surface. Liquid water on the skin surface in heat stress is a sure sign that body cooling rates are not being supported by the required rate of evaporation. It is an indisputable early warning sign of heat strain. It is as important an early warning sign as a red light on the dashboard of a car. It is not a dangerous event in itself, but it sends a clear message that trouble is on the way.

Visible sweating is the most common indicator of the first stage of heat strain. Unfortunately, it is the one that is most usually ignored. There are some who report they do nothing when they visibly sweat and claim it is just a routine consequence of their jobs or activities. They may be the same people who continue to operate their cars with red lights glowing on the dashboards. Neither practice makes sense.

6.6.2 Increased Heart Rate

Increasing the distribution of heat in the body by the forced convective flow of blood is the most effective defense against heat strain. It is reflexly triggered even in the early stages of heat loading. As heat strain increases, cardiac output and the circulation of blood increase as controlled, dependent variables (Fig. 98.3). Cardiac output is reflexly increased by a greater volume of blood ejected with each cardiac cycle (stroke volume) and also by increasing the heart rate itself. At the same time, peripheral vascular resistance is reflexly lowered to promote high flow rates in the circulation.

About 85% of this increased cardiac output may be directed to the skin alone (40). This becomes so powerful during the late stages of heat strain that the person becomes aware of a pounding and rapid pulse—a sure sign of heat strain. Supporting a high volume of blood flow throughout the body is an essential defense, especially at high levels of heat strain. Maintaining cardiac output in this circumstance by keeping cardiac filling pressure elevated is an important limiting factor in heat strain (130). Sensing a pounding pulse is a sure sign that it is time to take a break and find a place to cool off.

6.6.3 General Malaise and Deteriorated Abilities The early stages of heat strain are typically accompanied by a fall in systemic arterial blood pressure and compromised blood flow to the brain, especially for those who are not heat acclimatized and especially when the heat stress is coupled with exercise. There are several consequences. A person at this level of heat strain may find diminished psychomotor skills, periods of confusion, unexplained irritability with growing flu-like symptoms of lightheadedness, nausea, and muscle aches. Becoming clumsy with a job skill that is usually completed smoothly, efficiently, and easily sends a clear message of heat strain.
6.7 Heat Acclimatization
Most people in general good health develop some degree of heat acclimatization as a normal adjustment to working or exercising even moderately under a heat strain (131). Heat acclimatization is acquired while working in a warm environment, or even in a cool one, if someone wears thermally insulating clothing (132). With just an hour or so of activity each day, there is marked improvement in comfort in about a week. Some heat acclimatization effects begin as early as three days (133). There are many cardiovascular and thermoregulatory changes (70–72). Heat acclimatized people predictably develop an increased plasma volume at rest (72), increased circulating blood volume, and a greater cardiovascular reserve (70). This makes it easier to maintain systemic arterial pressure and avoid episodes of exercise-induced heat exhaustion (heat syncope).

Cardiovascular adjustments with heat acclimatization markedly improve the ability to distribute heat throughout the body, especially to the skin for heat loss to the environment. Blood pressure is maintained more easily in a normal dead zone because heat acclimatized people predictably develop an improved ability to reduce blood flow to viscera. This is a special bonus for adequately perfusing exercising muscle (42).

Heat acclimatization also enhances sweating responses (70), provides the ability to produce sweat at about a three times greater rate (p. 656 of Ref. 13), and decreases its electrolyte concentration (72), especially when sweating rates are low. People who are heat acclimatized also show greater precision in controlling the rate of sweating proportional to levels of hyperthermia and heat storage (134). In general, those who are heat acclimatized begin sweating sooner in heat strain and sweat at higher rates when needed (p. 181 of Ref. 1).

The major benefits of heat acclimatization are to reduce physiological strain, decrease peripheral pooling of blood, and cause a slower rate of heat storage and rise in deep body temperature under heat stress (70, 72). Because heat acclimatization also brings a greater reflexly reduced blood flow to splanchnic vascular beds, arterial blood pressure is more easily maintained. Heat acclimatization is not a permanent acquisition. Some loss of it begins even with just a few days of limited activity and discontinued heat stress (41).

Heat Stress
Thomas Adams, Ph.D.

7 Factors Affecting Heat Strain
7.1 Age

There are clear differences in responses to heat stress among age groups, but it takes some care to see the reasons. They may not be directly related to the factor of age itself. Some are traceable to differences in body geometry and its effect on heat dissipation and storage. Infants and young children, for example, have greater skin surface area to body mass ratios that increase their rates of heating, cooling, and water loss, compared to adults similarly exposed. Their smaller mass also, deprives them of tissue for heat storage. They also have smaller reservoirs for body water storage for the same reason. This means that they will experience thermal strain sooner than adults, whether the exposure is to heat or cold. Using an adult's thermal status to judge whether an infant or child is thermally safe and comfortable in thermal stress is naive and irresponsible (12). It may be a contributing factor in “sudden infant death syndrome” (9, 10, 12).

Age-related deterioration in cardiovascular function and reserve plays an important role in contributing to diminished thermoregulatory potential for the aged. This is not hard to understand considering how important this form of forced convection is in distributing body heat and storing it. Many of the aged also, have complicated medical histories that bear on thermoregulatory ability. Lowered aerobic capacity, reduced sweat gland density (135), and diminished capacity for sweating are also factors (136, 137), as are changes in body fluid distribution and thirst perception in this group (138, 139).

A general pattern is that the youngest and the oldest are at greater risk than others. Even healthy children, especially the very young, are at more risk in heat stress than adults, not because they lack intact thermoregulatory reflexes, but because of their large body surface area to mass ratio and their limited cardiovascular potential. For example, a neonate has a three times greater surface area to mass ratio (0.6 cm^{-1}), than an adult (0.2 cm^{-1}). Older people, especially those who have cardiovascular and peripheral vascular diseases, are the most susceptible to heat strain. There is great variation among older people, however, because of differences in general physical health and level of physical fitness (140). The most successful and least endangered of all in environmentally induced heat stress are young adults in good general health, who have good physical fitness, and who are heat acclimatized. Paradoxically, it is the young who most frequently succumb to exercise-induced heat exhaustion.

It is difficult to find scientifically documented differences in basic thermoregulatory reflex abilities for people of different ages, especially among the elderly (140–143). They may not have equal competencies for body temperature control, but the basic central nervous system control mechanisms (Fig. 98.3) appear to be intact. Differences among people based on age are more related to individual cardiovascular, respiratory, sudomotor, and peripheral vascular abilities and to factors of hydration and circulating blood volume. Although the basic neurophysiological control system works, its ability to force regulation differs as a function of age (138, 143).

7.1.1 The Young Based on their ability to sweat, control skin blood flow, and make appropriate changes in body position, even the youngest infants show that they have functioning, closed-loop, negative-feedback control systems (Fig. 98.3) for regulating body temperature (144). Most neonates of thirty-six or more weeks of gestation can sweat in response to a hot environment on the first day of life, although sweating was delayed a week or more for those who had a shorter gestation period (145).

Babies have a special challenge in retaining body water that makes them especially vulnerable in heat stress. Because of their thin skins, infants lose about 120 mL of water per kilogram of body weight daily (1), even without sweating. This accounts for about 290 kilojoules of heat per kilogram of body weight each day, which is more than half of their daily caloric intake. Even older children, especially those less than 5 years of age, are particularly susceptible to heat-induced disabilities. They are in special danger in severe exposure conditions, like those imposed by a sauna (146).

Some of the increased dangers children face in the heat result from their physical limitations for

storing and distributing heat. They are also at greater risk because they lack adult experiences in seeing and reacting appropriately to the early warning signs and symptoms of heat strain.

7.1.2 Older People People more than sixty-five years of age are overrepresented in heat-induced disabilities and deaths during heat waves (147, 148). Only some of the reasons are understood. In one study, for example, older men (64 to 76 years of age) had higher deep body temperatures and lower skin temperatures during controlled heat stress tests than younger men (20 to 24 years of age), and they had reduced sweating capacities (149) and reduced thirst sensitivity (139). These factors predispose heat-induced illnesses.

There is, however, another side to consider. There is no doubt that older people have more physical problems than those who are younger. Some carry the effects of injuries of long ago, and some have chronic illnesses. Cutaneous vasodilator responses are also weakened with age (150). On the face of it, there are several reasons to expect that older people are more endangered in a heat stress, and, of course, many are, but not all. There are many anecdotal reports of people in advanced age doing about as well as they ever did, and as well as anyone else, in the heat. For example, men and women, even into their seventies, showed little impairment in thermoregulatory ability or in the level of heat acclimatization in controlled tests of heat stress, as long as they were aerobically fit (140). Thermoregulatory ability for many older people is preserved whether or not they are heat acclimatized (151).

The ability to face heat stress successfully is retained even up to the age of eighty-six (141), as long as physical fitness is preserved. In addition, there are no differences between the heat responses of postmenopausal and younger women, except that the older women have a higher sodium ion concentration in forearm sweat (143). More important than age itself, the ability to counter heat stress depends on lean body mass, sweating ability, physical fitness, cardiovascular health, peripheral circulatory ability (152, 153), whole body hydration (141), and the level of heat acclimatization.

There is little doubt that both men and women benefit from being in good physical condition in heat stress (154). Some of this effect comes through changes in sweat gland function (155), and some results from increased circulating blood volume through plasma volume expansion (156). Both extend the upper limits of heat stress and exercise. Even though the circulation of blood plays a most important role in distributing body heat as an adjunct to successful thermoregulation, ischemic heart disease itself has no direct effect on a person's ability to maintain body temperature in a normal range, although it might compromise cardiopulmonary function (157).

7.2 Hydration and Osmolarity

By the same dynamics that body heat content is the net effect of a balance between heat gain and heat loss rates (Eq. (1)); Fig. 98.6B), so body water content and osmolarity are net balances of water and electrolyte influxes and effluxes (Fig. 98.14). They are regulated by their own closed-loop, negative-feedback control system (Fig. 98.15). Body water is gained by drinking it, by ingesting it in foods, and by obtaining it through metabolism. It is lost by respiration, by water diffusion through the skin (so-called, “insensible water loss”), by sweating, by bleeding, as in menstruation, and by the production of urine and feces. Each of these input and output functions brings about its own unique effect on total body water and its electrolyte density.

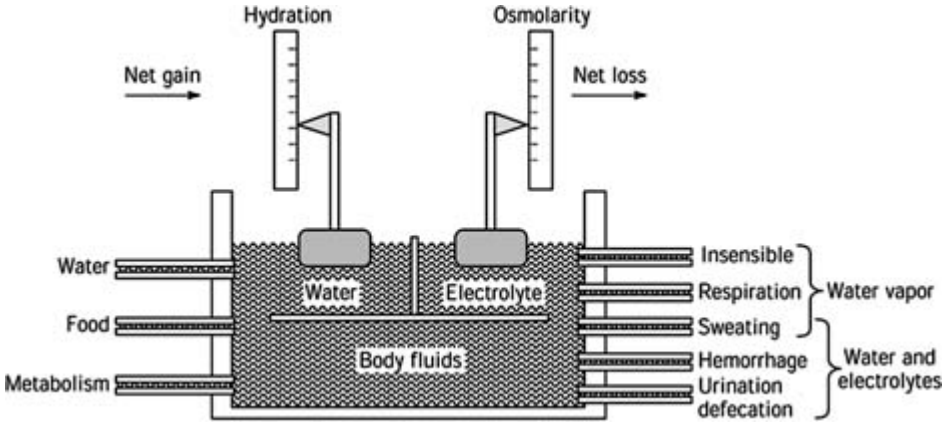

Figure 98.14. Metabolism along with beverages and food are sources of water and electrolytes that are distributed among all body fluid compartments. Water vapor is lost by diffusion across the skin ("insensible"), by every exhalation, and by sweating. Both body water and electrolytes are lost by sweating, by blood loss, and through excretions. The control system sketched regulates these fluxes to keep body fluid volumes and their electrolyte densities within dead-zone limits.

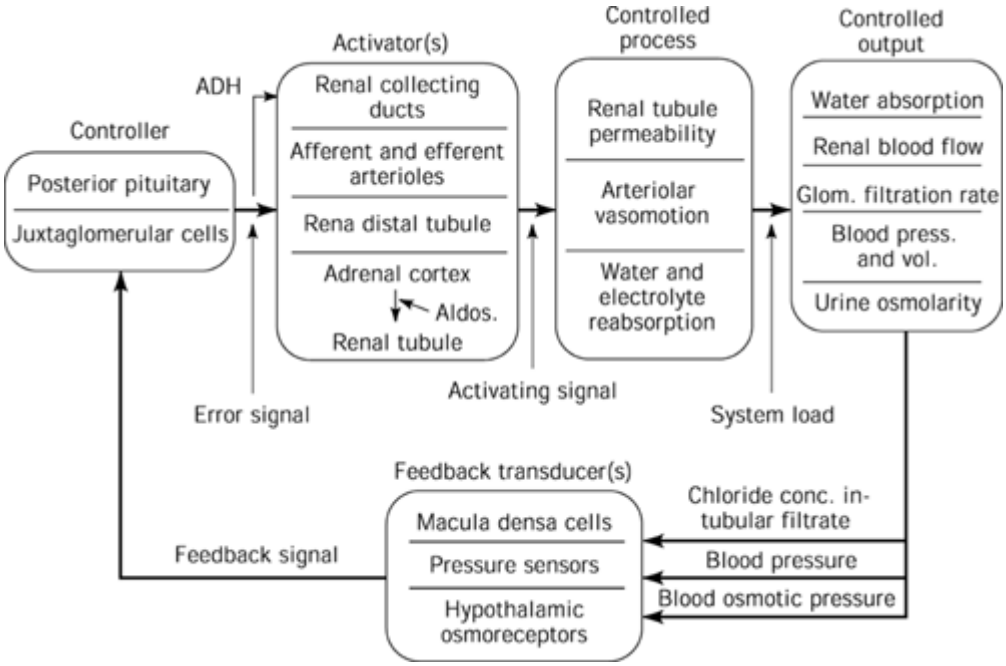

Figure 98.15. Body water and electrolytes are regulated through a negative-feedback control system that involves many organs, different regions of the kidney, and different hormones, including antidiuretic hormone (ADH) and aldosterone (Aldos.). Feedback effects are through blood volume, pressure, and electrolyte composition. An adult loses about 2.5 liters of water daily. About 500 mL is by diffusion across the skin, about 350 cc through respiration, about 1500 cc by urination, and about 150 cc by defecation (69).

Water is a unique molecule. It is chemically inert and electrically neutral, but is an essential medium and diluent for all of the body's electrochemical and biochemical processes. It is ubiquitous in all known life forms. Although the water molecule is a tightly bonded combination of elemental hydrogen and oxygen, some dissociates in body fluids to be a hydrogen ion donor. This is important for the control of body fluid compartment acid–base status (158). Water is the only molecule that freely diffuses passively along concentration gradients to penetrate all cells, tissues, and body fluid compartments, and it does so rapidly. Drinking water, for example, is just about as effective in

recovery from exercise-induced dehydration as intravenous infusion of a 0.45% saline solution (159).

Drinking plain water increases the body's hydration reservoir, but it dilutes its dissolved electrolytes, sometimes leaving a net balance of hyposmolarity (Figs. 98.14 and 98.15). Ingesting electrolytes in foods and seasonings does not affect whole body water stores directly, but it does increase osmolarity. Water is lost in a vapor phase with each exhalation, and it diffuses across intact skin to escape as an invisible vapor at the skin surface. Both processes decrease hydration and increase electrolyte concentrations. Sweating causes loss of both body water and electrolytes, especially sodium chloride, but only in diluted proportion to body fluids. Because sweat produced by atrichial glands is hyposmotic, sweating has the net effect of depleting body water, more than its electrolytes. Prolonged heavy sweating, however, challenges both.

Humans have a great, often life-sustaining, dependence on sweat gland activity for successfully confronting heat strain, but we are obliged to maintain body hydration and osmolarity. Paradoxically, we typically do not replace lost body water as well as some other animals (160). Even furred animals that do not use sweating for thermoregulation do better than we do in drinking as much water as they need after exercise and heat strain. Our failure to maintain body water and electrolyte stores isosmotically within dead zones of control (Fig. 98.4) has serious consequences in athletic performance, it threatens comfort and safety in heat stress, and it may be life-threatening.

Although both reduced body water and osmolarity contribute to thirst drives (Fig. 98.13), few people voluntarily drink enough water to reestablish a normal level of hydration after heat strain (160). Antidiuretic hormone (ADH) is not the only driving factor (Fig. 98.13) in attempts to rehydrate voluntarily (161). Osmolarity and hypovolemia have significant effects, too. Although sweating increases with mild hypohydration (about 2%), it decreases with greater loss of fluid volume (3%), and the salt concentration in sweat increases (162). Substantial hyperosmolarity with dehydration during exercise reduces sweating rates (163), but sweating does not cease until whole body dehydration is severe (26).

Dehydration is correlated with increased heat storage during heat strain, presumably because of a control system load error (Fig. 98.4) associated with decreased skin blood flow (164). This increase in heat storage occurs equally well among males and females, among those who are heat acclimatized and those who are not, and among all people independently of the level of physical fitness, assuming that they are in otherwise generally good health (165). Although there are cardiovascular and thermoregulatory compensations for mild levels of dehydration, severe levels adversely affect blood pressure and body temperature controls (166). There are dangers, however, in chronic dehydration besides those associated with heat strain. People who sweat heavily on the job and who do not adequately replace lost body fluids run a higher risk of uric acid kidney stone disease (167).

A normal amount of stored body water is important in physical performance in the heat. Dehydration diminishes athletic performance, even in the short term and even when sweating rates are low. Full hydration from periodic drinking of water, or better, using fluids with dilute carbohydrate and electrolyte concentrations, benefits long term physical activity (104), although carbohydrate concentration in ingested fluids might slow the rate of gastric emptying and slow fluid absorption (168). Gastric emptying is slowed during exercise and heat stress, compared to rest at neutral air temperature (169). It is unclear, however, how important this is in view of the speed at which water is distributed in the body (159).

Dehydration at any level is costly for thermoregulatory and cardiovascular responses to exercise in the heat, and it affects men and women equally (165). Heat strain-induced increases in heart rate and reductions in cardiac output during exercise are more related to the person's state of hypohydration than to plasma volume (170). It is unresolved whether hyperhydration improves thermoregulation for athletes (171, 172), and there is no evidence that it necessarily enhances specific physical

performance (171).

How dehydration affects thermoregulatory responses depends on its severity (173). Up to moderate levels of hypohydration reduce plasma volume, but not osmolarity, and progressively greater loss of body water increases osmolarity without further reduction in plasma volume. These differential effects have their own actions in the control of whole body water and electrolytes (Fig. 98.13). How plasma volume decreases in hydrated people during sweating in exercise is age-related, and those who are young (middle second decade) have less of a decrease than those in their late fourth and fifth decades of life (141). Hypohydration reduces the deep body temperature at which heat strain is tolerated (174).

But how does someone know when body hydration and osmolarity levels are adequately within control system dead zones? It is obviously impractical to obtain blood samples or analyze urine specimens in the field during athletic competitions or on the job. A couple of quick, subjective tests have some degree of reliability. It is a time-honored guideline to pay attention to the frequency of urination as a reflection of hydration. If someone urinates at about the same intervals and voids each time about the same volume during a hot day as during more temperate exposures, it is a reasonable, first-order indicator of adequate hydration. Urine color is also, acceptably correlated with its osmolality and specific gravity as a general, nonquantitative indicator of hydration (175). Voiding dark-colored urine signals dehydration. More precise and quantitative guidelines, however, are necessary to maintain optimum performance, effectiveness, and safety (176–178).

7.3 Medications and Alcohol

7.3.1 Medications and Recreational Drugs Several classes of pharmaceuticals reduce the ability to face heat stress successfully. Anticholinergic drugs, for example, some tricyclic antidepressants and antihistamines, may inhibit sweating (121), especially in the elderly (179). Others, like some sedatives, opioids and haloperidol, also interfere with thirst thresholds (180). Zonisamide impairs sweating and may produce a number of neurological effects that lead to hyperthermia, especially in children (181). Similarly, some appetite-depressant drugs increase metabolic heat production and induce peripheral vasoconstriction, both of which are endangering processes during heat stress, even to the point of death (182).

Antipsychotic medications, like pimozide and clomipramine, have an antidopaminergic action that increases the thermoregulatory set point. They also have anticholinergic side effects that place people who use these medications at higher risk when they are exposed to heat stress (183). Antidepressants, such as Prozac and lithium carbonate, may also induce heat intolerance, especially for those who work in the heat (184).

In contrast to weakening thermoregulatory ability by some drugs, other materials may, in fact, improve the development of heat acclimatization. Daily 250- and 500-mg doses of vitamin C (ascorbic acid), for example, improved the rate of heat acclimatization of young males (185).

Some drugs induce signs and symptoms of hyperthermia in the absence of environmental heat stress. Amphetamine-like drugs, dantrolene, for example, produce hyperthermia, and cause the breakdown of muscle tissue, inducing spontaneous intravascular coagulation and promote renal damage (186).

For adequately informed personal safety, all who use medications of any kind, prescription drugs, or over-the-counter products, need to consult frequently with their physicians to determine possible antithermoregulatory side effects of the drugs they take. These effects may come either from direct actions on the central nervous system and on cardiovascular responses or from the inhibition of sweating and induced levels of dehydration. These deleterious drug actions may appear as a direct effect of the pharmaceutical itself and also as a consequence of the way they interact with other medications taken at the same time.

7.3.2 Alcohol and Caffeine High doses of alcohol induce profound and debilitating effects, yet it is widely used in many societies and has been since prehistory. It is a well-known depressant for

central nervous system functions, it induces peripheral vasodilation, and it is a diuretic. There are many reasons to expect its use to be contraindicated for people who face thermal stress.

Despite its many actions in the body and its potency in high doses, however, low to moderate levels of alcohol intoxication have few consistent, deleterious effects on thermoregulation in the heat, for shifting the body's thermal set point or dead zone, changing skin temperature, or altering sweating responses (187–189). There is, however, an apparent effect of the level of alcohol intoxication. Whereas ingestion of a 2% alcohol beverage had no demonstrable diuretic effect on rehydration rate after mild dehydration from exercise in the heat, a 4% beverage slowed the process (189).

Alcohol use, though, presents a specific danger in the heat secondary to its direct pharmacological actions on thermoregulatory responses. It can reduce the precision of regulating systemic arterial blood pressure (Fig. 98.13), leading to orthostatic (postural) hypotension and heat-induced syncope. Because of these actions, alcohol has been implicated in twenty or so sauna-related deaths each year (190).

Similar to alcohol, caffeine is a diuretic, but in contrast to the effects of alcohol, it is a central nervous system stimulant. As such, it purportedly improves athletic performance, especially in the heat. Controlled studies, however, fail to support this claim (191).

7.4 Gender

Thermoregulatory abilities are so deeply rooted in our species that they appear to trancend variables associated with gender (192). Although there are differences between males and females at different ages in their responses to heat stress, the net effect of their responses give equal protection. Any gender differences are less important than factors of aerobic capacity, levels of heat acclimatization (193, 194), and physical fitness (192, 195). There is, however, a difference between athletic and nonathletic women in responses to controlled work in heat stress; the more physically fit people keep maintain cardiac output and peripheral blood flow better (196). There may also be gender differences in the physiological mechanisms for increasing cardiac output in exercise, but there is no net effect on cardiovascular competency (197).

Although some data indicate gender differences in preadolescent children: boys reportedly sweat at a slightly higher rate than girls, and they are more tolerant of heat stress, but these differences do not survive when factors of cardiovascular fitness, body size, and heat acclimatization are normalized (198). The effects of the menstrual cycle are also small (193, 198). If demonstrable at all (194), they are subtle and hard to demonstrate experimentally (199). There is, however, an extravascular movement of body fluid that reduces plasma volume during heat stress in women in the luteal phase of the menstrual cycle (200) and a shift in the sweating threshold (201), but it is not clear what, if any, effects these phenomena have on the level of heat strain.

Short-term heat stress is safe for women who have normal pregnancies (202) but may not be for those who have high-risk pregnancies (203). Moderate heat stress does not also induce uterine contractility in pregnant women, nor does it harm the fetus in late uncomplicated pregnancies (204). In fact, the ability to face heat stress is improved for some women in late pregnancy (205).

Heat Stress
Thomas Adams, Ph.D.

8 Summary and Conclusions

Heat stress challenges all creatures. Disabilities, dangers, and death from heat strain have dogged our species and others for as long as we have been on the planet. Heat stress is one of the all too many, unavoidable sharp edges of reality. Despite our unprecedented and unparalleled successes in developing technical defenses against heat stress, we still struggle to maintain comfort, safety, and

health when total body heat content and body temperature rise. Not all do it equally well, and some do not do it well enough. It is a good guess that unrecognized heat-induced illness, along with the diminished physical and psychological abilities it causes, contributes to injuries on the job and precipitates many ailments that are not always correctly diagnosed, treated, or identified as heat-related. People do not have to have high body temperatures to be victims of heat stress.

The weight of heat stress comes from high environmental temperature and humidity, as most would guess, and also from self-imposed elevations of metabolic heat production from heavy and prolonged work or exercise. Both disable and kill many each year. It is a surprise to some that people collapse from heat strain and die of heatstroke in winter, just as they do in the worst weather of summer. It is hard to be on guard unless people know they can be the target of heat stress and strain any time of year, in any season, and with any activity.

Building adequate defenses against the untoward consequences of heat requires careful analyses. It is not good enough, and it has never been, just to look at the thermometer, or form judgments about heat stress dangers to others based on one's own thermal comfort. Nor is it good enough to predict people's jeopardy based only on environmental measurements, no matter how precise and all-inclusive they are. Quantification of heat stress is valuable, but it does not predict an individual's peril. Heat stress is set by environmental circumstances, but heat strain, the cost to a person for remaining comfortable and safe, is what injures and kills. The only safe guideline for recognizing heat strain is that when people say they are hot, believe they are, no matter the exposure conditions or how comfortable others are. The responsibility is to examine each person's report of thermal discomfort and do whatever is necessary to protect them. No exceptions.

People vary greatly in their abilities to withstand heat stress. Infants, young children, some of the aged, and those in poor physical or mental health are particularly vulnerable. But most of us, most of the time, successfully balance personal and work circumstances to survive the heat and do whatever jobs we must in the face of it. Issues of obesity, general health, medication status, heat acclimatization, clothing, activity, and many other factors make it harder for some than for others. Many personal factors must be evaluated to understand each person's unique condition of heat strain in heat stress.

Despite wide variations in the way people cope with heat stress, there are some qualities of personal health that benefit us all. People are best prepared for the heat if they are in good health, have good physical fitness, are heat acclimatized, fully hydrated, and do not take medications, drugs or other agents that inhibit cardiovascular and sweating reflexes. They will then keep a large volume of blood circulating to distribute heat in the body, remove it quickly from exercising muscles, and deliver it to the skin for dissipation to the environment. They will also produce dilute sweat, at sweating rates precisely tuned to their need for evaporative heat loss. Benefits come from maintaining systemic arterial pressure, brain blood flow, full consciousness, and a sense of well-being, as well as from broadening safety margins when facing the heat.

Some environmental conditions are specially beneficial when we encounter heat. When we are indoors and there are no sources of high-intensity infrared radiation, exposing large areas of the skin to rapidly circulating, dry air promotes convective and evaporative heat loss. Within culturally defined limits, the less clothing, the better. It is different when thermal radiation is a major player in the heat stress game, as when we work out of doors in sunshine, or near hot machinery. Then, wearing a well-ventilated and lightweight hat and clothing that covers arms and legs, but still allows air circulation, creates effective barriers to infrared heat gain and places only limited restrictions on the body's ability to dissipate heat.

Because heat produced by muscle contraction can be a substantial contributor to overall heat stress, work and exercise in hot weather are best done when environmental heat stress is the least, most often in the morning and early evening. But it is an unobtainable luxury for most people to do the work they have to at the best times of the day. Most of us have to get on with whatever jobs we must,

no matter what extra stress it places on us. Still, it is possible to pace work periods, arrange frequent breaks, maintain hydration levels, and keep an eye out for the early warning signs and symptoms of heat strain.

Unsurvivable heat strain, like many of the other disasters that befall us, seldom comes unannounced. Few people, for example, find from the afternoon's mail that they are suddenly, without warning, bankrupt. More realistically, there is a long history of unpaid bills, an overdue mortgage, delinquent car payments, and growing credit charges. It is usually not a surprise when the end of financial solvency finally comes. Similarly with heat strain, if someone knows what to look for, there are many early signs that heat strain defenses are wearing thin, discomfort is growing, and heat-induced disabilities are on the way. Episodes of profuse, visible sweating, periods of fatigue, nausea, lightheadedness, postural instability, unexplained irritability, and many other signs and symptoms make themselves known before collapse from the heat.

Each of us has the responsibility to watch out for early indicators of heat strain in ourselves and also to look for them in others. No matter how comfortable we feel, periodic evaluations are necessary for our infants, our elderly, those who are physically or emotionally incapacitated, the socially isolated, and even for our pets. Accepting the idea that someone else might feel hot, even though we are cool ourselves, and that someone else might be cold, even though we feel hot ourselves, is a critical first step. Determining the unique basis for each person's distress and doing something about it is the important next step to minimize discomfort and prevent heat-induced illnesses and death.

Except for heat waves that seriously threaten everyone, there are few other circumstances when the able-bodied must cower in the protection of air conditioning. Given general good health and good judgment, we can usually do just about everything in the summer months that we normally enjoy or must do at other times of year. Getting out and working or exercising in the heat is, in fact, essential for acquiring heat acclimatization. Heat stress is not to be feared and avoided, but not knowing what to look for and what to do in heat strain is. As in successfully countering many other of life's challenges, heat stress is not dangerous as long as it is taken a little at a time and with adequate knowledge about ways to protect ourselves and others from its dangers.

Heat Stress

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Noise and Ultrasound
William W. Clark, Ph.D.

Introduction

Noise is America's most widespread nuisance. But excessive noise is more than just a nuisance. Day and night, at home or at work or play, excessive noise exposure annoys individuals, produces stress, impairs the ability to communicate, interferes with work and play activities, and, in high enough doses, produces permanent damage to the auditory system that can lead to significant hearing loss.

Although annoyance caused by noise affects all of us to some degree, this chapter describes the effects of excessive noise on hearing, and on the effects of ultrasonic stimulation on tissue. The chapter is organized in four sections. In the first, consideration is given to the physical characteristics of sound and the measurement of noise exposure. The second section considers the effects of excessive noise exposure within the range of human hearing, approximately 20 hertz (Hz) to 20 kilohertz (kHz). In the third section, a review of the effects of infrasonic exposure (<20 Hz) is provided. Finally, the last section reviews the effects of exposure to ultrasound (20 kHz to 20 MHz)

on humans.

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1 A World of Sound
What is sound? Acousticians define sound as “a particle disturbance in an elastic medium, which is propagated through the medium.” In order for a sound to occur, a medium must have density and elasticity. Although sound can occur in any medium with those characteristics, including most solids, liquids, and gases, we usually think about sound transmission in “our” medium, air. Air is composed of particles (air molecules) that have weight and elasticity. In fact, one cubic meter of air weighs about 1.3 kilograms (kg), and it is quite elastic, that is, it can easily be compressed into a volume much smaller than one cubic meter. This is a useful fact for scuba divers who can carry one hour's worth of breathing air (about 1500 liters) in a 20-L tank.

The information provided above allows us to answer one of the questions we all were asked in elementary school: If a tree falls in the forest and no one is there to hear it, does it make a sound? The answer, from an acoustic point of view is a resounding “Yes.” But audiologists, speech pathologists, teachers, and other professionals are concerned about the sense of hearing, that is, the perception of an acoustic event by a human listener. Adding a perceptual requirement to the definition then produces another definition: “Sound is a compression wave propagated through a medium that is capable of producing a sensation in the human ear” (1). Now, when the tree question is asked again, the answer is “No.”

The preceding discussion highlights an important distinction between two different ways of considering sound. Engineers and scientists are concerned with sound as an energy that can be measured and quantified; no consideration is usually given to whether the sound can be perceived by humans or not. However, hearing health professionals are usually concerned about the *effects* of sound on humans: what and how we hear, what sounds please us, what sounds annoy us, what sounds interfere with our ability to communicate with each other, and what sounds can be damaging to our hearing. These definitions are necessarily more complex than “simple” quantitative descriptions of acoustic energy, and often are expressed in perceptual terms, like “loudness” or “pitch.”

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2 Measurement of sound
A general description of a sound should include a description of *what* the sound is and *how much* of it is present. A *metathetic continuum* is used to describe the *what* quantity, and a *prothetic continuum* is used to describe the *how much* quantity. In acoustics and audiology, frequency of the sound is the metathetic variable, and the intensity or sound pressure level of the sound is the prothetic variable.

First, let us consider frequency. *Frequency* is defined as the number of periodic repetitions of a sound in one second, that is, the number of cycles per second of that sound. By convention, the term “hertz” (Hz) is used to label the frequency of a sound. A sound of 1000 Hz contains 1000 cycles in one second. Similarly, a sound of 20 Hz repeats 20 times per second. As the frequency of a sound changes from “low” to “high,” the perception associated with frequency (known as the *pitch*) also changes from “low” to “high.” Note that the perceptual attribute, the pitch, does not get *bigger* as the

frequency goes from low to high; it simply *changes* from one attribute, low pitch, to a different attribute, high pitch. This is what is meant by a metathetic continuum. The frequency of a sound is determined by the characteristics of the sound source. A tuba and a piccolo produce different frequency sounds because they differ in size.

The second dimension is the "how much" dimension. By this, we are referring to the amount of energy present in the sound, expressed commonly as its intensity. In acoustics, energy or *intensity* is defined as the acoustic power flowing through a unit of area, and the units of measurement are watts per meter squared (W/m^2). In practice, engineers usually measure the pressure variations produced by the acoustic power, and the units are newtons per meter squared (N/m^2), or other equivalent measures expressed in dynes or pascals. These units are metric equivalents to a unit more familiar to us: pounds per square inch. Therefore, the energy, or intensity continuum, is a prothetic continuum: As intensity increases, the perceptual attribute, the loudness of a sound also increases—it's not different, there is just more of it.

2.1 Frequency and Period

As mentioned, the frequency of a sound is the number of periodic oscillations per second, expressed in Hz. The *period* of a sound is defined as the amount of time required to complete one cycle, and is the reciprocal of the frequency:

$$F = 1/p, \quad \text{and} \quad p = 1/f$$

Therefore, the period of a 1000-Hz tone is 1 millisecond (0.001 sec), and the frequency of a tone whose period is 0.05 sec is 20 Hz.

2.2 Speed of Sound

Although the frequency of a sound is dependent upon the characteristics of the source, the *speed of sound* is dependent upon the characteristics of the medium, namely, the elasticity, density, and temperature of the medium. Sound travels faster in water than in air because water is denser and less compressible than air. The speed of sound is also faster at higher temperatures. In air, sound travels at approximately 340 m/sec (1125 ft/sec) at a temperature of 72°F (22°C). We understand from common experience that some amount of time is required for sound to reach our ears. From the outfield bleachers, the crack of the bat is heard after the batter is observed hitting the ball. And, traveling at about 1/5 mile per second, we hear the sound of distant thunder some time after seeing the flash of lightning, the number of seconds telling us how for away the lightning struck (5 sec = 1 mi). In water at a temperature of 0°C, sound travels at a speed of approximately 4700 f/sec, or about 4 times faster than in air.

2.3 Wavelength

Knowledge about the speed of sound allows us to calculate the other important variable of sound: its wavelength. Wavelength, abbreviated by the Greek symbol lambda, is the distance between two identical points on a periodic signal. It is equal to the speed divided by the frequency:

$$\lambda = c/f$$

At 340 m/sec, the wavelength of a 1000-Hz tone is:

$$\frac{340\,\text{m/sec}}{1000\,\text{Hz}} = 0.34\,\text{m/cycle} = 13.4\,\text{in./cycle}$$

Considering that a 1000-Hz tone has a wavelength of (about) 1 ft, wavelengths of other audible frequencies can easily be estimated by remembering that doubling the frequency causes the wavelength to decrease by half and halving the frequency increases the wavelength by a factor of 2. Using this rubric, the table (Table 99.1) can be constructed.

Table 99.1. Relation Between Frequency in Hertz and Wavelength

Frequency (Hz)	Wavelength (approx.)
125	8 ft
250	4 ft
500	2 ft
1000	1 ft
2000	6 in.
4000	3 in.
8000	1.5 in.

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3 Hearing sensitivity
3.1 Hearing Sensitivity: Frequency Domain
Humans cannot hear sounds of all frequencies. The range of human hearing extends from a low-frequency limit of about 20 Hz to a high-frequency limit of about 20 kilohertz (kHz) for excellent, young ears. Signals below 20 Hz are not perceived as sound, and sounds in this range are described as "infrasound." Sounds with frequencies above 20 kHz are also not perceived, and these sounds are called "ultrasound." Although ultrasonic signals are useful for cleaning jewelry, for producing fetal images, and for motion detectors, they cannot be perceived, and therefore are not sounds by Albers' definition. Descriptions of the biological effects of infrasonic and ultrasonic exposure are provided at the end of this chapter.
3.2 Intensity or Sound Pressure
The strength or power of a sound is described by its *intensity*, or the power per unit area the source imposes on the medium. A tuning fork, for example, does work as it vibrates and pushes air molecules back and forth. Each oscillation of the fork causes the air molecules next to it to be alternatively squeezed together and pulled apart. These "local pressure" disturbances are then propagated through the medium. Because it is much easier to measure pressure than intensity, sound level meters are designed to measure the atmospheric pressure variations caused by the sound, rather than the actual intensity of the sound.

The human ear is sensitive over a tremendous range of intensities. At threshold, a good, young, normal ear can detect an acoustic intensity of 10^{-12} W/m^2, a very small quantity indeed! That same young ear can be exposed to an intensity of 10^2 W/m^2 for a brief period without sustaining damage. The range from threshold to maximum tolerable level is called the dynamic range of the ear, and the ratio is 10^{14}:1, that is, 100 thousand billion to 1! The ratio of pressure variations (in air) for these intensities is 10^7 to one.

These large pressure variations can best be understood by an analogy. Imagine a very large eardrum, which moves back and forth 1 ft at threshold. How far would that eardrum move at the maximum tolerable level? When asked that question, most elementary school children respond with guesses of 100 to 500 ft; a few adventuresome souls may hazard a 1-mi estimate. However, the answer is 1894 miles! An eardrum in St. Louis that moves back and forth 1 ft at threshold, would move from St.

Louis to San Francisco to New York to St. Louis for a very loud sound.

Because these large ratios were difficult to deal with, scientists and engineers invented a shorthand method to describe the strength of sound: the *decibel scale* (dB). A complete description of the derivation of the decibel scale is beyond the scope of this chapter. However, decibels are commonly used to express the sound pressure level of a given sound, and the ratio of intensities, or pressures, of two sounds to each other. Three characteristics of the decibel scale are relevant to the discussion. These are:

1. The scale is logarithmic.
2. It requires a stated reference value.
3. "0" dB does not mean there is no sound; rather it means the measured quantity is equivalent to the reference value.

In hearing science, the decibel scale is referenced to the threshold of human hearing (10^{-12} W/m^2 for intensity and the equivalent pressure of 2×10^{-5} Pa), and the strength of sound is referred to as the "sound pressure level" (SPL) in decibels. The formulas for decibels are given below for informational purposes only.

$$\text{Intensity level}: \ \text{dB IL} = 10 \log_{10}(I_{\text{measured}}/I_{\text{reference}}), \text{where } I_{\text{reference}} = 10^{-12}\ \text{W/m}^2 \text{Sound pressure level} = \quad (1)$$

In decibels, then, the range of human hearing extends from 0 dB SPL to about 140 dB SPL.

A further complication of the decibel scale is that the measures as stated above give no consideration to whether a sound is audible to a human listener or not. An ultrasonic jewelry cleaner may produce 140 dB SPL at 30 kHz, but it would be inaudible. Therefore, a filter network was added to approximate the human response to sound at moderate intensities. This network is called the "A-weighted filter network," and sound pressure levels determined with the A-weighting network in place are noted as "sound pressure level, dBA."

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4 When is a sound a noise?
The definition of "noise" is actually rather complex. In acoustics, *noise* refers to any signal that is aperiodic. In engineering, "noise" usually means a signal that interferes with the quality or detection of another signal. In psychoacoustics, noise is usually defined as "unwanted sound." While this definition is probably the most useful for our purposes, even it can be problematic. Is rock music "noise"? The answer depends upon who is hearing it. Similarly, while a loud rattle coming from the engine of a car is most assuredly a "noise" to the owner, it may carry useful information to the mechanic whose job it is to repair the engine, and would not be considered "noise."

Noise also differs in the way it affects people. In low doses, noise can be soothing, and can be "wanted" sound. Patrons of libraries are less distracted by footsteps or page-turning when an air conditioner or ventilator produces a soft sound that masks the irregular noises. In moderate doses, noise *annoys* us. It makes communication difficult, affects task performance, increases blood pressure, and causes stress. In high doses, noise can cause permanent hearing losses.

Perhaps the most general, and most useful, definition of noise is the one proposed by Kryter (2):

Noise is an “acoustic signal which can negatively affect the physiological or psychological well-being of an individual.” This definition covers all the effects listed above. In this chapter we will limit our discussion to one aspect of annoyance caused by noise, interference with speech communication, and more generally to the risk of permanent hearing loss posed by excessive exposure to occupational or recreational noise.

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5 Speech communication in noise
Background noise affects the ability to communicate orally. A graph showing the relation between background noise level, talker to listener distance, and vocal effort required for effective speech communication is shown in Fig. 99.1.

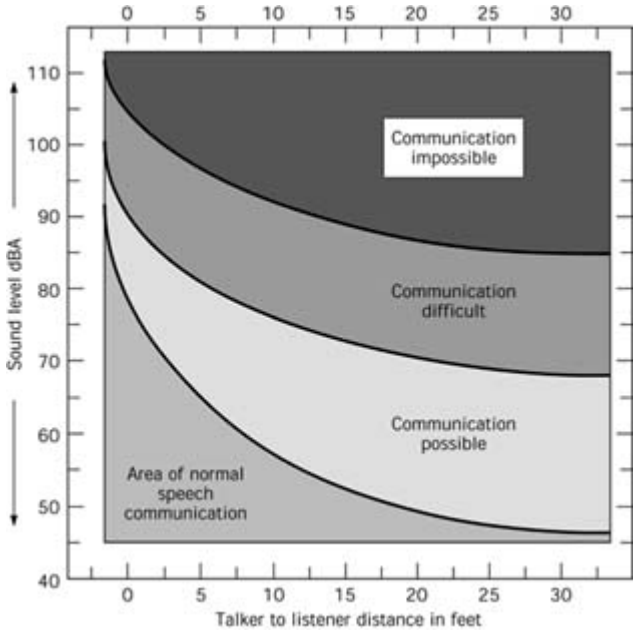

Figure 99.1. Speech communication as a function of background level and talker to listener distance in feet. Adapted from Ref. 3.

The vertical axis is the A-weighted sound level of background noise measured in decibels. The horizontal axis is the distance between the talker and listener in feet. The regions below the contours are those combinations of distance, background noise levels, and vocal outputs wherein speech communication is practical between young adults who speak similar dialects of American English. The line labeled “expected voice level” reflects the fact that the usual talker unconsciously raises his voice level when he is surrounded by noise.

Consider a situation where the background level is 50 dBA. Normal speech communication can occur at talker-to-listener distances of about 20 ft, at distances greater than 20 ft communication is still possible, but it is necessary to raise one's voice level. In a background level of 60 dBA, the normal communication range is reduced to about 8 ft; at greater distances communication is possible, but only with increased vocal effort. For higher background levels, for example, 80 dBA, it is necessary to shout at distances greater than 5 ft, and communication is difficult. In many industrial settings the background noise level is at or above 80 dBA; in these settings communication is difficult for distances greater than 5 ft without shouting, and, for levels above 90 dBA,

communication is impossible at distances greater than 10–15 ft. Clearly, speech communication is difficult or impossible for individuals who must work or choose to play in environments where the background noise levels are above 80 dBA.

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6 How does excessive noise affect hearing?
6.1 Mechanisms of Noise-Induced Hearing Loss
The ear is injured by noise in two very different ways, depending upon the level of the exposure. If the ear is exposed to a very high-level, short-duration exposure in which the peak sound pressure level exceeds 140 dB SPL, the acoustic energy in the signal can stretch the delicate inner ear tissues beyond their elastic limits, and rip or tear them apart. This type of damage is called *acoustic trauma*; it occurs instantaneously and results in an immediate hearing loss that is usually permanent. The organ of Corti becomes detached from the basilar membrane, deteriorates, and is replaced by a single layer of scar tissue that re-establishes the integrity of the fluid compartments of the inner ear. The hearing loss is often accompanied by tinnitus, a sensation of ringing in the ears, which usually (but not always) subsides within a few hours or days after the exposure.

Because the ear is damaged mechanically by impulsive sounds, it matters little what the duration of the signal is; the important variable is the peak sound pressure level. Noises in the environment capable of producing acoustic trauma usually come from explosive events: a firecracker detonating near the head (170 dB SPL), a toy cap gun fired near the ear (155 dB SPL), or the report of a pistol, high-powered rifle, or shotgun (160–170 dB SPL).

Exposures to noise between 90 and 140 dBA damage the cochlea metabolically rather than mechanically. In this case, the potential for damage and hearing loss depends on the levels and the duration of exposure. This type of injury is called *noise-induced hearing loss* (NIHL) and, in contrast to acoustic trauma, it is cumulative and insidious, growing slowly over years of exposure. Noise-induced hearing loss, commonly associated with workplace noise but in reality caused by any exposure that exceeds a daily average of 90 dBA regularly over a period of years, proceeds in three stages.

In the first stage, sensory cells are killed by excessive exposure to noise. The cells do not regenerate, but are replaced by scar tissue. The losses are cumulative and insidious, and do not elevate thresholds for pure-tone signals. In fact, up to 50% of the outer hair cells in the apical turn of the cochlea can be killed without elevating thresholds for low-frequency pure tones.

In the second stage, which starts after a few weeks, to a few years of exposure, depending upon the level, beginning hearing losses can be detected audiometrically. However, these losses occur in the frequency region around 4 kHz. Because these losses do not affect speech understanding significantly, they are seldom detected unless the hearing is tested for some other reason (i.e., annual audiometry in a hearing conservation program).

Finally, with continued exposure for decades, losses continue to accumulate at 4 kHz, although at a slower rate than in the first decade, and they spread to the lower frequencies, which are important for speech understanding. It is at this point the patient becomes aware of a problem that has been progressing for decades. If the diagnosis is noise-induced hearing loss, the recommendation made by the physician or audiologist is to avoid excessive exposure to noise and to wear hearing protection around necessary exposures. Of course, by the time this recommendation is made, much of the damage has already been done.

Photomicrographs of a normal inner ear and one permanently damaged by noise exposure are shown in Figs. 99.2 and 99.3.

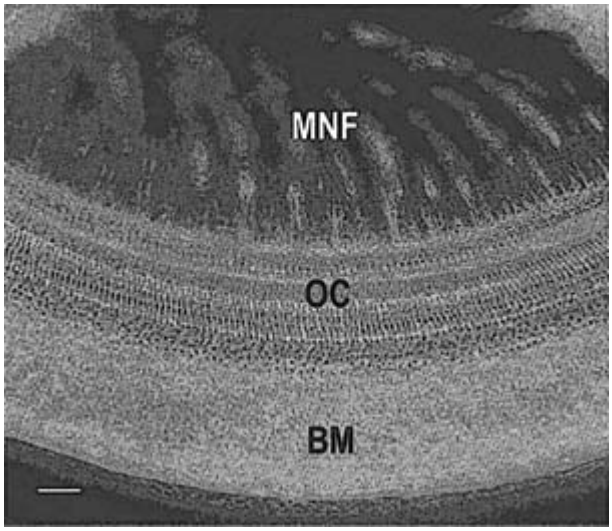

Figure 99.2. A microscopic view of the hearing portion of the inner ear, the organ of Corti (OC), which rests on a thin, elastic membrane called the basilar membrane (BM). Nerve fibers (MNF) in the inner ear are in contact with sensory cells in the organ of Corti. There are large fluid spaces in the inner ear that surround the organ of Corti and basilar membrane. The inner ear is stimulated when sound waves strike the eardrum, causing it to vibrate. Movement of the eardrum is transmitted to the fluids of the inner ear. Waves in the inner ear fluids cause the basilar membrane and organ of Corti to vibrate in a frequency-specific manner. Motion of the basilar membrane stimulates the sensory cells in the organ of Corti, which then stimulate the adjacent nerve fibers. These nerve fibers transmit electrical signals to the brain, where the auditory sounds are interpreted. (Bar equals 50 mm.) Courtesy of B.A. Bohne.

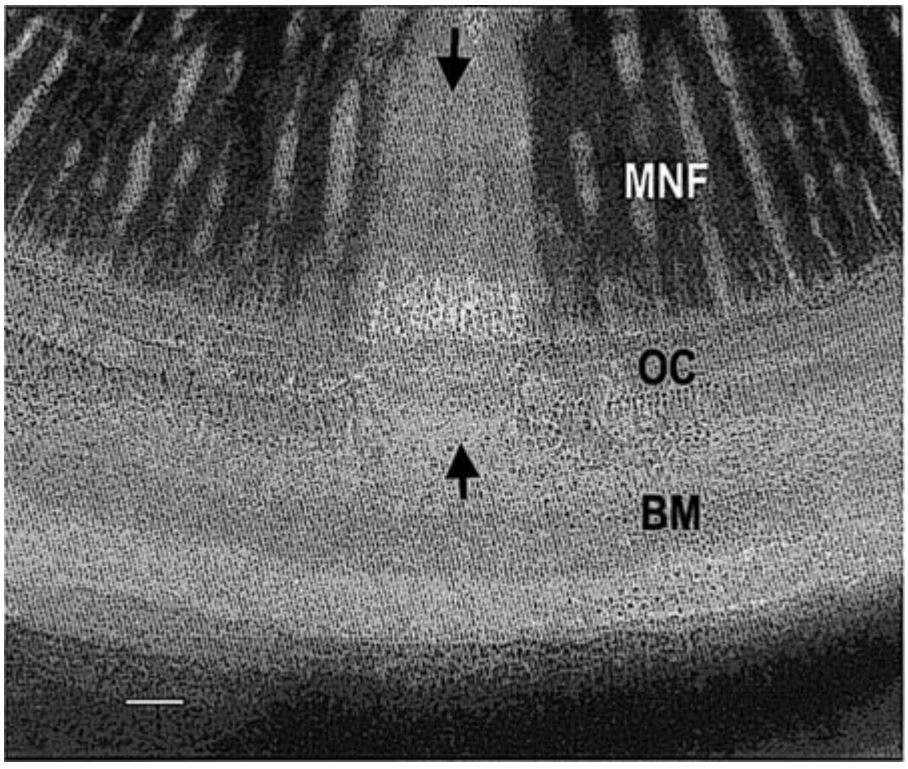

Figure 99.3. A microscopic view of an inner ear that was permanently damaged by too much noise. In the center, the up arrow points to an area of the organ of Corti (OC), which has disappeared

following the exposure. The nerve fibers (MNF) that were originally in contact with the sensory cells in the missing portion of the organ of Corti have also been permanently destroyed (down arrow). Although the basilar membrane (BM) remains intact at this location, no sensory cells are left to be stimulated, and no nerve fibers are left to carry auditory information to the brain. Thus individuals with this damage would have a mild permanent hearing loss. When this type of damage covers a broader area on the basilar membrane, the individual's hearing loss is more severe and it may affect his/her ability to communicate. (Bar equals 50 mm). Courtesy of B.A. Bohne.

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7 How much noise is too much?
If the ear of an individual is exposed to noise of sufficient strength, and/or of sufficient duration, a sensorineural hearing loss can occur. As stated, the hazard associated with a particular noise exposure depends not only upon the strength or level of the sound, but also its spectral characteristics, its temporal pattern, the number or repetitions, and the duration of the exposure. Further complicating the attempt to provide a simple descriptor for hearing hazard is the fact that individuals vary widely in their susceptibility to noise exposure; it is not possible to specify an exposure limit that is guaranteed to protect everyone. An additional complication is that because the effects of noise often go unnoticed by the patient, precise exposure histories are nearly impossible to obtain.

One way of thinking about the hazard to hearing from sound exposure is to consider the dynamic range of the human ear. This range is shown in Fig. 99.4. The bottom curve on the graph represents auditory sensitivity for young, normal human ears. Signals presented at levels below the bottom graph are inaudible, and obviously pose no risk of producing a hearing loss. At the other extreme is the threshold of pain, about 140 dB SPL. Sounds presented in excess of the pain threshold could present a risk of noise-induced hearing loss for just one short exposure; however, a precise estimate of the threshold for injury from a single brief exposure cannot be made at this time (4). Although considerable evidence suggests the ear can be injured by impulsive sounds with peak levels above 160 dB SPL (4, 5), several studies have failed to document permanent injuries for brief continuous exposures at levels of up to 140 dB SPL (6–8). The Federal noise standard, OSHA 1910.95 (9), prohibits single exposures above 140 dBA. In light of the scientific evidence, this exposure limit is reasonable.

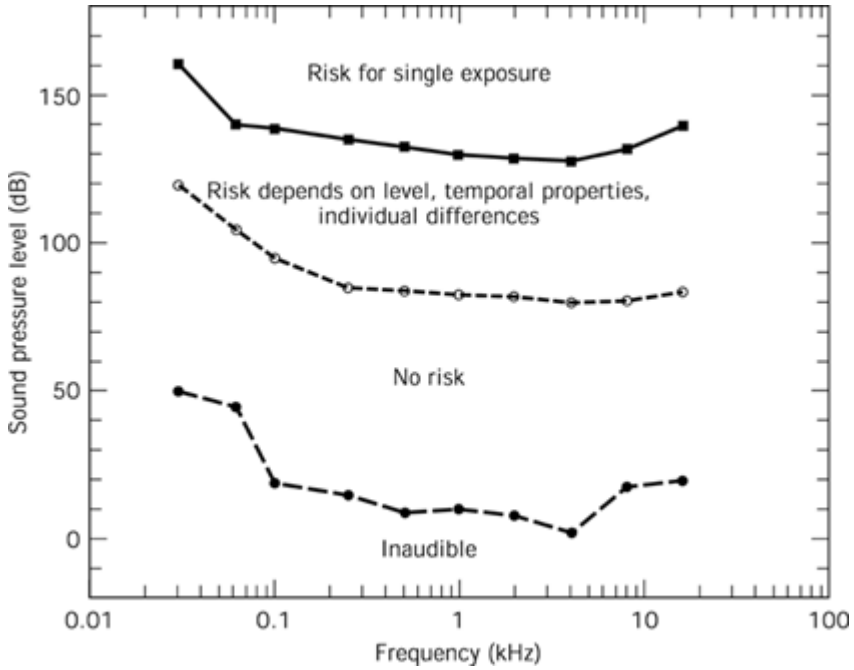

Figure 99.4. Categorization of the range of human hearing with respect to the risk of hearing loss. Closed circles = audibility; open circles, risk of TTS; closed squares, permanent injury. Adapted from Ref. 6.

Between the extremes of the threshold of pain and the threshold of audibility are two categories: risk and no risk. The “no risk” category can be called “effective quiet” or safe levels of exposure. Exposures in this range present no risk of acoustic injury, regardless of the duration of the exposure, the number of exposures, or the temporal spacing of the exposures. The “no risk” category is bounded on the upper side by levels that will not produce a measurable temporary threshold shift (TTS). These levels are also consistent with exposure limits specified by the relatively new American National Standard, ANSI S3.44 (10). At 4.0 kHz, the frequency most affected by noise, ANSI S3.44 specifies a level of 75 dB SPL as the lower limit of permanent threshold shift (PTS). That is, exposure centered at 4.0 kHz for nearly a lifetime (8 h/d) will produce no PTS in any percentile of the population. Figure 99.4 suggests a value of 74 dB SPL at 4 kHz. At 2 kHz ANSI specifies a value of 80 dB, whereas Fig. 99.4 suggests 78 dB. Thus, for noise with energy in the 2–4 kHz region, the correspondence between ANSI S 3.44 and laboratory experiments of TTS is excellent. At lower frequencies the risk estimates in Fig. 99.4 are more conservative than those promulgated by ANSI. However, it should be noted that the ANSI data predict the threshold for permanent hearing loss, and the Committee on Hearing, Bioacoustics, and Biomechanics (CHABA) data predict the threshold for temporary hearing loss.

When the ear is exposed continuously between 80 and 140 dBA for long periods, permanent hearing losses can occur. These exposures occur commonly in the workplace and in the leisure environment.

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8 Measurement of Noise exposure
Noise exposure associated with the workplace has been known to produce hearing loss for centuries. In fact, “boilermakers' deafness” was the term coined to describe the now familiar bilateral sensorineural hearing loss associated with excessive exposure to occupational noise. Largely on the

basis of knowledge gained through field studies of hearing loss in industrial workers and military personnel, the U.S. Department of Labor promulgated regulations in the 1970s and 1980s designed to protect the hearing of employees who work in noisy environments (9). The regulations specified that employees be protected against the hazardous effects of noise when daily sound levels exceed those listed in Table 99.2

Table 99.2. OSHA Maximum Daily Noise Exposure Limit[a]

Duration Per Day (h)	Sound Level (dBA)
16	85
8	90
6	92
4	95
3	97
2	100
1.5	102
1	105
1/2	110
1/4 or less	115

[a] Source: Adapted from Table G-16a of Ref. 9

The levels stated in the table represent the maximum allowable daily noise exposure, or the "permissible exposure limit" (PEL), as specified by OSHA and other federal agencies. The PEL for an 8-h exposure is referred to as the "criterion;" it reflects the sound level in dBA, which reaches the PEL after 8 h of exposure. Note that for exposure, that differ from 8 h, the allowable daily exposure level is increased or decreased by 5 dB for each halving or doubling of exposure duration. Ninety decibels is allowed for 8 h daily, 95 dB for 4 h daily, etc. Each of the exposures listed in the table represents an equivalent "time-weighted average" (TWA) exposure of 90 dBA for 8 h. By definition an 8-h TWA of 90 dB represents 100% of the allowable "dose."

When the daily noise exposure is composed of two or more periods of exposure at different levels, their effects are combined by the following rule:

$$C_1/T_1 + C_2/T_2 + \cdots + C_n/T_n$$

where C is the exposure duration at a given level; and T the allowable duration at that level.

"Percent allowable dose" is then calculated by multiplying the result by 100%. That is,

$$D = 100(C_1/T_1 + C_2/T_2 + \cdots + C_n/T_n)$$

All exposures between 80 and 130 dBA are required to be integrated into the dose calculation. Exposures below the so-called "threshold" are not counted in the calculation of daily exposure; threshold values range from 80 to 90 dBA among various regulations. For example, consider the following daily noise exposure for a sheet metal worker:

Activity	Level (dBA)	Duration (h)
Grinding	92	2.0
Buffing	85	2.5
Cutting	100	0.5
Packaging	75	2.0
Lunch, breaks	79	1.0

Calculation of Daily Dose is made as:

Activity	C/T	Dose (%)
Grinding	2/6	33
Buffing	2.5/16	16
Cutting	0.5/2	25
Packaging	2/ infinity	0
Lunch, breaks	1/ infinity	0
Total	0.74	74

Therefore, this employee's exposure would not exceed OSHA's PEL. The dose could also be expressed as a TWA level in decibels by calculating the 8-h exposure level that would result in the same dose:

$$\text{TWA} = 16.61 \log_{10}(\text{dose}/100) + 90$$

or 87.8 dBA. It is important to remember that “dose” and “TWA” really refer to the same measurement: the 8-h equivalent exposure for any measured duration or combination of levels and durations, expressed as percent or decibels.

As amended in 1983, the current U.S. occupational noise exposure standard identifies a TWA of 85 dBA, or 50% dose, as an “action level.” Workers covered by the standard who are exposed above the action level must be provided an effective hearing conservation program, including annual audiometric evaluations, personal hearing protection if desired, and education programs. With a daily noise exposure of 74%, or a TWA above 85 dBA, the sheet metal worker described should be in a company hearing conservation program.

The exposure limits set by OSHA were empirically determined from epidemiological and laboratory data concerning hearing damage from noise exposure and were designed to protect employees against sustaining a material impairment in hearing after a working lifetime. They were derived by subtracting the percent of workers sustaining a material impairment in hearing as a function of exposure level from a control population without occupational exposure. The resultant percentage is the “percent risk” or “percent additional risk” of a material impairment in hearing after, say, 40 yr of exposure, above that expected from presbycusis and sociocusis alone. Estimates of percent risk vary depending upon which criteria and databases are used; on the basis of evaluation of all the data, it can be concluded that the PEL of 90 dBA, with the 85 dBA action level, if enforced, would protect

virtually the entire working population from occupational noise-induced hearing loss.

The OSHA noise standards are useful to the physician in arriving at a diagnosis, and for the audiologist in determining whether a recommendation about hearing protection should be made. First, because workers exposed to excessive occupational noise should be in a hearing conservation program, evidence of exposure history and prior company-obtained audiograms may be available for consideration. If the worker is not in a hearing conservation program, he or she may not work in significant occupational noise. Unfortunately, because not all workers are covered by OSHA standards and because enforcement has been weak, lack of participation in a hearing conservation program by a worker does not guarantee he or she has not been exposed to excessive occupational noise. However, in evaluating a patient, if it is determined that exposure to occupational noise did not exceed a TWA of 85 dBA, or a dose of 50%, then exposure to occupational noise should be ruled out of the etiology.

The American Conference of Government Industrial Hygienists has also listed guidelines for occupational exposure to noise (11). These limits are specified as “threshold limit values” (TLVs), and they differ from the OSHA standards in several important ways. First, they specify the criterion level as a daily exposure of 85 dBA, rather than the 90-dBA TWA specified by OSHA. Second, an exchange rate of 3 dB is used rather than the 5-dB exchange rate employed by OSHA. These two differences make the ACGIH TLV more conservative than the OSHA PEL for most exposures, particularly when the exposure level fluctuates during the work shift. However, the TLV is specified by ACGIH as the minimum exposure at which one should consider implementing a hearing conservation program; it does no imply an upper limit of tolerable exposure. Viewed in this way, there is no conflict between the ACGIH TLV and the OSHA PEL.

Exposure Assessment

Two general types of exposure assessment are commonly used in industry: area noise surveys and personal noise dosimetry. Area surveys are used to identify job locations where the TWA exposure may exceed 85 dBA; they are conducted by placing a sound level meter in a specific location and sampling the noise field. Exposures are then calculated based upon the amount of time an employee works in that specific location. Area surveys are also useful in determining the sources of exposure in an industrial environment and for planning noise control engineering strategies for reducing exposure.

Occupational exposures can be measured directly by using personal noise dosimeters. These devices are small, computerized integrating sound level meters that can record the minute-by-minute sound exposure throughout the workday. They are worn on a belt or in a pocket, and the microphone is positioned on the shoulder, approximately 5 in. lateral to the ear. Technological advances in microprocessor design, incorporating low power consumption and component miniaturization, have led to sophisticated, small, lightweight dosimeters that can be worn unobtrusively. A distinct advantage to using dosimetry over other methods is that the measurement instrument travels with the worker and can therefore provide a more accurate assessment of exposure as he or she moves among different noise environments during the work day.

Exposure assessment using dosimetry does have some disadvantages. Because the instrument is mounted on the shoulder, reflection of sound off the body adds about 2 dB to the exposure assessment. In addition, it is nearly impossible to prevent bumping or touching the surface of the microphone during a normal workday. Contact with the microphone, even with a windscreen in place, will always increase the dose measure, and for short-duration, high-level impacts, the exposure can be inflated dramatically. Finally, because the dosimeter travels with the worker rather than staying under the control of the professional assessing the exposure, errors of commission and omission can occur. For example, a dosimeter attached to a jacket, which is then deposited in a locker before the workshift begins, will record the exposure of the jacket, rather than that of the worker.

9 Types of occupational noise exposure
According to a report published by the EPA in 1981, there are more then 9 million Americans exposed to daily average noise levels above 85 dBA. The breakdown is shown in Table 99.3.

Table 99.3. Workers Exposed to Average Daily Noise Levels in Excess of 85 dBA by Employment Area[a]

Agriculture	323,000
Mining	400,000
Construction	513,000
Manufacturing and utilities	5,124,000
Transportation	1,934,000
Military	976,000
Total	9,270,000

[a] From Ref. 12.

These numbers are undoubtedly outdated, but no more recent estimates are available. Although improvements in hearing conservation programs, advances in noise control engineering technology, and downsizing in major industries have undoubtedly reduced the numbers of individuals exposed to excessive noise, it is still safe to conclude that occupational noise exposure is a factor in causing hearing loss for millions of American workers.

It is impossible to specify precisely all particular job descriptions for which excessive exposure is a risk. However, as shown in Table 99.4, the textile industry, processing lumber and wood products, the food industry, and metal manufacturing industries employ large numbers of workers, a large percentage of whom work in noisy environments.

Table 99.4. Estimate of Production Workers Exposure to a TWA of 85 dB and Above[a]

Industry	Thousands of Workers Exposed to Over 85 dBA	Percentage of Workers Exposed to Over 85 dBA
Food and kindred products	820	70%
Tobacco manufacturers	48	76%
Textile mill products	855	95%
Apparel and related products	12	1%
Lumber and wood products	542	100%
Furniture and	236.6	55%

fixtures		
Paper and allied products	395	71%
Printing and publishing	132	20%
Chemicals and allied products	137	23%
Petroleum and coal products	58	50%
Rubber and plastics products	266	50%
Leather and leather products	3	1%
Stone, clay, and glass products	416	75%
Primary metals		
Primary steel	325	67%
Foundries	189	70%
Primary nonferrous	63	27%
Fabricated metal products	786	70%
Machinery, except electric	956	70%
Electrical machinery	959	70%
Transportation equipment	880	65%
Utilities	445	71%
Total	6524	59.3%

[a] From Ref. 13.

As effective as the federal regulations may be, if enforced, at protecting hearing in the workplace, they fail to consider hearing loss produced by noise exposure outside the workplace, and recent evidence suggests that these exposures are potentially hazardous for millions of Americans.

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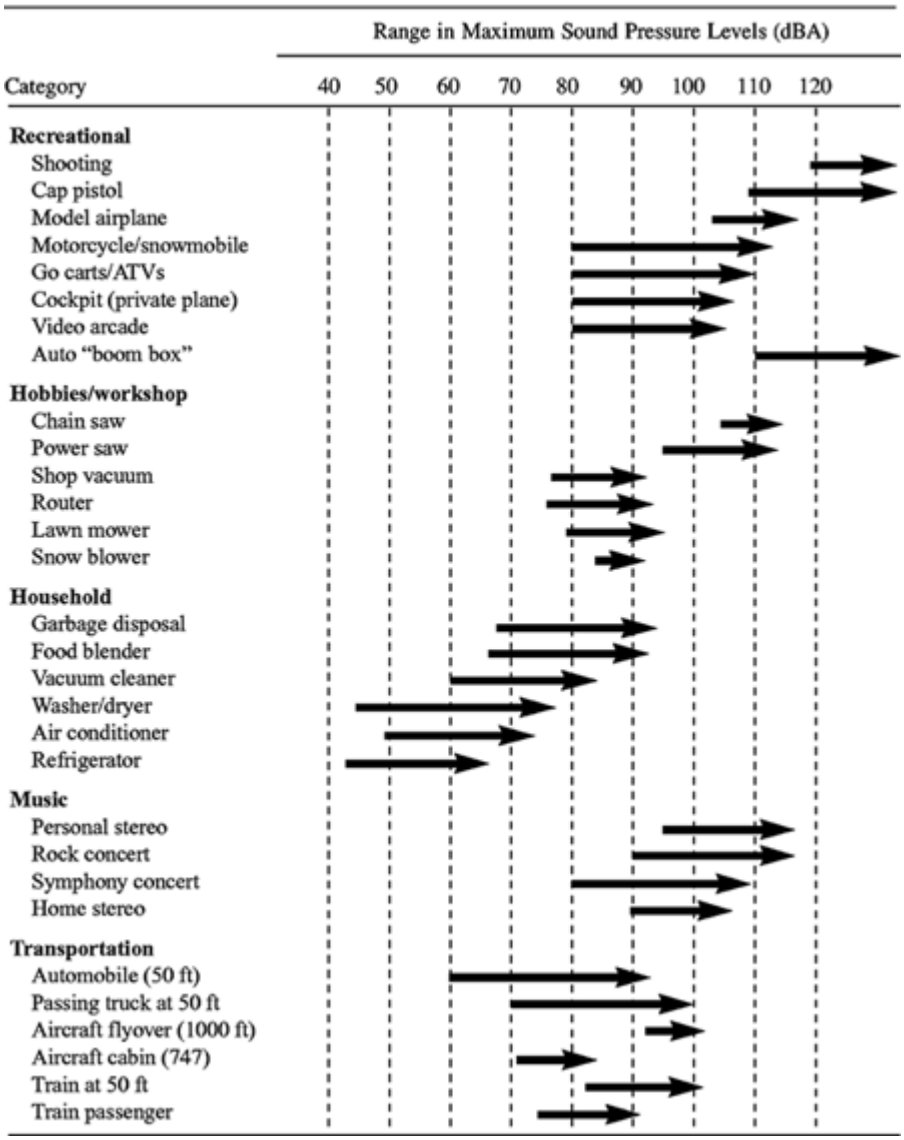
10 Types of nonoccupational exposure

There are numerous sources of noise in the environment that have the potential to produce noise-induced hearing loss. The types of exposure sources span the recreational preferences of Americans. Evidence has been mounting over the past two decades that there are sources of noise exposure outside the workplace that are potentially damaging. Precisely what the effects of these exposures are on an eventual noise-induced hearing loss has been the topic of many studies. Obviously, implicit in the assessment of the role of nonoccupational or recreational noise on NIHL is a determination not only of the level of exposure possible, but also some information about the typical exposure level

and pattern for groups of listeners.

A partial list of significant sources and maximum levels of nonoccupational noise is given in Table 99.5, which was used to demonstrate typical sound levels. If one considers a reading of >90 dBA as the borderline between "safe" and "dangerous" noise exposure, it is seen that nearly everything on the list, with the exception of household items such as refrigerators, falls in the "dangerous" category. Information about maximum levels does not, in and of itself, indicate a dangerous noise exposure (unless the continuous level exceeds 140 dB SPL); the hazards from exposure to noise from any device listed depend on the level and the duration of exposure for a typical consumer of that noise.

Table 99.5. Maximum Sound Pressure Levels for Common Sources of Nonoccupational Noises[a]



[a] Adapted from Ref. 14.

This report will be limited to an assessment of the effects of the two major sources of noise in the leisure environment: the discharge of firearms during hunting and target-shooting activities, and listening to music, either at concerts or through personal stereos.

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11 Hunting and target shooting
It is well known that individuals exposed to gunfire may sustain hearing loss associated with these exposures. Reported peak sound levels from rifles and shotguns have ranged from 132 dBA for .22 caliber rifles to more than 172 dBA for high-powered rifles and shotguns. Clinical reports documenting hearing loss after exposure to shooting can be found in the literature since the 1800s (15).

Numerous studies have attempted to assess the prevalence of hunting or target shooting in the general population. On the basis of these surveys it is estimated that more than 50% of men in the American industrial workforce fire guns at least occasionally. The National Rifle Association estimates that 70 million Americans own guns, and 20 million purchase hunting licenses each year (16). The severity of injury produced by impulsive noise exposure and the prevalence of shooting by Americans make gun noise America's most serious nonoccupational noise hazard.

Because of the logarithmic nature of the decibel scale, it is difficult to grasp how much acoustic energy is in a single gunshot. Consider the following example. An individual is exposed to a single report of a high-powered rifle at 165 dB SPL and a duration of 0.003 sec. How long would that individual have to work in an occupational noise environment in which the sound level was 90 dBA until the acoustic energy received was equal to the gunshot? The answer is almost a full work week of 8-h work days. In other words, one bullet equals 1 wk of hazardous occupational noise exposure. Because shells are often packaged in boxes of 50, shooting one box of shells is equivalent to working in a 90 dBA environment for a full year! An avid target shooter can produce an entire year's worth of hazardous occupational exposure in just a few minutes on the target range.

One method of determining the role of shooting on hearing loss is to compare audiometric data in groups of individuals who engage in shooting with a matched group who do not. Variations of such an approach have been reported in a number of studies. Virtually all of them show significant effects on hearing produced by gunfire noise, with the ear contralateral to the firearm exhibiting thresholds worse than the ipsilateral ear by about 15 dB for high-frequency (3–8-kHz) stimuli, and up to 30 dB for avid shooters.

Because shooting is so prevalent in our culture, it is the most important source of excessive noise outside the workplace. However, there are other significant nonoccupational sources of excessive noise exposure.

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12 Listening to amplified music
Rock Concerts
There is a large body of research published within the past two decades that detail exposures to individuals attending rock concerts and noisy discotheques. An analysis of all the data indicated the geometric mean of all published sound levels from rock concerts was 103.4 dBA (5). In general, it is reasonable to conclude that attendees at rock concerts or noisy discotheques are routinely exposed to sound levels above 100 dBA. Studies of temporary threshold shift (TTS) after exposure to rock

music have most often considered only the hearing levels of performers; a few studies have shown TTSs in listeners attending rock concerts. Generally, these studies show that most listeners sustain moderate TTSs (up to 30 dB at 4 kHz), which recover within a few hours to a few days after the exposure. The risk of sustaining a permanent hearing loss from attending rock concerts is small, and is limited to those who frequently attend such events. However, attendance at rock concerts remains an important contributor to cumulative noise dose for many Americans.

Personal Stereos

Increased use and availability of personal listening devices, such as the Sony Walkman, has led to general concern about potentially hazardous exposures, particularly for younger listeners. The question of whether listening to music through headphones may cause hearing loss depends on, among other things, the volume level selected by the listener, the amount of time spent listening, the pattern of listening behavior, the susceptibility of the individual's ear to noise damage, and other noisy activities that will contribute to the individual's lifetime dose of noise.

Although several studies have suggested that personal stereos are capable of producing exposures above 120 dBA, analysis of listening habits suggests that most users of personal stereos listen at volume levels that do not pose a risk of hearing loss. Fewer than 5% of users select volume levels and listen frequently enough to risk any hearing loss whatsoever.

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13 The keys to prevention and management

With so many diverse sources of excessive noise exposure in our work and play environments, identifying strategies to prevent hazardous exposures, to protect the hearing of individuals who must or choose to be exposed, and to offer methods of rehabilitation for those who must communicate in a noisy environment or who must cope with a noise-induced hearing loss, is a daunting task. However, it should be remembered that, unlike other diseases or injuries, noise-induced hearing loss is preventable. It can be avoided by reducing excessive exposure, or by protecting our ears during exposure.

If it is that easy, then why do so many people have noise-induced hearing loss? The answer lies in the insidious way in which noise-induced hearing loss creeps up on its victims. By the time enough damage has accumulated to produce a functional impairment, it is far too late to prevent the loss. Add to that the fact that protecting hearing is not generally considered a “macho” thing to do and that exposure to some loud noises can be exciting, and one has all the ingredients for a noise-induced hearing loss. It has been stated that prevention of excessive noise exposure would be more easily accomplished if the ear would bleed after a rock concert or an afternoon of shooting. What is needed is an approach that informs the patient about the potential for noise to cause a hearing loss before it is too late.

Key 1 Education

Whether in the workplace or at home, the key to prevention is education. Several national professional associations have been working to provide educational curricula about hazardous noise for elementary and secondary school children. These curricula are designed for use by science or health teachers to train “healthy hearing habits” for young ears, before the damage begins to accrue. Axelsson and Clark (17) have suggested schools invite “hearing professionals” to augment the curriculum with real-life experiences to help get the message across to children. Of course, professionals involved in aural rehabilitation would be ideal candidates for such a position.

Federal law requires regular education programs for employees exposed to potentially hazardous noise. However, these programs are only required to consider workplace noise, and they are often only given to employees in high-noise environments. However, since the ear does not know the

difference between an occupational and a recreational exposure to hazardous noise, education programs should be provided to all employees, and the emphasis should be placed on global hearing health and not restricted to job-related exposures.

Key 2 Prevention of Exposure

The second key is to prevent excessive exposure to noise. In the workplace, emphasis on engineering control of noise emission has reduced occupational exposures for many kinds of jobs. For example, lightweight fiber materials have replaced sheet metal in several manufacturing operations, and glues are now used to bond airplane wings, rather than the noisy rivets used in prior decades.

Administrative controls can also reduce employee exposure. An example of an administrative control is to assign workers to noisy jobs only part of the workday, and to quiet areas for the rest. By careful placing of individuals, exposures can be reduced, even though the noise in the plant is not.

Administrative and engineering controls can also be employed in the home. One can avoid excessive exposure to unwanted noise, and become a judicious consumer of wanted noise. Are rock concerts your fancy? By all means, enjoy them, but limit attendance to the special concerts you really like. And don't participate in other noisy activities on the day you attend the concert (mow the lawn another day).

Key 3 Wear Hearing Protection

In situations where the noise cannot be eliminated, hearing protectors should be worn. The two most commonly used protectors are earplugs or muffs. Earplugs come in a variety of styles and sizes. Recommended are the foam-type plugs, which are squeezed gently between the thumb and forefinger, and inserted into the external ear canal. The foam then expands and forms a seal. Other types of earplugs are made of plastic or silicone, and some are custom-fit for the user. The advantages of earplugs are their small size, comfort, and the fact that they are disposable. However, some individuals find the plug and the resulting occlusion of the ear canal uncomfortable.

The other type of hearing protector is a muff that fits over the ear. The advantage of this type of protection is that it is heavier and often provides a little better attenuation than the smaller earplug. Muffs are also reusable, and when kept in good condition can be considerably cheaper than disposable earplugs. In occupational environments it is easier to see that a worker is wearing a muff than a plug. A disadvantage of the muff-type protector is that a seal must be made between the earmuff cushion and the side of the head; any break in the seal renders the muff useless. Individuals who wear eyeglasses have a difficult time wearing the muffs because the temple piece of the eyeglass interferes with the seal.

In home environments, it is recommended that individuals wear hearing protection anytime they are exposed to loud, unnecessary sound. The type of plug or muff selected is of secondary importance. There is an adage in hearing conservation that says: “The most effective hearing protective device is one that is worn.” Comfort is of utmost importance. Most individuals will find the foam plugs the protector of choice. They are cheap, comfortable, disposable, and readily available at hardware and drug stores.

All hearing protectors are sold with a listing of the “noise reduction rating” (NRR). This rating refers to the decibel attenuation of the muff observed under laboratory test conditions, and varies from about 15 to 35 among various plugs or muffs. Although the NRR is useful for comparing among hearing protectors, it does not describe the actual attenuation one would expect in practice. In fact, studies have shown that muffs or plugs with NRRs of 25–30 actually only provide about 10 dB of protection when fit by the workers in actual working environments. But, as a matter of fact, most industrial and many environmental noise sources are in the 85–95 dBA range. In these environments, it is only necessary to reduce the level to below 85 dBA to make the environment safe, even for a working lifetime. Therefore, hearing protectors with attenuations of greater than 10 dB are not needed, and if they are used, they present additional problems for the user.

An individual working or playing in a 90-dB environment and wearing a hearing protector that

provides 25 dB of attenuation will have difficulty understanding speech while he is wearing the protectors. Many workers fear they will not hear warning shouts from co-workers if they wear hearing protection, and for the worker using a protector with more than the necessary attenuation, this is a valid concern. In this scenario, it is far better to recommend a hearing protector with more modest attenuation rating, and speech understanding will be preserved.

Special types of hearing protectors have been developed for special situations. One type, the "musician's" earplug, is specially developed to provide a flat attenuation. Unlike the traditional plug, which makes speech or music sound muffled, the "musician's" plug provide a much more realistic sound to the user, and, although they are expensive, are preferred by musicians and others who desire a more realistic quality to their auditory perception.

Another type of earmuff incorporated a microphone and amplifier into its design. Sometimes called the "hunter's earmuff," these protectors attenuate high-level sounds, like the report of a shotgun, but amplify low-level sounds, like the snapping of a twig by prey. They are particularly useful in environments characterized by high-level, impulsive sounds.

Finally, the field of active noise cancellation (ANC) technology has reached the hearing protector market, and several protectors are now commercially available that incorporate ANC. First developed by the military for use in tanks, ANC utilizes a very fast computer that samples the noise and generates a "mirror image" of it, which is then played along with the source noise, thus cancelling it. Although the field is still in its infancy, ANC is an effective means to cancel low-frequency noise, and hearing protectors using it generate an extra 5–10 dB of attenuation in the low frequencies, reducing the masking of speech considerably. Hearing protectors incorporating ANC are expensive (about $300), but look for the price to drop rapidly as the technology advances.

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14 Biological Effects of Infrasound

Infrasound is usually considered to include the acoustic frequency range from 0.1 to 20 Hz (18). This range is below the range of human auditory sensitivity, although individuals can perceive high-level signals lower than 20 Hz as pressure fluctuations. Although there are studies showing hazardous effects of intense infrasonic exposure in animal subjects, only one study appears to document permanent hearing loss in humans. In that study, Tonndorf (19) described scarring in the tympanic membranes of German submariners assigned to snorkel submarines.

Hazardous exposures to infrasound appear to be limited to exposures that produce levels of greater than 130 dB SPL at the ear. In humans, these exposures are usually transient or of short duration. A partial list of exposures from natural or manmade activities is included in Table 99.6.

Table 99.6. Sources of Infrasound Found in Nature and in Man-Made Activities[a]

Source	Predominant Frequency (Hz)	Est. Max. SPL (dB)
Natural		
Thunder		
Earthquake		

Ocean waves	<1	
Wind (100 km/h)	<1	135
Manmade		
Sonic booms	1–20	120–160
Jet engines	1–20	135
Helicopters	1–20	115
Large rockets	1–20	150
Diesel engines	10–20	110
Air bags	10–20	170
Door slams	1–20	150
Manmade activities		
Running	<2	90
Swimming	<2	140
Ear cleaning	3–5	185
Vibrating finger	1–5	170
Diving	0.1–5	180
Snorkel submarines	5–20	140
Blowing in one's ear		170

[a] Adapted from Ref. 20.

It is interesting to note that the only source listed in Table 99.6 causing lengthy exposures, the snorkel submarines, is the one exposure documented to cause permanent damage to the human auditory system. Nixon and Johnson (21) reviewed studies of temporary threshold shift (TTS) in volunteer subjects after exposure to infrasound. Although the data are meager, they concluded that infrasound does not cause TTS for exposures below 140 dB and continuing for less than 30 min. Higher-level, short-duration exposures (up to 142 dB for 5 min) also did not generally cause TTS. The few subjects who did experience TTSs had them in the high frequencies (2–6 kHz), even though the exposures were to very low-frequency stimuli.

Only a few studies have addressed the hazardous effects of infrasound in animals. A comprehensive report of anatomical effects observed in chinchillas exposed to infrasonic stimuli (1, 10, 20 Hz) at levels of 150, 160, and 170 dB SPL detailed extensive pathology (22). Subjects exposed to the highest-level, lowest-frequency stimuli sustained tympanic membrane perforations, stapes subluxations, bleeding in the middle ear, strial pathology, Reissner's membrane rupture, endolymphatic hydrops, and saccular wall rupture. Only the animals exposed at 20 Hz sustained significant damage to the sensory receptor cells. It should be remembered that the chinchilla is much more susceptible to damage from noise exposure than humans (by about 20 dB); so the effects noted in the report would be limited to continuous exposures that exceed 170 dB SPL.

But what about impulse noise? Unlike continuous exposure, impulsive sounds produce rapid changes in atmospheric pressure. The two most common sources of impulsive infrasonic exposures come from sonic booms and from the detonation of automobile air bags. Sonic booms from low-flying (<1000 ft) aircraft are relatively rare, and usually are limited to military personnel. Personnel exposed to 30 sonic booms daily for two 30-d periods at levels up to 157 dB SPL showed no evidence of hearing loss (23). Although these booms can startle listeners, shake dishes in cabinets, rattle windows, and cause cracks in building foundations, they do not cause hearing loss.

Sonic booms from high-flying (>10,000 ft) aircraft lose most of the higher-frequency energy by the time the boom strikes the ground, and thus become infrasonic in nature. Typically, a community

might experience booms in the range of 121–140 dB peak sound pressure level. Because a 10,000-ft minimum is used in the United States in those few areas where sonic booms are allowed, sonic booms should not be expected to constitute a hazard to human hearing.

More common are exposures from airbag deployment. Recently, publication of case studies of hearing loss from airbag deployment (24, 25), have suggested that airbags are capable of causing noise-induced permanent hearing loss. Studies of exposures in cats (26) have documented permanent damage to the auditory system from airbag deployments of approximately 170 dB peak sound pressure level. The addition of side airbags to passenger vehicles, which must inflate much faster than dashboard-mounted units because the distance between the collision and the passenger is much shorter than for front-end collisions, may increase the risk. Rapid inflation of an airbag causes an impulsive sound that has its maximum energy in the infrasonic frequency range. The expanding gas inside the airbag, generated from burning powder, also generates a noise burst of lesser energy, but with much higher frequency content. Of the two components, the noise burst causes more TTS than the infrasonic impulse. In fact, the infrasonic signal may "load" the middle ear, and actually attenuate high-frequency sound from reaching the inner ear (26).

The data reviewed suggest that the biological effects infrasound do not pose a significant threat to human hearing. However, there may be some physiological or psychological effects from prolonged exposure to infrasound. Verzini et al. (27) described laboratory and field studies of the physiological and psychological effects of infrasound in volunteer subjects. Subjects were exposed in the field and inside a specially constructed pressure chamber to pure tones (10 Hz at 110 dB SPL), and to a 1/3-octave band of filtered boiler noise (10 Hz at 105+–2 dB SPL). They measured changes in heart rate, galvanic skin response, peripheral temperature, body resonances, and subjective assessment of the anxiety produced by the exposures. No differences in the physiological variable were observed. However, subjects felt more anxiety inside the pressure chamber, and they rated all sounds as more stressful under laboratory rather than field conditions. Although body resonances were felt, particularly in the chest and in the ears, they did not contribute significantly to the anxiety felt by the subjects. Low-frequency noise exposures similar to those experienced by Verzini's subjects probably occur for those exposed to high-amplitude music from "boom boxes." Although extremely annoying, these exposures probably do not cause hearing loss or any other physiological pathology.

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15 Biological Effects of Ultrasound
Although the human auditory system does not respond to acoustic signals above approximately 20 kHz, intense acoustic signals at very high frequencies (750 kHz to 8 MHz) are used diagnostically to provide images of human tissue. Ultrasonographic imaging has been used as an effective diagnostic tool for more than 30 yr. During that period, there has been no documented epidemiological evidence of adverse effects in patients caused by exposure to ultrasound (28). However, technological advances that have greatly increased the sensitivity of the imaging techniques have been accompanied by large increases in the acoustic output levels of ultrasonographic equipment. These advances have led to increasing use of the techniques clinically, and they may increase the risk of injury to patients or health care providers.

Laboratory studies have shown that ultrasound is capable of producing serious biological damage if the intensity is sufficiently high. Damage is produced from thermal as well as nonthermal effects. Both mechanisms are important, and the mode of damage depends upon the exposure parameters used. Excellent reviews of the biological effects of ultrasound are available (29, 30). The following information is adapted largely from those reviews.

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16 Temperature
Much of the information about the effects of temperature on adult and fetal tissue relates to the effects of hypothermia in the absence of ultrasound. Ultrasonic stimulation causes an increase in temperature of tissue during stimulation. Resulting hyperthermia from the stimulation may cause damaging effects, either due to the absolute temperature elevation or due to rapid changes in temperature. There may be synergistic effects between external stimuli and the internal core temperature of the patient; for example, a febrile patient may be more susceptible to ultrasound tissue damage than an afebrile patient.

Temperature increases within the human body may be due to fever or to hypothermia. There is a difference between these two factors in that fever results in an elevation of the body's "set point" for thermoregulation, whereas hypothermia does not, even though much higher temperatures may be encountered. Fever is considered to be an adaptive mechanism that destroys invading viral or bacterial agents that cannot tolerate high temperatures. Fever is accompanied by the production of an endogenous pyrogen released by leucocytes and shifts the body's thermostat to a higher level. On the other hand, hyperthermia does not induce pyrogen release, but, when a certain temperature is reached, it may induce the release of heat shock proteins. In the environment, hyperthermia may result from exposure to hot water, hot air, or sunshine. In contrast to environmentally induced hyperthermia, ultrasound exposures use microwave or radio frequency energy transmitted along a narrow beam. The absorption of ultrasonic energy results in rapid increase in temperature along the area of the beam. The time constant for ultrasonic absorption of heat is much too fast (on the order of seconds) for any protection to be afforded by the release of heat shock proteins, which require many minutes of exposure before their protective mechanisms are activated.

Homeothermia refers to the capacity of most mammals to maintain a constant internal body temperature. For humans, a "normal" core temperature is considered to be 37°C, although skin temperatures are considerably below that (31–34°C), and organs with very high metabolic activity, such as the liver, can have temperatures as high as 39°C. Core temperatures of other mammals commonly used as experimental subjects, such as dogs, mice, rats, sheep, and goats have higher core temperatures (39–40°C). When evaluating the safety of temperature effects from data obtained in animal subjects, the difference in core temperatures needs to be taken into account. A temperature of 41°C in a guinea pig represents a 1.5°C elevation above normal core temperature; the same temperature in a human would be 4°C above core.

In humans the physiological effects of temperature elevations up to 40.5°C are reversible. They include circulatory collapse, muscular cramps, and exhaustion. Sustained temperatures above 41.5°C are barely compatible with life, and a temperature above 43°C is an ominous warning of death by heat stroke. Although biological tissue can withstand larger variations in temperature, it is known that temperature elevations exceeding 6°C can cause cell death. Smaller elevations can cause significant biological effects, including increased heart rate, leakage of proteins through capillary membranes, edema, and production of heat shock proteins.

Embryos, fetuses, and fetal tissue present additional challenges. In mammals, fetal temperature is usually 0.5–1°C higher than the maternal core temperature. The embryos and fetuses of all species, including humans, are susceptible to increases in temperature. Early effects are usually lethal. At later stages, developmental effects are observed. These include anencephaly/exencephaly, encephalocele, microphthalmia, micrencephaly, and disorders of locomotion, among others. The type and extent of damage depends upon the species studied, the developmental stage during exposure, and the dose of heat delivered to the embryo. These effects are all severe, and represent a

serious hazard from heating of embryonic tissue. In many cases, developing neuroepithelial cells are damaged by heat, and the death of these cells results in defects in neural tube closure.

Local hypothermia can also produce lesions in humans. In the skin, a temperature above 47°C induces erythema and pain; above 55°C, a blistering, and above 60°C for 1 min necrosis. The threshold level for irreversible damage in fatty tissue, muscle, cartilage, and gut is 43°C. Local hyperthermia is used clinically to destroy more active (and warmer) cancer cells while sparing neighboring normal cells. This is accomplished by heating the desired tissue to just above 42°C.

Therefore, the greatest concerns for safety for ultrasound use in clinical diagnosis are for stimuli that raise temperature above 42°C, or change tissue temperature by more than 4°C, and additional precautions to prevent fetal anomalies.

Interrogation of tissue by an ultrasonic beam produces narrow, localized regions of tissue heating. In addition, the extent of heating depends upon both acoustic and biological properties of the tissue. Dense materials, such as bone teeth, and optic lenses have high acoustic absorption coefficients, and are differentially heated more than soft tissue. Bone has an absorption coefficient at least 30 times that of the adjacent soft tissue; the tissue is also heated by the bone. As mentioned, the most sensitive target for ultrasound biological effects is the developing fetus. During the early stages of development (approximately 60 d gestation), the fetus has low mass and a low acoustic absorption coefficient. As bone develops, the potential risk for damage to the developing neuroepithelial tissue increases.

Based in part upon the evidence reviewed, the World Federation of Ultrasound in Medicine and Biology (WFUMB) issued consensus statements on thermal issues, which were published in 1998 (29). It concluded that diagnostic ultrasound applications which use the so-called B-mode imaging do not operate at levels capable of producing harmful temperature elevations. Its use in medicine is therefore not contraindicated on thermal grounds. Systems that used Doppler diagnostic equipment can produce biologically significant temperature rises, specifically at bone/soft tissue interfaces. It recommended that elevated temperature effects be minimized by keeping the time for which the beam passes through any one point to a minimum. The WFUMB also recommended that the lowest output power consistent with obtaining the desired diagnostic information be used. Finally, it labeled all procedures which prevent tissue heating above 38.5°C as safe, even for obstetric applications.

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17 Acoustic Cavitation
Acoustic cavitation is defined as sound-induced activation of gas-filled cavities. It is a physical phenomenon, present in all forms of liquids and gases. There are two types of cavitation effects: inertial and noninertial. *Inertial cavitation* occurs when a gas-filled cavity in a liquid expands in response to being driven during a part of an acoustic cycle, then “collapses” or relaxes to a small fraction of its original volume. While the cavity, or bubble, is collapsing, liquid is drawn inward, thus the “inertial” effect.

At the end of the collapse, shock waves can propagate through the gas, and be emitted into the liquid. These shock waves can produce acoustic pressures of several hundreds of megapascals and generate temperatures of several thousands of degrees Kelvin. The collapse of the bubble can also produce free radicals that can yield reactive elements. In some cases the collapse causes emission of a flash of light, which has been termed *sonoluminescence*. With periodic stimulation, bubbles sometimes oscillate, collapsing, regrouping, expanding, and collapsing again. Occasionally they disintegrate into smaller bubbles, which sometimes are dissolved. Cavity collapse can also cause jets

of liquid to be ejected away from the collapse area; the momentum of these jets can damage tissue structures.

Noninertial cavitation refers to acoustic effects not caused by inertial actions of the fluids. These effects include formation of jets, surface distortion, and heat generation. In general, noinertial cavitation effects are observed at acoustic pressures lower than those required to produce inertial cavitation effects. Whether a bubble responds with inertial or noninertial cavitation depends, upon other things, upon the pressure, the acoustic frequency, and the initial bubble size. Noninertial cavitation is also called *stable cavitation*. It refers to the continuous oscillation of bubbles in response to alternating positive and negative pressures in the acoustic field, and it exists for a number of cycles with continuing stimulation.

Biophysical Considerations

A wide variety of physical, chemical, and biophysical effects can be produced by ultrasonic stimulation through the action of inertial and noninertial cavitation. Although the physical behavior is very complex, considerable insight has been gained through the study of simplified models. Studies of cavitation activity by physicists and acousticians have been spurred not only by health considerations for ultrasound, but also on practical grounds. Initial fascination with sonoluminescense has led to understanding of the large amounts of energy released during bubble collapse, and ultimately to proposals for devices, such as pumps, motors, and loudspeakers that are driven acoustically.

The major biophysical effects of cavitation activity are summarized as:

1. Linear resonance. As long as the driving force is not too high, spherical bubbles respond to sinusoidal stimulation linearly; that is, both the pressure in the liquid and the radius of the bubble varies sinusoidally with the driving force. Therefore, the bubble responds as a harmonic oscillator with a resonance frequency that is inversely related to the bubble volume, or, alternatively, the resting or average bubble radius. For a bubble with a radius of 10 mm, the resonance frequency is 0.33 MHz (29).
2. Scattering. When an ultrasonic signal impinges upon any object that has a different acoustic impedance than the medium it is traveling in, such as a gas bubble in a fluid, much of the energy is scattered or reradiated into the medium. It is just this reason that gas-containing particles are particularly effective as contrast agents for diagnostic ultrasound (30).
3. Heat production. The part of the energy that is not scattered when an ultrasonic wave strikes a bubble is converted into heat. When cavitation occurs in tissue, acoustic absorption coefficients can increase by as much as twofold. That is, for a given intensity of ultrasound beam, the rate of heat production would double.
4. Diffusion and rectified diffusion. As a bubble contracts and expands sinusoidally in the presence of a continuous ultrasonic wave, gas diffuses sinusoidally from the fluid into and out of the bubble. Even in a sound field where the acoustic pressure varies sinusoidally, the inward flow of gas exceeds the outward flow. Consequently, the net effect is an increase in volume of the bubble. This process is called *rectified diffusion*, and it results in bubble growth. Increase is bubble size through rectified diffusion has been observed in mammalian tissue (31), and it also plays a major role in bubble dynamics associated with lithotripsy fields.
5. Radiation forces on bubbles. Cavitation activity is affected strongly by net forces, called *acoustic radiation forces*, which act on bubbles. These forces cause bubbles to move around, to change their radii, and to combine with each other. For example, in an acoustic standing wave, smaller bubbles accumulate at pressure nodes, and bubbles larger than resonance size accumulate at pressure antinodes, as would be expected. In a plane progressive wave, bubbles move away from the source, sometimes at high speed. Bubbles smaller than resonance size may attract each other and coalesce, contributing to bubble growth.
6. Attraction of cells to a vibrating bubble. In a liquid medium, oscillating bubbles will attract particles with densities higher than the surrounding medium, such as red blood cells. Aggregation

of red blood cells can affect cavitation damage.

7. Acoustic microstreaming. As bubbles oscillate, the fluid surrounding the bubble is moved, sometimes with great velocity, around the bubble. Microstreaming effects have been related to the following types of damage: hemolysis, release of protein, degradation of DNA in solution, release of ATP from erythrocytes, and mechanical damage to plant cells. The mechanism of damage is thought to be related to the large shear forces generated by microstreaming effects, particularly near the walls of cells.
8. Inertial effects. These include sonoluminescence, production of free radicals, and destructive pressure pulses, as described.

The biological effects of cavitation depend upon the mechanism of stimulation (continuous or pulsed), and the amount of stimulation, and the substrate, cells in suspension, plants or insects, or mammals. In mammals, effects of cavitation include lesions of lung tissue and focal lesions of the brain, and irreversible hind limb paralysis. Some therapeutic findings have also been reported, including blood vessel repair. It is interesting to note that many of the destructive effects of ultrasound have been reported at clinically therapeutic levels. A summary of the major bioeffects of cavitation is given in Table 99.7.

Table 99.7. Summary of Relevant Cavitation-Related Bioeffects[a]

Effect	Frequency (MHz)	Pulse Duration or Continuous Wave	Exposure Parameters	Exposure Time	Duty Factor	Remarks	I
Bubble growth in guinea pig hind limb	0.75	CW	Temp. avg. effective Int = 110 mW/cm^2	7–70 min		Bubbles observed ultrasonically after 30 min	3
		Physiotherapy 2-ms pulses	Temp. max. effective Int. = 240 mW/cm^2		50%		
Bubble growth in gels	0.75	CW	P_r = 65 kPa	1–5 min		Bubble growth threshold for CW; pulsed exposure is below threshold	3
	0.75	100 ms	P_r = 1 MPa	5 min	50%		
Tissue regeneration	3.50	2 ms	I_{SPTA} = 0.1 W/cm^2 Temp. max. effective Int = 0.5 W/cm^2	5 min 3 per week	20%	Physical therapy; beneficial effect due to stable cavitation	
Kidney damage	shock wave	1-ms pulse	P_c = 100 MPa P_r = 10 MPa	1500 shocks in 15 min		*In vivo*, in dogs, robust effect	3
Drosophila larvae killed	2.50	1 ms	I_{SPTA} = 3 mW/cm^2	2.5 min	0.06%	Indicates *in vivo* conditions	3

			I_{SPPA} = 50 W/cm^2			under which diagnostic ultrasound intensities may cause cavitation effects	
Lung damage in mice	1.2	10 ms	P_c = 0.7 MPa I_{SPTA} = 1 mW/cm^2	3.0 min	0.1–0.01%		3
Mutagenicity	1.0	CW	I_{SPTA} = 35 W/cm^2	10–180 s		Rotating test tube; effect due to enhanced cavitation	3 4
	1.0	CW	I_{SPTA} = 35 W/cm^2	120 s	—		
Chromosome single-strand breaks	1.61	CW	I_{SPTA} = 8 W/cm^2	10 or 30 min	—	Cavitation-induced toxic sonochemicals responsible for effect	4
Free radicals detected in aqueous sols	1.0	6.5 ms	I_{SPTA} = 2.5 W/cm^2 I_{SPTA} = 90 W/cm^2 P_r = 2 MPa	10 min	2.6%	Detected in aqueous solutions *in vitro*, not observed *in vivo*	4
Hind limb paralysis in mouse neonate	1.0	CW	I_{SPTA} = 289 W/cm^2	500 ms	—	Threshold for paralysis in mouse	4
Necrosis in cat brains	1.0–8.0	CW	I_{SPTA} = 500 W/cm^2 *in situ*	0.5 s	—	*In vivo* focal lesions; robust effect; I_2t intensity/time constant for theshold	4
Cavitation in blood	0.5–1.6	CW	I_{SPTA} = 16 W/cm^2		—	Bubbles not detected in canine flowing blood, although produced *in vitro* in water	4

[a] Adapted from Ref. 29.

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18 Summary

Ultrasonic stimulation, although not audible, can cause adverse biological responses in humans, plants, and other animals. Thresholds for damage are time dependent for thermal effects and time independent for cavitation effects. The magnitude of the effect, however, depends upon the total duration for any exposure once the threshold has been exceeded. Thermal effects, and the risk of damage or death, is greatest during embryonic development; the presence of a fever may exacerbate the risk of ultrasound damage from thermal effects.

Cavitation effects are considered to be responsible for most of the adverse biological effects produced by ultrasonic stimulation. Significant biological effects, such as cell death and irreversible damage to lung tissue, have been observed experimentally in mammals including nonhuman primates. Effects were noted at pressure/duration combination similar to levels currently available in diagnostic ultrasound equipment.

Based upon its review of extant scientific data, the World Federation of Ultrasound in Medicine and Biology (WFUMB) published a list of recommendations for the safe use of ultrasound (30). These recommendations are listed in the following.

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19 Recommendations: Thermal Effects

- A diagnostic exposure that produces a maximum *in situ* temperature rise of no more than 1.5°C above normal physiological levels (37°C) may be used clinically without reservation on thermal grounds.
- A diagnostic exposure that elevates embryonic and fetal *in situ* temperature above 41°C (4°C above normal temperature) for 5 min or more should be considered potentially hazardous.
- For diagnostic ultrasound systems that are capable of producing a tissue temperature increase >1.5°C above normal, users should be provided with worst-case estimates of temperature increase for all pertinent operating models.
- The risk of adverse effects of heating is increased with the duration of exposure. Thus safety guidelines should include an appropriate duration factor.
- Care should be taken to avoid unnecessary additional embryonic and fetal risk from ultrasound examinations in febrile patients.
- If temperatures above 41°C may occur at the surface of an intracavitary transducer when in use, such equipment should provide temperature information to the user during equipment operation.

Noise and Ultrasound
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20 Recommendations: Nonthermal effects

- The possible occurrence of cavitation, either inertial or noninertial, should be considered in assessing the safety of diagnostic ultrasound and of other forms of medical ultrasound.
- Caution is required in applying results of *in vitro* ultrasound biological effect studies to medical ultrasound exposures *in vivo*.
- It has been shown experimentally that acoustic cavitation can alter mammalian tissues. It is therefore important to consider its significance in medical applications of ultrasound.
- Currently available animal data indicate that it is prudent to reduce ultrasound exposure of human postnatal lung to the minimum necessary to obtain the required diagnostic information.
- Estimates of tissue field parameters at the point of interest should be based of derated values calculated according to an appropriate specified model and be extrapolated linearly from small signal characterization of source–field relationships.
- The acoustic *pressure amplitude* at the point of interest for a given frequency should be used as a *primary* index of the potential for adverse, nonthermal biological effects of an ultrasound exposure.
- A risk–benefit analysis should be performed if anticipated acoustic pressure amplitude at the surface of postnatal lung tissue exceeds 1 MPa.
- Safety evaluations should consider the characteristics of the site of ultrasound exposure. Thresholds for nonthermal biological effects are lowest in:

  1. tissues that naturally contain gas bodies, e.g., postnatal lung and intestine, and
  2. all tissues in the presence of introduced gas bodies, e.g., ultrasonic contrast agents

- *In vitro* studies: Because the probability of cavitation is much greater for *in vitro* conditions, one must be cautious in applying *in vitro* experimental results to the clinical situation.
- Contrast agents: Gas bodies introduced by a contrast agent increase the probability of cavitation. A physician should take this into account when considering the benefit–risk ratio of an examination.
- Pulmonary capillary bleeding: In considering the significance of ultrasound-induced pulmonary red blood cell extravasation and capillary bleeding, one must realize that these effects also can occur as a result of coughing and can occur spontaneously in neonates. For the most part, unless there is extensive hemorrhage, the clinical significance is negligible, and its occurrence would be difficult to detect. Nevertheless, it is prudent to reduce ultrasound exposure to the postnatal lungs to the minimum necessary to obtain the required diagnostic information.
- B-mode imaging: When tissue–gas interfaces or contrast agents are not present, the use of B-mode imaging need not be withheld because of concern for ultrasound safety. This statement also applies to endoscopic, transvaginal, and transcutaneous applications. When tissue–gas interfaces or contrast agents are present, ultrasound exposure levels and durations should be reduced to the minimum necessary to obtain the required diagnostic information.
- Doppler: When tissue–gas interfaces or contrast agents are not present, and where there is no risk of significant temperature elevation, the use of diagnostic Doppler equipment need not be withheld because of concern for ultrasound safety. When any of the above conditions might be present, ultrasound exposure levels and durations should be reduced to the minimum necessary to obtain the required diagnostic information.
- Information about clinically relevant quantities describing, for example, the anticipated temperature elevation or the potential for cavitation should made available to health care professionals. Methods for making this information available include, for example, the continuously updated display of a thermal index and mechanical index, and the classification of ultrasound fields.
- Education: Diagnostic ultrasound has potential for both false-positive and false-negative results. Misdiagnosis is far more dangerous than any effect that might result from the ultrasound exposure. Therefore, diagnostic ultrasound should be performed only by persons with sufficient training and

education.

Noise and Ultrasound

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Electric and Magnetic Fields and Occupational Health
Leeka I. Kheifets, Ph.D.

1 Introduction

Electric and magnetic fields (EMF) are ubiquitous. The earth has static electric fields, which produce lightning during thunderstorms, and geomagnetic fields created by electric currents within its core. Electric and magnetic fields are also produced during electric power generation, transmission, and use.

Electric power has generally been considered safe during the more than 100 years of its use, although shocks and burns from direct contact with electrical conductors are a recognized health

hazard. Of the approximately 1100 deaths from electric shock that occur each year in the United States, about three-fourths result from unsafe operation of household appliances; accidents in the workplace account for the rest (1). The possible health consequences of electric and magnetic field exposure are a much more recent concern.

Power-frequency EMF exposure—unavoidable since the use of electricity has spread throughout the world—has been under investigation since the early 1970s. Investigations have included epidemiologic as well as *in vitro* and *in vivo* laboratory studies encompassing a wide range of diseases. The literature on EMF and health is vast, comprising over 1000 published studies, and has been reviewed in depth by several authoritative committees. Of note are reviews by the National Research Council of the National Academy of Sciences (NAS) (2), the National Institute of Environmental Health Sciences (NIEHS) (3), and the U.K. National Radiological Protection Board (NRPB) (4).

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2 The Nature of Electric and Magnetic Fields
Electric power systems in the United States, Canada, and Mexico generate and transmit electricity as alternating current (ac), which oscillates at a frequency of 60 cycles per second, or 60 hertz (Hz). Most of the rest of the world generates power at 50Hz. Power-frequency 50- and 60-Hz fields occupy the extremely low-frequency (ELF), nonionizing range of the electromagnetic spectrum (Fig. 100.1). The ELF range includes frequencies from 3 to 3000Hz. Above 3000Hz are, in order of increasing frequency or decreasing wavelength, radio waves, microwaves, infrared radiation, visible light, ultraviolet radiation, x-rays, and gamma rays. Microwaves have enough photon energy to heat tissue; ionizing radiation like x-rays and gamma rays can damage biological systems by breaking chemical bonds. Extremely low-frequency electric and magnetic fields can neither break bonds nor heat tissue, and the electric currents they induce in the body are very weak.

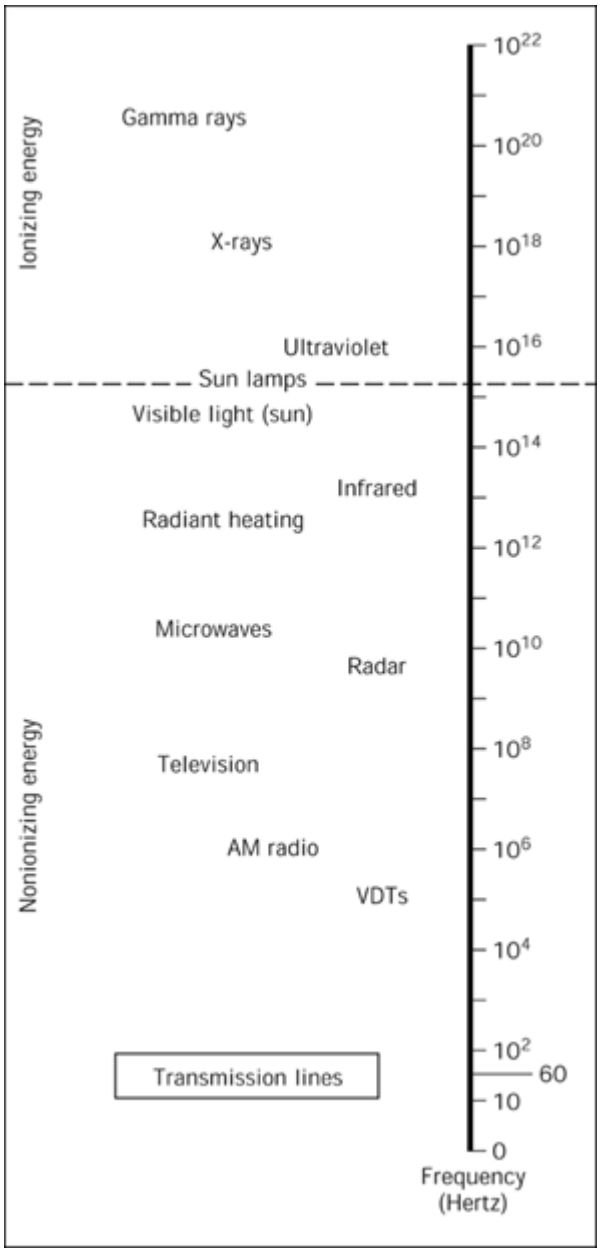

Figure 100.1. The electromagnetic spectrum.

Power-frequency fields have very long wavelengths of about 5000km. Exposure distances are much shorter than this wavelength; under these circumstances, electric and magnetic fields are independent. Electric fields, measured in volts per meter (V/m) or kilovolts per meter (1kV/m = 1000V/m), are produced by electric charges. Magnetic fields are created by moving electric charges, or current, measured in amperes (A). Electric fields are present when an electrical device is connected to an outlet even when turned off, and both electric and magnetic fields are present when the device is turned on. Magnetic fields are measured in tesla (T), millitesla (mT), or microtesla (mT); 1T = 1000mT, and 1mT = 1000mT. Magnetic field measurements may also be expressed in gauss (G) or milligauss (mG), where 1mT = 10mG.

Electric field strength increases with increasing voltage, or electric potential; magnetic field strength increases with increasing current. Both electric and magnetic fields decline rapidly with distance from their source, with a faster decline of fields from point sources such as machinery and a slower decline of fields from power lines. Electric fields are further reduced when shielded by conducting objects like buildings and have little penetrative ability; magnetic fields, on the other hand, are capable of penetrating tissue and are not easily shielded.

Occupational exposure to electric and magnetic fields occurs from proximity to large motors as well as from wiring in buildings and the use of computers, office machines, and heating and air conditioning systems. Power transmission and distribution facilities are other sources.

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3 Exposure Assessment
Accurate assessment of EMF exposure has presented many difficulties in epidemiologic studies and continues to be a considerable challenge. EMF have several unique characteristics that make them more difficult to measure than most other types of exposures. EMF are not readily detectable, are variable in time and space, and are to some extent present in all environments (5). Additionally, electric fields are both perturbed and intensified by conducting objects like the human body, so that fields measured at various points on the body's surface have different values. Because of the complexity of exposure circumstances, exposure reports from workers are not reliable.
3.1 Exposure Surrogates
Because for most studies of EMF health effects, the relevant exposures are those that occurred in the past, the use of surrogate indexes is necessary. The use of surrogates likely leads to misclassification and/or bias. Surrogates for occupational EMF measurements used in epidemiologic studies include job titles, work histories, and present-day area and personal measurements.

Early occupational studies used job titles as an exposure surrogate (6, 7). Job titles alone, however, do not yield accurate exposure estimates. Of equal or greater importance are specific industry, work environments, and specific tasks performed. Magnetic field exposure in the electric utility industry, for example, is substantially lower among electricians using de-energized equipment in new facility construction than in those doing repair or maintenance work with energized equipment in existing facilities. Electricians working outside the utility industry are likely to experience different exposure patterns than those working in the utility industry. EMF exposures in nonelectrical occupations could also be higher than job title alone would predict; administrative assistants or managers working in power plants, for example, may experience higher exposures than their counterparts working in an office environment. Exposure assessments using only job title or occupational group are thus likely to misclassify exposures in individual workers.

Recent research has estimated historical exposures using measurements collected for specific job titles among the present-day workforce, particularly in the electric utility industry (8–11). Exposure assessment strategies in a number of studies have made use of measurements for both job title and usual work environment (12, 13). Measurements for specific tasks were used in one study of EMF health effects (14, 15) and in several exposure characterization studies (16, 17). More recent studies have employed quantitative job–exposure matrices based on personal monitoring and/or area magnetic field measurements. This approach, however, is still fundamentally tied to job title, since average exposure levels for a job title are assigned to individual workers. A recent analysis by Kelsh et al. (18) shows the contribution of various parameters to overall exposure within and between worker variability, work environment, company and job variability.
3.2 Exposure Measurement
Exposure meters that can be held in the hand (Fig. 100.2) or worn on a belt are used to measure electric and magnetic fields. Selection of the appropriate meter, as well as regular calibration, is essential for maximal quality, quantity, and relevance of exposure data. Instruments vary in sophistication and function. Some can survey field strengths; others can capture waveforms and count transient fields. The most sophisticated instruments are capable of a number of complex functions, such as calculating the resultant from field strengths measured along three orthogonal axes, recording data over time, and generating pass bands for estimating fundamental and harmonic

fields. For further detail, see guidelines (19, 20) that recommend appropriate instrumentation.

Figure 100.2. EMDEX II (Electric and Magnetic Field Digital Exposure) exposure meter.

As instrumentation facilitates the gathering and storage of large amounts of information, data collection, analysis, and management assume special importance. Appropriate and well-documented procedures for handling data are necessary to ensure their quality and integrity. Freshly collected data should be regularly examined for consistency, completeness, and accuracy.

Another important part of exposure assessment is measurement protocol. Which protocol is most suitable is determined by assessment objectives. For example, spot measurements in specific locations or measurements along a specific path to allow plotting of contours or profiles of field strengths may be adequate to characterize sources and spatial variability. Twenty-four-hour stationary measurements or personal measurements may be more useful in situations where temporal variability is likely to be large (Fig. 100.3).

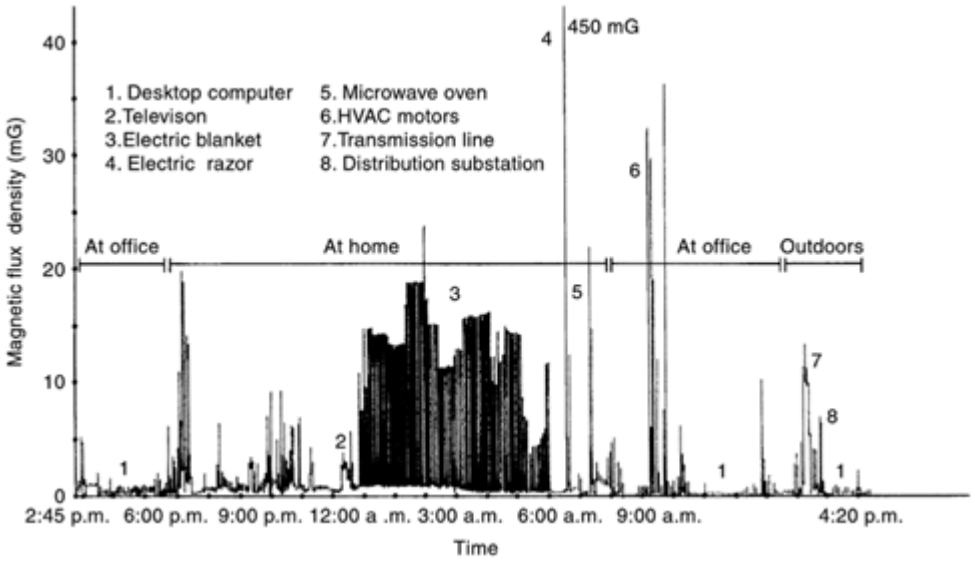

Figure 100.3. Personal magnetic field exposure. Fields from different sources encountered throughout the day vary widely. HVAC, heating ventilation, and air conditioning.

Because error in measurements of EMF can be large, evaluation of factors that may contribute to uncertainty is advisable. In addition, estimating observed overall uncertainty for protocol development, as well as uncertainty introduced by various factors, can help in analysis and interpretation of results.

3.3 Sampling Strategy and Protocol Development

Exposure assessment is complicated by the high temporal and spatial variability of EMF, as previously noted, and by limited understanding of the contributions of different sources to total exposure. Thus an important component of an effective assessment program is selection of a sampling scheme. The sampling scheme must maximize the precision of the quantities being measured. To do so, the number of measurements, the diversity of locations, and the need for repeated measurements must be taken into account. Lack of knowledge about the biological relevance of different characteristics of exposure, or exposure metrics, makes a decision on what to measure difficult. Researchers have developed guidelines for determining which exposure metrics to use in measurement studies (19, 20). At least a time-weighted average magnetic field exposure measurement is suggested, though alternative metrics may be of interest. These guidelines for protocol development also discuss sampling strategies, sample size, sampling parameters, and resource limitations. Additionally, questionnaires and other time–activity record-keeping protocols are covered, along with documentation of methods and results and handling of data.

Most studies of magnetic field exposure are based on nonrandom samples of volunteers. (21). Nonrandom, or purposeful, sampling could give rise to bias if volunteers are not representative of a whole group of workers. If, on the other hand, participants do represent their job classification and perform tasks that are typical of their jobs, nonrandom samples may provide representative exposure estimates. Another potential source of bias in studies using either random or nonrandom sampling is the measurement process. To avoid bias, obtainment of exposure measurements should strive not to alter normal behavior and performance at work.

Since exposure assessment is likely to be complex, pilot studies are recommended. These preliminary studies should test sampling, instrumentation, time–activity record-keeping, subject participation, and quality assurance procedures.

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4 Occupational Exposures

Occupational EMF exposures are considerably higher than nonoccupational ones, which are usually in the 0.01–0.3mT range. Occupational exposures have been studied most extensively in the electric utility industry. Average exposures have been found to be higher in “electrical occupations” than in other occupations such as office work, ranging from 0.4–0.6mT for electricians and electrical engineers to approximately 1.0mT for power line workers. Welders have the highest average exposures at 3.7mT. Average measurements, or arithmetic means, however, can be strongly influenced by a few high measurements. Geometric means, which are not thus influenced, are much lower for some occupations. Geometric means are 0.2–0.3mT for electricians and electrical engineers, 0.4mT for power line workers, and 0.6mT for welders.

Much less is known about exposures in nonelectrical occupations; few data, if any, are available for many jobs and industrial environments. Of note in the few surveys conducted are high exposures among railway engine drivers (about 4mT) and seamstresses (about 3mT). The best information on

work exposures among the general population is available in a survey conducted by Zaffanella and Kalton (22). The survey included 525 workers employed in a variety of occupations (Table 100.1). The largest geometric mean (0.16mT) during work occurred in electrical and service occupations. Technical, sales, and administrative support positions had a geometric mean of 0.11mT; managerial and professional specialty occupations, 0.10mT; and precision production, craft and repair work, operation, fabrication, and labor, 0.09mT. At 0.05mT, farming, forestry, and fishing occupations had the lowest geometric mean. Work exposures were often significantly higher and more variable than other exposures; people spent significantly more time, for example, in fields exceeding 1.6mT at work than at home (Fig. 100.4). Nevertheless, average work exposures for the general population are low, with about 4% exposed to magnetic fields above 0.5mT (22).

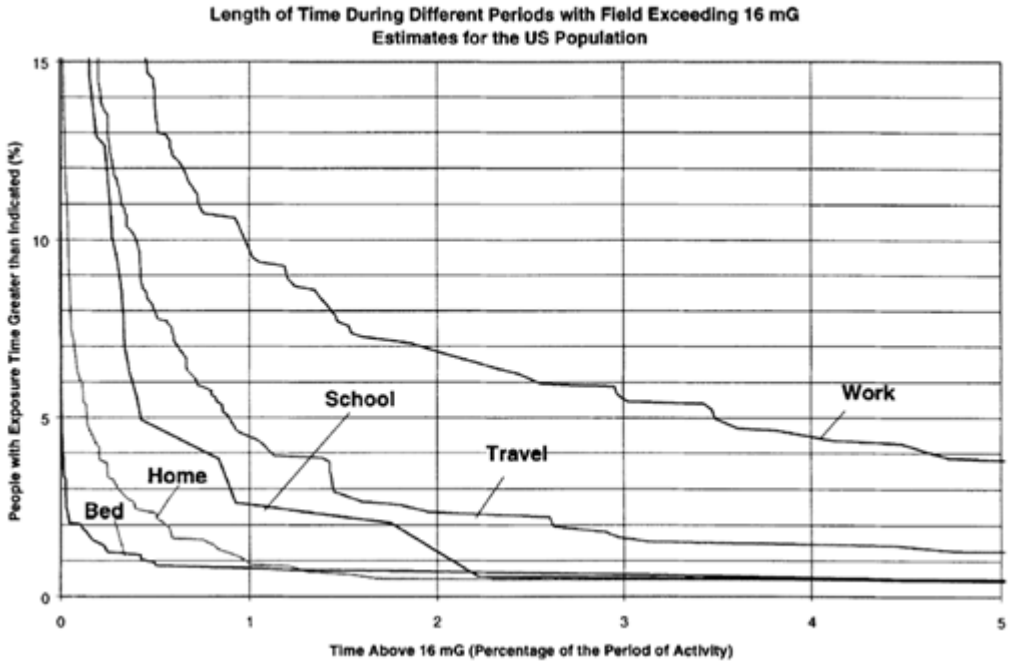

Figure 100.4. Estimated U.S. population distributions of times above 16mG for different activity periods. From Ref. 22.

Table 100.1. Parameters of the Distributions of Average Magnetic Field During Work for Different Types of Occupations[a]

Description	Number of People Surveyed	Mean (mT)	Standard Deviation (mT)	Geometric Mean (mT)	Geometric Standard Deviation
Managerial and professional specialty occupations	204	0.164	0.282	0.099	2.47
Technical, sales, and administrative supports occupation	166	0.158	0.167	0.109	2.30
(Protective, food, health, cleaning, and	71	0.274	0.442	0.159	2.55

personal) service occupations					
Farming, forestry, and fishing occupations	19	0.091	0.141	0.045	2.97
Precision production, craft, and repair occupations, and operators, fabricators, and laborers	128	0.173	0.415	0.089	2.80
Electrical occupations[b]	16	0.215	0.162	0.161	2.25

[a] *Source*: From Ref. 22.

[b] Electrical occupations are those classified as such by Dr. Samuel Milham in his study of leukemia mortality in men occupationally exposed to electric and magnetic fields (EMF) (3). The electrical occupations include: electronic technicians, radio and telegraph operators, electricians, linemen (power and telephone), television and radio repairmen, power station operators, aluminum workers, welderse and flame cutters, motion picture projectionists, electrical engineers, streetcar and subway motormen.

5 Acute Effects of Emf Exposure

5.1 Perception

Humans can detect electric fields of 5 to 10kV/m. At this field strength, a slight vibration of the hair, felt as a tingling sensation, occurs. Electrical workers may experience contact currents known as microshocks. It has been suggested that microshocks can affect cells and tissues, even causing chromosomal abnormalities (23). Evidence, however, is unsubstantial.

Power-frequency magnetic fields are detectable as transient flashes of light (24) at very high field strengths of 3–5mT. These flashes, known as magnetophosphenes, are perceived as flickering visual phenomena. Similar phenomena are caused by nonphotic stimulation, such as optical pressure and mechanical shock, and by direct application of weak electric currents to the head. Magnetophosphenes are produced in the retina, rather than the optic nerve or visual cortex (25). The threshold current density for induction of magnetophosphenes in the retina is approximately 10 milliamperes per square meter (mA/m^2) at 20Hz, an order of magnitude less than the threshold for 60-Hz currents.

Magnetophosphenes are one of the few universally recognized physiological effects of magnetic field exposure in humans. They do not, however, appear to cause retinal lesions or any other permanent damage (26).

5.2 Induced Currents

Time-varying, ac electric and magnetic fields—including power-frequency fields—as well as movement through static fields induce electric currents in the body. Currents induced by EMF can be measured according to current density, the amount of current flowing through a unit cross-sectional

area of the body. Induced current density depends upon the frequency and magnitude of electric and magnetic fields. Adverse biological effects, such as neural and cardiac stimulation, are produced by induced current densities of above 1000 mA/m^2 (see Exposure Guidelines section). This level, however, is much greater than levels experienced in normally encountered fields. At 60Hz, current density in grounded humans in a 100-V/m vertical electric field measures about $25mA/m^2$ in the torso; in a 1mT 60-Hz magnetic field, average current density is $1–2mA/m^2$ (2).

Current densities for electric and magnetic fields vary between humans and different species of animals according to body size, shape, and orientation to a field (Fig. 100.5). In laboratory animal experiments, both electric and magnetic field levels must be increased 5–15 times to model current densities in human beings.

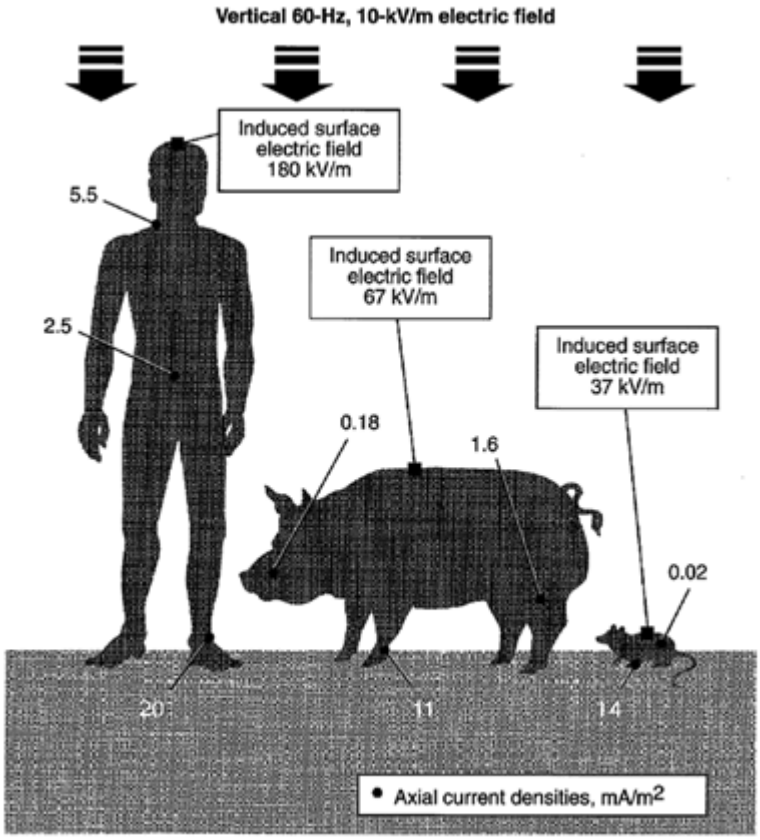

Figure 100.5. Electric and magnetic field interactions with different species. Current densities vary according to body size, shape, and orientation to a field. From Ref. 27.

5.3 Central Nervous System

Concern about the potential effects of exposure to EMF on the central nervous system was first generated in the 1960s by studies of utility workers in the Soviet Union (28). These studies reported symptoms such as headache, fatigue, and insomnia among workers in extra-high-voltage switchyards. Subsequent studies in several western countries, however, failed to confirm any adverse effects on the general health of utility workers (29, 30). Laboratory studies of volunteers have included electroencephalogram (EEG) activity, sleep disturbances, and cognition and performance under various exposure conditions. Exposures tested included intermittent combinations, found in some occupational environments, of 6kV/m and 10mT; 9kV/m and 20mT; and 12kV/m and 30mT. These exposures were found in some studies to affect cerebral potentials and sleep patterns (31, 32). The magnitude of alteration of observed effects, is generally of the order of 10% or less, and results are well within normal ranges for the parameters assessed. There are a number of potential sources of error in many of the studies, and there is not a consistent dose–response relationship. Though results are inconsistent and effects subtle, they provide some evidence of a biological response to

EMF in humans. Current evidence is insufficient to indicate that daytime exposure to extremely low-frequency EMF at occupational levels presents a health risk.

5.4 Cardiovascular System

Study of occupational EMF exposure found that exposure to 50-Hz fields directly under transmission lines produces no change in mean heart rate (33). A more recent investigation suggests that certain electric and magnetic field combinations may produce cardiovascular effects. Slowing of the heart rate in male volunteers has been reported in some laboratory-based studies (31). The magnitude of the observed effects, is small (<10% change from the mean), and the underlying biological mechanism is unknown.

Heart-rate reactivity is a response to consciously perceived stimuli, such as anxiety or exercise. Heart-rate variability (HRV) is an unconscious slowing or stimulation of heart rate governed by the autonomic nervous system. HRV is caused by neuronal and cardiovascular reflexes involved in such processes as control of blood pressure, body temperature, and respiration. Studies conducted by Sastre et al. (34) found that 20-mT intermittent magnetic fields altered heart-rate variability. No effect was found with exposure to 1-mT intermittent or 20-mT continuous fields. In a more recent study, volunteers were exposed overnight to both intermittent and continuous 20-mT fields; no effects on HRV were observed (35). A follow-up study of identical design using 90-mT fields also reported no field-related differences in HRV (36). Although there appear to be no residual effects in the exposed volunteers and despite apparently conflicting data among studies, these results provided the basis for the biological hypothesis linking magnetic field exposure, heart-rate variability, and acute cardiovascular disease (see Cardiovascular Disease section). A new analysis of data to develop a better understanding of reasons for differences in results has recently been published (37). This multistudy analysis suggests that reduction in Heart Rate Variability (HRV) is apparent only in studies with concomitant sleep interruption (37).

5.5 Melatonin

Melatonin, a hormone produced by the pineal gland, is involved in regulation of biological rhythms. Production of melatonin has a definite circadian rhythm; circulating levels are high at night and low during the day. The possibility of long-term disruption of this rhythm in humans has been little studied, although it has been suggested that the use of artificial light at night, shift work, alcohol consumption, and exposure to electric and magnetic fields can chronically interrupt melatonin synthesis. In animals, manipulation of melatonin levels seems to affect the development of several types of cancer, most notably mammary tumors. Recent reviews indicate that melatonin, acting through a number of antiproliferative, antioxidative, and immunostimulatory mechanisms, has oncostatic capabilities (38, 39).

Most laboratory studies of sheep, baboons, and humans exposed to EMF have found no effect on either circulating melatonin or its major urinary metabolite. In contrast, most small animal studies report that EMF suppress different elements of melatonin synthesis, secretion, or metabolism. Despite the abundance of data associating EMF exposure with melatonin suppression in these studies, results have been difficult to reproduce even within the same laboratory (39).

Several recent field studies with electric utility, railway, and garment workers, as well as video display terminal (VDT) operators, suggest that EMF exposure suppresses melatonin (40–42). Also relevant is a study by Kaune et al. (43), which provides evidence that residential exposure to both power-frequency magnetic fields and light at night reduces nocturnal urinary concentrations of the primary metabolite of melatonin. Effects, which were relatively small, were observed mostly in women using certain medications.

5.6 Electromagnetic Hypersensitivity

Reports of sensitivity to electric and magnetic fields first appeared in the late 1970s when VDTs became part of the modern office. Adverse reactions have been reported among thousands of VDT operators, primarily in Sweden (for recent reviews, see Ref. 44). Symptoms reported have included eyestrain, fatigue, headache, difficulty in concentrating, dizziness, and disturbances in sleep patterns. Dermatological problems such as itching, burning, stinging, dry skin, rosacea, and seborrhetic eczema on the face have also been reported. Symptoms are experienced intermittently when they

first appear, worsen with time and finally interfere with ability to work or to tolerate the work environment (45).

Double-blind, controlled laboratory studies (e.g., Refs. 45, 46) have not found consistent associations between actual exposures and either subjective symptoms or biochemical measures. Moreover, study subjects have reported an increase in symptoms when they thought that they were being exposed, regardless of actual exposure conditions (47). To date, no convincing, double-blind challenge studies have conclusively established the existence of hypersensitivity to EMF or proposed a mechanism for this hypersensitivity.

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6 Chronic Effects
Investigation of long-term EMF health effects has focused on cancer, reproductive disorders, and neurobehavioral and neurodegenerative effects. Recently, cardiovascular disease has been added to the list.
6.1 Cancer
6.1.1 Experimental Studies *In vitro* studies of the possible carcinogenicity of electric and magnetic fields have investigated a variety of processes in a number of cell lines and tissue cultures, under a wide range of exposure conditions. Among exposures used in these experiments were sinusoidal, pulsed, and sawtooth-shaped magnetic fields; electric fields; and combined electric and magnetic fields. Investigators have examined static magnetic fields, static electric fields, and combined static and time-varying fields as well. Studies have also included co-exposure of fields with other carcinogens, such as ionizing radiation, ultraviolet light, and chemical mutagens.

An extensive review of studies of the genotoxic effects of EMF by McCann et al. (48, 49) concludes that electric and magnetic fields are not likely to damage genetic material. Although a number of the studies reviewed reported positive genotoxic effects, they need independent replication. A preponderance of high-quality studies have been negative.

Studies of gene expression—the process by which genes direct protein synthesis—have reported conflicting results. Several studies have suggested that exposure to weak magnetic fields may alter this process at the transcription, translation, and protein synthesis stages (50–52). However, effects were small, with less than a twofold enhancement. Other studies with better experimental control reported that magnetic field exposure has no significant effect (53, 54).

A simplified model of carcinogenesis, a multistep process, proposes three discrete stages. The first stage, damage to genetic material, is known as initiation. The second, promotion, entails stimulation of initiated cells to grow into a tumor. Third is progression, stimulation of tumor cells to invade surrounding tissues and metastasize to distal sites. Various agents may act as cancer initiators, promoters, or progressors, or be involved in more than one stage of carcinogenesis. In multiple studies, exposure to EMF has failed to induce mutations (55), chromosome breakage, or other cellular changes that usually occur when normal cells are transformed into tumor cells (56). Since exposure to EMF does not appear to initiate cancer, researchers have hypothesized that EMF may act as a cancer promoter or progressor.

Investigations studying the potential role of EMF on signal transduction—important in regulating intracellular processes—have emphasized calcium flux, cell proliferation, receptor-mediated signaling pathways, enzyme synthesis and activity, and apoptosis. Some evidence suggests that relatively strong magnetic fields of more than 100mT can influence cell growth and signal transduction (2).

Recently, some researchers (57–59) have reported complete blocking of antiproliferative action of melatonin and tamoxifen by a 1.2-mT field. The use of extremely low fields, as well as several other aspects of experimental design, raises questions about this finding; nevertheless, it is unique in that it appears to have been replicated in several laboratories. An effort to replicate and extend this work is underway. Other important new work is focusing on cell differentiation and cell–cell communication.

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7 Exposure Guidelines
Several national and international organizations have formulated guidelines establishing limits for occupational electric and magnetic field exposure. These organizations include the International Radiation Protection Association/International Non-Ionizing Radiation Committee (IRPA/INIRC) (206), the Comit Europeen de Normalization Electrotechnique (CENELEC) (207), the National Radiological Protection Board (NRPB) in the United Kingdom (208), the Deutsches Institut für Normung-Verband Deutscher Elektrotechniker (DIN/VDE) (209), the American Conference of Governmental Industrial Hygienists (ACGIH) (204), and the International Commission on Non-Ionizing Radiation Protection (ICNIRP) (205). The basis of the guidelines is prevention of stimulation of nerves and muscle by induced currents and avoidance of such known effects as magnetophosphenes and cardiac fibrillation. Guidelines focus on acute EMF effects and do not cover potential long-term effects, such as cancer, because they are not considered to be sufficiently well-established for guideline setting.

Definite hazards are posed by exposures above 1000mA/m^2. At these exposures, rhythmic cardiac function, such as extrasystole and ventricular fibrillation, are disturbed. Induced current densities of 100–1000mA/m^2 appear unlikely to produce adverse health effects. A maximum tissue dose of 10mA/m^2 induced current density is specified by all the occupational guidelines and incorporates a safety factor of about 10. This dose also represents an upper limit for endogenous currents that occur naturally in the body; estimates for these currents are based on electroencephalograms and electrocardiograms (ECGs), electrophysiological recordings of the brain and heart. In addition to the 10-mA/m^2 limit for workers, ICNIRP specifies a maximum tissue dose of 2mA/m^2 for the general public.

Though specifying the same limit of induced current density, different guidelines are based on biophysical models that estimate the relationship between external magnetic fields and induced currents using different assumptions. These models, in conjunction with different safety factors, thus yield different values for exposure limits, shown in Table 100.5. Table 100.5 gives whole-body exposures; several guidelines permit limits 5–20 times higher for exposure to limbs (19). Previous guidelines specified lower limits for the “whole working day” but permitted considerably higher exposures for short periods of time (hours). Later guidelines (ACGIH and ICNIRP) (204, 205, 210) specify momentary, or ceiling, limits. The elimination of relaxed limits for shorter exposures, as well as the introduction of ceiling values, makes a key difference. Overall magnetic field guidelines have become progressively more stringent, culminating with the latest ICNIRP guidelines (205, 211) (Fig. 100.6).

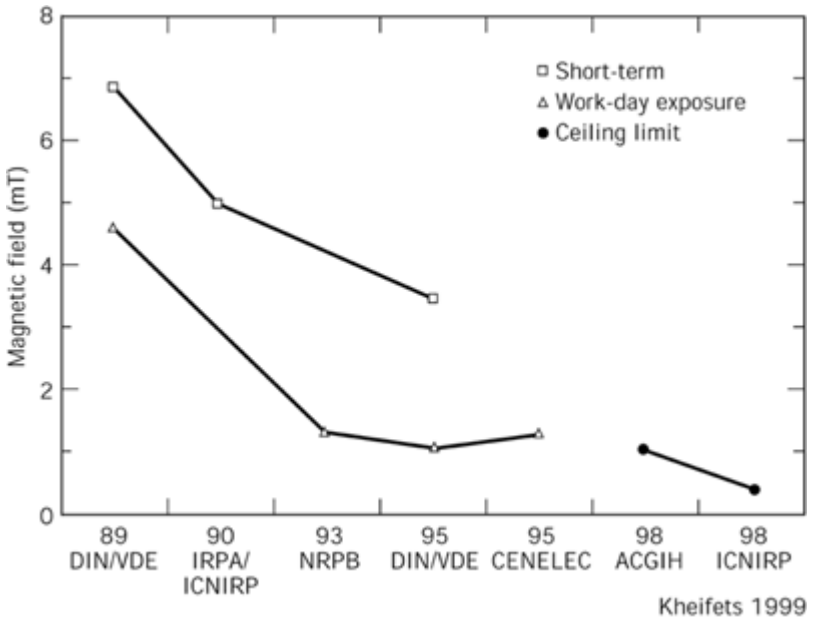

Figure 100.6. Changes in occupational magnetic field exposure limits. DIN/VDE, Deutsches Institut für Normung-Verband Deutscher Elektrotechniker; IRPA/INIRC, International Radiation Protection Association/International Non-Ionizing Radiation Committee; NRPB, National Radiological Protection Board (U.K.); CENELEC, Comite European de Normalization Electrotechnique; ACGIH, American Conference of Governmental Industrial Hygienists; ICNIRP, International Commission on Non-Ionizing Radiation Protection.

Table 100.5. Occupational Exposure Guidelines for Power Frequency Fields

			Exposure Limit	
Organization[a]	**Year**	**Exposure Duration**	**Magnetic Field (mT)**	**Electric Field (kV/m)**
DIN/VDE (209)	1989	Work-day	4.6	19
		Short-term (5min/h)	6.9	29
IRPA/INIRC (206)	1990	Work-day	0.5	10
		Short-term (2h/d)	5.0	30
NRPB (208)	1993	Work-day	1.3	10
DIN/VDE (209)	1995	Work-day	1.1	18
		Short-term (2h/d)	2.1	30
		Short-term (1h/d)	3.5	30
CENELEC (207)	1995	Work-day	1.3	25

ACGIH (204)	1998 Ceiling value	1	25
ICNIRP (205)	1998 Ceiling value	0.4	8

[a] DIN/VDE, Deutsches Institut für Normung-Verband Deutscher Elektrotechniker; IRPA/INIRC, International Radiation Protection Association/International Non-Ionizing Radiation Committee; NRPB, National Radiological Protection Board (U.K.); CENELEC, Comite European de Normalization Electrotechnique; ACGIH, American Conference of Governmental Industrial Hygienists; ICNIRP, International Commission on Non-Ionizing Radiation Protection.

The new ICNIRP guidelines cover both occupational and nonoccupational exposure to time-varying electric and magnetic fields with frequencies up to 300gigahertz (GHz), and to contact currents with frequencies up to 110GHz. Only ACGIH has specifically stated permissible levels for workers with pacemakers.

The ICNIRP guidelines specify a "basic restriction" and a "reference level." The basic restriction is an internal body dose that cannot be exceeded; the reference level is the corresponding external field exposure. The new ICNIRP reference levels are frequency-dependent within the power-frequency range, and do not permit relaxation of exposure limits for short time periods or for exposures to limbs.

The guidelines state that "reference levels are intended to be spatially averaged over the entire body of the individual." Higher exposures are permitted to portions of the body if the reference level for the whole body and the basic restriction are not exceeded. ICNIRP guidelines are based on dosimetric modeling that considers the human body an isotropic homogeneous mass of spherical shape. New induced current models that incorporate anatomically correct body shape and pinpoint tissue-specific conductivity are not used.

The guidelines permit electric field exposures at twice the reference levels for occupational exposures, if "adverse indirect effects from contact with electrically charged conductors can be excluded." Magnetic field reference levels limit induced currents due to direct field coupling; electric field reference levels restrict induced currents from both direct field coupling and indirect effects.

Because higher frequencies induce higher current density, ICNIRP's occupational electric and magnetic field reference levels for 25–820-Hz fields are frequency dependent. Reference levels are $500/f$ kV/m for electric fields and $25/f$mT for magnetic fields, where f is frequency in Hz. Reference levels are thus 8.3kV/m and 0.42mT, or 4.2G, for 60-Hz fields and 10kV/m and 0.5mT (5G) for 50-Hz fields. Reference levels for the general public are 4.2kV/m and 0.083mT (0.83G) for 60-Hz and 5kV/m and 0.1mT (1G) for 50-Hz fields. For contact currents, the occupational reference level is 1.0mA at frequencies up to 2.5kHz. The purpose of this limit is apparently to "avoid shock," but since only about 40% of men can perceive 60-Hz contact currents of 1mA (212), limiting even perception of contact current is implied.

ICNIRP guidelines include formulas for combined exposures of different frequencies. They also advise that coincident electric and magnetic fields "should be considered separately and not additively." Finally, ICNIRP urges that, in the event that the basic restriction is exceeded, protective measures be used. These measures include engineering and administrative controls, as well as personal protection programs and medical surveillance. Compliance procedures, however, are not specified in the guidelines.

8 Exposure Management

Exposure to electric and magnetic fields in the workplace can be reduced in a number of ways. The engineering reference *Electric and Magnetic Field Management Reference* (213) describes various options for reducing fields from electrical facilities and transmission and distribution lines. In addition to field-reduction techniques illustrated by engineering case studies, this reference covers basic theory and calculations and includes terminology, unit conversions, and a reference list.

The first step in exposure management is EMF measurement and assessment (see Exposure Assessment section). Assessment strategies may combine measurements of field levels with patterns of time spent in different activities and locations to estimate personal exposure.

8.1 Low-EMF Design

Power system components, such as circuit currents, conductors, equipment, and facilities, can be designed or modified to minimize EMF without compromising cost or performance. Low-EMF computer monitors are a good example of design improvement that has neither increased cost nor decreased functionality.

Improving design before installation is an easier task than modifying existing equipment and facilities. Whether field reductions are global or local (applied to an entire facility or system or to part of it) affects the nature and impact of modifications. The addition of cancellation loop wires (in which current induced by a power line's magnetic field creates another field that partially cancels the original one) to only a portion of a transmission line, for example, results in little system loss or line impedance, whereas modification to the entire line may have enough impact to warrant serious consideration.

The term *net current* refers to current in a conductor that is not balanced by an equal and opposite current in a nearby conductor. Net currents often occur in building wiring in neutral conductors that are close together. These currents produce high magnetic fields that decrease less with distance than balanced currents. Since shielding is not practical, often wiring must be modified so that incoming current balances return currents in neutral wires.

8.2 Shielding Electric and Magnetic Fields

Shielding sources of electric and magnetic fields can effectively reduce exposure. Electric fields are easily shielded by conducting objects—including screens, walls, trees, and shrubs. Magnetic fields are not shielded by most materials. Shields have been developed, however, based on induced currents in conductive materials, magnetic flux patterns in high-permeability materials, or both.

Magnetic field shielding technology derives from technologies developed to shield radio waves and microwaves. High-permeability alloys were initially used to shield static or direct current (dc) fields; application to power-frequency, ac fields was only moderately successful. More recently, composite shields combining conducting materials with sheet steel have been found to effectively reduce magnetic fields.

Wires conducting current can cancel magnetic fields through passive or active shielding. Active shielding makes use of currents or voltages derived from independent power sources to cancel magnetic fields. Passive shielding, on the other hand, employs materials or circuits without using additional power sources.

Electric field exposures can be reduced by shielding people rather than field sources. Work areas or Faraday cages can provide highly effective shielding. For high-voltage line workers, wearing conductive suits and working in insulated buckets virtually eliminates power-frequency electric field exposure.

Magnetic fields in work areas can be shielded either passively or actively. Shielding may be based, like shielding of sources, on conductive or high-permeability patterns, alone or in combination.

8.3 Reducing EMF Exposure by Selective Use of Space and Time

Altering activity patterns or time spent in the presence of electric and magnetic fields is another

approach to reducing exposure. Exposure reduction measures may include establishment of regulations limiting time spent in high-exposure areas. In extra-high-voltage substations in Russia, for example, time spent in areas with electric fields over 5kV/m is limited to 1h/d. Access to areas with high EMF, such as those where energized equipment is in use, may also be restricted. Finally, facilities and equipment may be arranged such that fields are lowered in frequently occupied areas. High-EMF areas in office buildings, for instance, could be designated storage or filing areas, and electrical panels could be installed in janitors' closets rather than work areas. Similarly, VDTs in schools can be arranged back-to-back, so that students are seated away from the back panels of computers.

8.4 Evaluating Field Management Options

Evaluation of field management programs includes, in addition to field reduction, issues of safety and reliability. Safety codes covering power system design and modification have been established. Design and modifications must comply with The National Electrical Safety Code (NESC) (214), the National Electrical Code (NEC) (215), and other safety codes, such as state codes and building and structural codes. Minimum design standards for utility-owned wiring and equipment in the United States can be found in the NESC; the NEC contains standards for consumer-owned wiring and equipment.

Compliance with the NEC code, which is incorporated into local ordinances, is required by the Occupational Safety and Health Administration (OSHA). State utility commissions use NESC standards. Additionally, city, county, and state governments have installation codes. These codes have been tested over many years and have been proven adequate to ensure safety. Any design or modification that would violate any code requires review and approval and every EMF management option should be tested against established standards.

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9 Summary

The widespread introduction of electrical power, electric light, and electrical and electronic devices during the past 100 years has clearly improved the standard of living and benefited modern societies. Power-frequency EMF exposure—unavoidable since the use of electricity has spread throughout the world—has been under investigation since the early 1970s. Investigations have included epidemiologic as well as *in vitro* and *in vivo* laboratory studies encompassing a wide range of diseases. The literature on EMF and health is vast, comprising over 1000 published studies, and has been reviewed in depth by several authoritative committees; of note are reviews by the U.K. National Radiological Protection Board (4), the National Academy of Sciences (2), which focuses on residential exposures, and the National Institute of Environmental Health Sciences (3). The focus of this chapter is on occupational exposures to electric and magnetic fields. In addition to a review of both cellular and animal data, the chapter details numerous occupational epidemiologic studies and includes a description of exposure guidelines and exposure assessment and management techniques.

Electric field strength increases with increasing voltage, or electric potential; magnetic field strength increases with increasing current. Both electric and magnetic fields decline rapidly with distance from their source, with a faster decline of fields from point sources such as machinery and a slower decline of fields from power lines. Electric fields are further reduced when shielded by conducting objects like buildings; magnetic fields, on the other hand, are not easily shielded. Occupational exposure to electric and magnetic fields occurs from proximity to large motors as well as from wiring in buildings and the use of computers, office machines, and heating and air conditioning systems. Power transmission and distribution facilities are other sources.

Accurate assessment of EMF exposure represents a considerable challenge. Electric and magnetic

fields have several unique characteristics that make them more difficult to study than most other types of exposures. They are not readily detectable, are variable in time and space, and are to some extent present in all environments. Exposure assessment is further complicated by limited understanding of the contributions of different sources to total exposure and by lack of understanding of what the relevant exposure metric might be. Portable exposure meters that can be held in the hand or worn on a belt can be used to measure electric and magnetic fields. More sophisticated stationary instruments can capture waveforms and transient fields. Detailed guidelines that recommend appropriate instrumentation, sampling strategies, sampling parameters, and time–activity-keeping protocols have been developed. At least a time-weighted average magnetic field exposure measurement is suggested, though alternative metrics may be of interest.

The best information on work exposures among the general population is available from a "1000-person survey" (22). Occupational EMF exposures are considerably higher than nonoccupational ones. Nevertheless, average work exposures for the general population are low, with only 4% exposed to magnetic fields above 0.5mT. Occupational exposures have been studied most extensively in the electric utility industry. Average exposures have been found to be higher in "electrical occupations" than in other occupations such as office work. Much less is known about exposures in nonelectrical occupations; few data, if any, are available for many jobs and industrial environments.

Investigation of long-term EMF health effects has focused on cancer, reproductive disorders, and neurobehavioral and neurodegenerative effects. Recently, cardiovascular disease has been added to the list.

In vitro studies of the possible carcinogenicity of electric and magnetic fields have investigated a variety of processes in a number of cell lines and tissue cultures, under a wide range of exposure conditions. Since exposure to EMF does not appear to initiate cancer, researchers have hypothesized a role in cancer promotion or progression. *In vitro* research on the carcinogenicity of EMF has been plagued by a lack of consistency and reproducibility. Recent reviews (3, 2) have concluded that cellular effects have been observed for exposures above 100–500mT, although mechanisms for these effects are not known. Overall, a coherent picture is lacking. Although sporadic EMF effects have been reported in some animal studies, most have been negative. Of the approaches to evaluating EMF as a potential health hazard, toxicologic experiments provide the most consistently negative data. In particular, data on leukemia in experimental animals are negative.

About 100 epidemiologic studies have investigated the possible association between magnetic fields in occupational settings and numerous types of cancer. Several of these studies also examined electric fields as a risk factor. Studies have varied widely in design and quality and have used a number of different methods to assess exposures in a wide range of occupations. Despite considerable heterogeneity in results, an increase in risk of leukemia and brain tumors in electrical workers has been noted in many studies.

Study limitations and the possibility that chance alone could be responsible for positive findings are important considerations in evaluating results. Many of the occupational studies were secondary analyses of existing data collected for other purposes than testing the EMF hypothesis. The magnitude and direction of biases and confounding, often present in epidemiologic studies, are not well understood in studies of EMF. Also, sources of potential bias vary from study to study. Although some have been eliminated as study design has improved, others remain. Inconsistencies, lack of a clear dose–response relationship, the small magnitude of reported elevations in risk, and large misclassification and measurement error are among the main difficulties in the interpretation of results. Additionally, several endpoints have not been rigorously examined in a sufficient number of studies.

Improved methodology in occupational studies has not resulted in higher estimates of risk. It is unlikely that a large overall risk has been overlooked. However, since many studies have reported

some elevation in cancer risk, chance alone as an explanation seems unlikely. The potential role of EMF exposure in cancer etiology thus remains uncertain. Because of the ubiquity of EMF exposure, however, even a small risk could have substantial public health consequences. Future studies based on exposure matrices that incorporate both jobs and locations might reduce misclassification. Nevertheless, only development of relevant exposure metrics and improvements in methodology that will reduce between-worker and day-to-day variability are likely to reduce measurement error sufficiently to provide conclusive results.

Clinical studies conducted by Sastre et al. (34) have suggested that exposure to magnetic fields can alter heart-rate variability. Although this work has not been reproduced in subsequent studies, it prompted an analysis of electric utility worker studies that found an increase in risk for arrhythmia-related disease and myocardial infarction. Although these findings raise an important possibility, they need to be interpreted with caution, as they are first to raise this possibility.

There is little support for an association between EMF exposure and adverse pregnancy outcomes. Methodological problems such as the difficulty of studying EMF exposure levels that are very close to background, possible omission of early miscarriages, and information and recall bias may weaken this conclusion.

Investigation of potential EMF effects on neurodegenerative diseases is in its infancy. Currently, the most interesting suggestion is that electric shock may play a role in the development of amytrophic lateral sclerosis. Studies incorporating better exposure assessment methods, including assessment of contact currents, more accurate diagnosis of diseases, and adjustments for potential confounding from occupational exposures to substances such as solvents might clarify the issue.

Reports of sensitivity to electric and magnetic fields have been connected most often with VDT use. To date, however, no double-blind challenge studies have conclusively established the existence of hypersensitivity to EMF or proposed a mechanism for it.

Several national and international organizations have formulated guidelines establishing limits for occupational electric and magnetic field exposure. The basis of the guidelines is prevention of stimulation of nerves and muscle by induced currents and avoidance of such known effects as magnetophosphenes and cardiac fibrillation. Guidelines focus on acute EMF effects and do not cover potential long-term effects, such as cancer, which are not considered to be sufficiently well established for guideline formulation. Overall magnetic field guidelines have become progressively more stringent, culminating with the latest ICNIRP guidelines. The ICNIRP guidelines define a "basic restriction" as an internal body dose that cannot be exceeded and a "reference level" as the corresponding external field exposure. The reference levels for 60-Hz fields are 8.3kV/m for electric fields and 0.42mT for magnetic fields. ICNIRP urges that, in the event that the basic restriction is exceeded, protective measures be used. These measures include engineering and administrative controls, as well as personal protection programs and medical surveillance.

Pacemakers and implantable cardioverter defibrillators (ICDs) have enabled many cardiac patients to return to work. Very high electric and magnetic fields in the workplace can interfere with the functioning of pacemakers and ICDs. The threshold for magnetic field interference appears to be in the range of 0.2–1.2mT; for electric field interference, above 1.5–2kV/m (203).

Various options for reducing exposure to electric and magnetic fields produced by power generation, transmission, and use in the workplace are available. Power system components, such as circuit currents, conductors, equipment, and facilities, can be designed or modified to minimize EMF without compromising cost or performance. Shielding sources of electric and magnetic fields can effectively reduce exposure. Electric fields are easily shielded by conducting objects—including screens, walls, trees, and shrubs. Magnetic fields are not shielded by most materials. Composite shields have been developed, however, using conducting materials combined with sheet steel. Magnetic fields can also be reduced through passive or active cancellation by wires conducting

current. Altering activity patterns or time spent in the presence of electric and magnetic fields is another approach to reducing exposure. Finally, facilities and equipment may be arranged such that fields are lowered in frequently occupied areas. Evaluation of field management programs should include, in addition to field reduction, consideration of safety and reliability.

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1 Introduction

Radio-frequency radiation (RFR) is a type of nonionizing electromagnetic energy. Electromagnetic energy is the propagation of energy by time-varying electric and magnetic fields. The fields are described by three vector quantities: electric-field strength, magnetic-field strength, and propagation vector, as shown in Figure 101.1

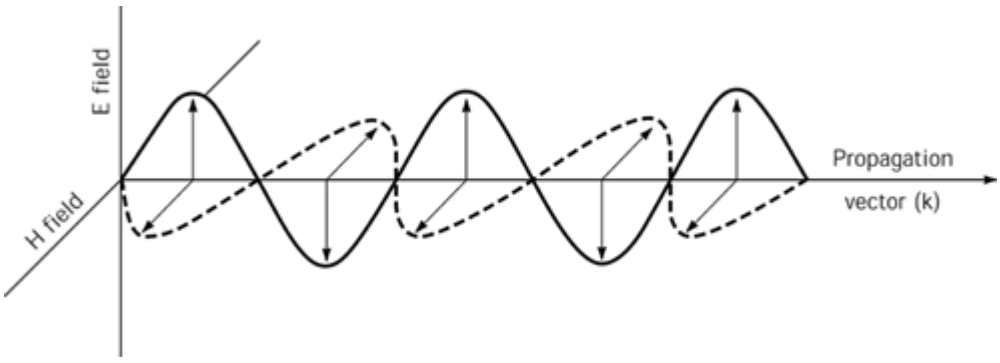

Figure 101.1. Propagation Vector: Time-varying electric and magnetic fields.

Radiation may be described by frequency, wavelength, and photon energy. RFR is described by frequency. Frequency is the number of wave cycles that pass a point in space in a second, and the unit is the hertz (Hz). Sometimes, the interaction of RFR with matter is described by the wavelength, which is the length of one complete wave cycle (see Table 101.1).

Table 101.1. Physical Characteristics of Radio-Frequency Fields

Region	Frequency	Wavelength
Microwave	300 GHz[a] to 300 MHz[b]	1 mm[c] to 1 m[d]
Radiowave	300 MHz to 3 kHz[e]	1 m to 100 km[f]

[a] Gigahertz.
[b] Megahertz.
[c] Millimeter.
[d] Meter.
[e] Kilohertz.
[f] Kilometer.

For the purposes of this chapter, the boundaries of the RF spectral region are 3 kilohertz (kHz) to 300 gigahertz (GHz). Usually, microwave radiation is considered a subset of RFR; however, an alternate convention treats radiowave and microwave radiation as two spectral regions, as shown in Table 101.1.

1.1 Characteristics

RF emissions may be pulsed or continuous wave (CW). A CW device emits RF energy continuously when in operation, whereas pulsed sources emit RFR in a noncontinuous, cyclic manner, characterized by switching emissions on and off. Hence, the duty cycle of pulsed sources, which is equal to the "on time" is equal to the "on time + off time," is less than unity.

RFR output may be modulated. A modulated emission has two components, carrier wave and the modulating signal. The carrier wave is higher in frequency, and carries the information, and the signal is lower in frequency. Modulation is accomplished when some characteristic (e.g., amplitude, frequency, or phase) of the carrier wave is varied by the modulating signal. For example, if the amplitude of the carrier wave is modulated at the frequency of the signal, the waveform is frequency modulated (FM). Other forms of modulation include amplitude modulation (AM), phase modulation (PM), pulse modulation, frequency-division multiple access (FDMA), time-division multiple access (TDMA) and code-division multiple-access (CDMA). Polarization describes the time-varying direction and amplitude of the E-field vector. A field may be linearly, circularly, or elliptically polarized. A field lacking polarization would show no spatial preference in the vibrations of the electric field.

1.2 Quantities and Units

Exposure to RFR may be characterized by the seven quantities listed in Table 101.2. The SAR is the dosimetric quantity that describes RF power deposition or the rate of RF energy absorption as,

$$\mathrm{SAR} = \frac{\sigma E_i^2}{\rho} \qquad (1)$$

where s is the tissue conductivity in siemens per meter (S/m) E_i is the internal electric field in volts per meter (V/m), and r is the tissue density in kilograms per cubic meter (kg/m^3). The SAR is the fundamental quantity of the exposure criteria because it has been found to be the most reliable single predictor of the potential for biological effects in test animals. The whole-body average (WBA) SAR used in the exposure criteria is 0.4 W/kg.

Table 101.2. Important Quantities and Units

Quantity	Abbreviation	Units	Description

Specific absorption rate	SAR	Watts per kilogram (W/kg)	RF dose rate
Specific absorption	SA	Joules per kilogram (J/kg)	RF dose
Electric-field strength	E	Volts per meter (V/m)	Intensity of E field
Magnetic-field strength	H	Amperes per meter (A/m)	Intensity of H field
Power density	W, S	Milliwatts per centimeter square (mW/cm^2)	Power incident on a surface÷surface area
Contact current	I_c	Milliamperes	Current flow into body
Induced current	I_i	Milliamperes	Current flow induced within the body

The SA is the time integral of the SAR and, as such, is the RF dose in J/kg. For much of the RF spectral region, the averaging time is 6 minutes, which results in an acceptable whole-body SA of (0.4 W/kg×360 seconds) 144 J/kg.

SAR and SA are difficult to determine outside of the laboratory, so *E*, *H* and *W* are usually evaluated to determine exposure to RF fields. Exposure guidelines are written in terms of the field strength or power density that will maintain the SAR at a safe level. In general, *E* and *H* may be used throughout the RF spectral region, whereas *W* is most applicable to microwaves.

I_c and I_i are associated with relatively low frequency RF fields, less than 100 MHz. I_c may occur when one contacts a conductive object that is illuminated by the RF field and RF current flows into the body. I_i occurs when exposure to RF fields induces currents within the body which may flow to ground or circulate as eddy currents.

1.3 Generation

RFR is generated by the acceleration of electric charges in oscillatory circuits. Significant generators at the lower RF frequencies are power grid tubes (RF vacuum tubes). Higher frequency (microwave) generators include microwave vacuum tubes (e.g., klystrons, magnetrons, and traveling wave tubes) and solid-state devices (e.g., Gunn diode and tunnel diodes).

Sources of RFR are both natural and man-made. Natural sources include terrestrial and extraterrestrial sources, and even the human body. Major man-made sources are shown in Table 101.3 and reviews are available (1–3). The source that has most consistently demonstrated the potential for overexposure during normal use is the unshielded dielectric heater (also called plastic sealers) (4–7). Induction heaters have demonstrated the potential for overexposures to the magnetic field (8). Certain maintenance activities associated with broadcasting (9) and radar (10) have the potential for overexposure.

Table 101.3. Major Sources of Exposure to RF Radiation

Sources	Uses	Comments
Dielectric heaters	Heat, form, seal, or emboss	Operational band 1–

	dielectric materials like plastics	100 MHz primary is 27.12 MHz
Induction heaters	Heat, harden, forge, weld, anneal, or temper conductive materials (metals)	250 to 500 kHz
Microwave heaters	Dry, cure, heat, or bake materials such as foods, wood, paper, or films	915 and 2450 MHz
Welding	RF-stabilized welding used for pipe, tubing, beam, and plate welding	0.4 to 100 MHz with harmonics
Radar	Acquisition, tracking, and traffic control	Primarily 1–15 GHz
Communications	Fixed systems (satellite communications, microwave, high-frequency, tropospheric scatter)	0.8 to 15 GHz
	Mobile systems (two-way transceivers, wireless devices, two-way pagers)	27 MHz to 3 GHz
Broadcasting	AM radio	535–1605 kHz
	FM radio	88–108 MHz
	VHF-TV	54–72, 76–88, 174–216 MHz
	UHF-TV	470–890 MHz
Diathermy	Shortwave or microwave diathermy in physiotherapy	13, 27, 915, or 2450 MHz

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2 Exposure Assessment
Exposure assessment involves modeling and/or measurement to estimate the intensity of RF fields in space or to estimate the SAR within tissues. SAR determination is usually restricted to laboratory measurement or to computer modeling in support of dosimetry. Workplace evaluation typically involve measurement or modeling E, H, or W.
2.1 Modeling
Numerical modeling may be used to estimate W or E in the area surrounding certain antennas. For example, the far-field hazard distance for a circular aperture antenna may be estimated from

$$r = \sqrt{\frac{PG}{4\pi \mathrm{EL}}} \qquad (2)$$

where r is distance in centimeters (cm), *P* is power in watts (W), *G* is absolute gain (dimensionless), and EL is the exposure limit (W/cm^2). If, it is assumed that there is 100% ground reflection, this

becomes $r = \sqrt{(PG/\pi EL)}$.

Dosimetric studies utilize dielectric characteristics of various human tissues at the wavelength of interest to estimate the SAR. Numerous computational methods have been used, but the finite-difference time-domain (FDTD) method is used most often. This method models the body as a large number of rectangular cells which are assigned frequency-dependent dielectric properties of permittivity, conductivity, and permeability. In the simplest case, the cells may all be assigned the same dielectric properties to produce a homogeneous model. More complex models include dielectric properties of a large number of tissue types.

2.2 Measurement

Currently, there are no RFR dosimeters or personal exposure monitors so field measurements are made with broadband instruments that are calibrated for a broad frequency range. In the calibrated band, the instrumental response is largely independent of frequency, so that the instrument exhibits a relatively constant sensitivity versus frequency. The major components of a broadband instrument are the probe (antenna elements and detectors) and the metering instrumentation that are typically separate assemblies that are connected with a cable or lead. Instruments may be dedicated to the *E* or *H* field, or both, depending upon the type of antenna used. Linear antennas (monopoles or dipoles) are used for *E* fields, and loop antennas (coils) are used for *H* fields. Most modern broadband instrument utilize three mutually orthogonal antennas in an array so that the antenna reception pattern is as nearly isotropic. Thermocouples and diodes are the most frequently used detectors.

2.3 Evaluation

Workplace evaluations involve determining the spatial average exposure. The spatial average is an arithmetic average determined along the vertical dimension of a worker, but with the worker absent. This is necessary because the human body is so conductive that it will perturb or modify the RF field, and the exposure guidelines are in terms of non-perturbed fields, the operator must be absent during evaluation. A nonconductive (dielectric) stickman, typically made from polyvinyl chloride (PVC) tubing, is substituted for the worker. The average is determined along the tubing at a minimum of 10 locations, from 0 to 200 cm (1, 2).

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3 Interactions with Matter and Dosimetry

Studies of interactions with matter and dosimetry include both experimental and numerical evaluations. The general findings from these studies are summarized in the paragraphs below.

3.1 Energy Transfer

When the human body is exposed to RFR, the radiation may be reflected, refracted, transmitted, absorbed, or scattered. When RFR is incident on or transmitted into tissues, there are complex interactions because the human body is composed of layers of tissues that have different dielectric characteristics. The penetration depth into tissues is greatest for relatively long wavelengths, and decreases with decreasing wavelength until, at frequencies above about 30 GHz, the energies are absorbed topically, similar to infrared radiation.

RFR interacts with tissues at the cellular, molecular and atomic levels. There are three modes of tissue interaction at the molecular level: polar molecule alignment, molecular rotation and vibration, and the transfer of kinetic energy to free electrons and ions (10a). Alignment of polar molecules with the *E* field is an ubiquitous mechanism. The major polar molecule in the body is the water molecule. Subsequently, the absorption of RF energy is higher in tissues of high water content (muscle) than in tissues with low water content (fat). Vibrational and rotational modes of absorption are important in intramolecular interactions. The oscillation of free electrons and ions associated with biological macromolecules might have functional consequences for those molecules.

Factors important in the absorption of RF energy include wavelength, polarization, body size and dielectric properties, and the presence of conductive (reflective) objects in the local environment. Some studies have suggested that absorption by the body is greater when the electromagnetic energy is in the form of plane waves (RFR having a planar front) than when the body is exposed in the near field (RF fields very near a source) of a source (11, 12), although this has not been observed by other researchers (13).

Absorption results in the conversion of RF electromagnetic energy to some other form of energy. Typically, the absorbed energy increases molecular motion, thereby increasing the total energy of the system which is realized as heat. This produces thermal effects to the exposed tissues.

3.2 Whole-Body Exposure and Absorption

The distribution of the RF field lines in the space surrounding the human body is disturbed, or perturbed, by the body. Standing waves may form on the exposed side of the body whereas, on the side of the body opposite the radiator, an RF shadow may form. This may be either a whole-body (14, 15) or partial-body shadow (16), depending upon the type of exposure.

The body demonstrates a frequency dependency in its ability to absorb RFR, a phenomenon called geometrical resonance. The maximum SAR is observed when body length (height) is around 40% of the incident wavelength and the direction of the E-field vector is parallel with the body. For an ungrounded man of standard height, this would occur at a frequency around 70 MHz. Because geometrical resonance is directly related to wavelength and inversely related to frequency, the resonance frequency would be less than 70 MHz for taller individuals because they couple well with longer wavelengths. Conversely, the resonance frequency would be greater than 70 MHz for shorter individuals, because they couple better with shorter wavelengths.

When an individual is exposed at a frequency beneath the resonance frequency, the ability of the body to absorb RF energy decreases rapidly. In fact, studies have shown that below-resonance absorption decreases with an f^n dependence, where n = 1.7 to 3 (17, 18). Exposure at a frequency above the resonant frequency results in gradually diminished absorption, becoming asymptotic as the frequency increases (17).

For a given body height, there are two exposure conditions, free space and grounded, that produce different values of resonance frequency. Free-space absorption occurs when an individual is not in conductive contact with earth. For standard man, this is around 70 MHz, as mentioned earlier. Resonance is shifted to a lower frequency if exposure occurs when the body is in conductive contact with earth (grounded condition). In general, the grounded resonance frequency is about one-half the free-space resonance frequency (17).

3.3 Partial-Body Resonance and Hot Spots

Geometrical resonance has also been demonstrated for body parts. For example, the resonance of the head has been reported to be around 350 to 450 MHz (19, 20).

Typically, whole-body exposure produces inhomogeneous absorption of RF energy. This may produce spatial-peak or localized values of absorption on the order of around twenty times higher than the whole-body average. These areas of relatively high local SARs are often called hot spots.

Inhomogeneous absorption has been well illustrated in studies of local RF fields from portable cellular telephones, where SARs were highest near the surface of the tissues nearest the radiator. Peak values were observed in various anatomical locations including the eye (21, 22), ear (23), skin above the ear (24), skin behind the ear (24, 25), and skin of the face (23, 26).

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4 Biological and Health Effects
This section will survey long-term studies, ocular effects, behavioral effects, reproductive and developmental effects, and cancer. For the interested reader, some worthwhile reviews of biological effects are available (2, 27–33).
4.1 Experimental Studies
Both *in vitro* and *in vivo* studies include have been performed. These have evaluated the responses of most major organs and systems, including special senses, central nervous, reproductive and developmental, hematopoietic, immunological, and neuroendocrine.

4.1.1 Long-term Studies Prausnitz and Susskind (34) found no differences in body weights of mice exposed to 10-GHz, pulsed microwaves (estimated WBA-SAR≅50 W/kg) but the controls had a higher death rate than the exposed animals. The authors attributed this to RF-induced thermal stress, essentially a fever, which may have helped the exposed animals combat a pneumonia outbreak that occurred during the experiment. Spalding, Freyman, and Holland (35) exposed mice (800 MHz, WBA-SAR≅1.3 W/kg) and found that voluntary activity and bloodborne parameters were not significantly different. The exposed mice lived longer than the control mice, although this was not statistically significant. No significant differences were observed in bloodborne end points, tumor incidence and type, and macro- and microscopic evaluations during necropsy for rats exposed to electromagnetic pulses (peak E = 447,000 V/m, 250 million pulses delivered over 94 weeks (36).

In an evaluation (50-MHz, 2.5-GHz) using rats and rabbits, researchers found that blood cholesterol and sulfhydryl levels decreased throughout the experiment, while urinary 17-ketosteroid increased (36a). However, these findings were not replicated by D'Andrea et al. (37) who exposed rats (2.45 GHz, WBA-SARs of 0.11 to 0.18 W/kg). They observed a difference in the levels of 17-ketosteroid between exposed and control groups during the adaptation period that may be due to stress induced by handling and housing conditions. No significant differences were found in body mass, food and water consumption, blood levels of cholinesterase, and poststudy evaluations for electrolyte levels, ion gaps, and CO_2. Significant differences were observed in two of four behavioral tests, but these may be of "little biologic significance." In another report, they found statistically significant differences in three behavioral tests, where rats were intermittently exposed (2.45 GHz, 0.7 W/kg) (38).

White rabbits (2450 MHz, WBA-SAR≅1.7 W/kg) had a significant reduction in red blood cell counts (RBC) and food intake, but not in water consumption, white blood cell count (WBC), ocular changes, and coat condition (39). Other researchers used the same species and frequency (WBA-SAR≅1.5 W/kg) and determined statistically significant reductions in albumin, calcium, and eosinophils. No significant changes were found in postexposure bloodborne end points, albumin levels in the exposed animals had decreased, and globulin levels had increased. Pathologic findings showed a significant difference in the myeloid/erythroid ratio in bone marrow samples from the sternum. "The biologic importance of this finding is questionable since the hematologic (erythrocyte and leukocyte counts) parameters did not differ between treated and control rabbits." No significant differences were noted in the other 38 parameters evaluated (40, 41).

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5 Exposure Guidelines and Standards
In the United States the exposure guidelines most often used are IEEE C95.1-1991 (227) and the

American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs) (228). C95.1 recommends RFR exposure limits between 3 kHz and 300 GHz, by way of two sets of exposure criteria called the controlled environment (CE) and the uncontrolled environment (UE). A simple definition of the two environments is as follows: Individuals who work in the CE know that they are being exposed to RFR, and those in the UE have no knowledge or control of their exposure. For the human whole-body resonance spectral region, from about 3 MHz to 6 GHz, exposure criteria for the CE are five times higher than corresponding values in the UE. Outside the resonance range, the exposure limits are identical. The TLVs address 30 kHz to 300 GHz and are identical to the exposure limits in the CE within this band.

The exposure limits in C95.1, in terms of power density or field strength, are called maximum permissible exposures (MPEs). Field strength and power density are surrogate measures of exposure because the fundamental quantity of the exposure criteria is the SAR, as mentioned earlier. The MPEs are exposure limits that are derived to maintain the WBA-SAR below given values, 0.4 W/kg in the CE and 0.08 W/kg in the UE. The WBA-SAR for the CE is derived from studies with test animals where reversible behavior disruption occurred at WBA-SARs around 4 W/kg. A tenfold safety (uncertainty) factor was applied to this number to arrive at the exposure criterion, 0.4 W/kg. The WBA-SAR for the UE is based on the same body of biological effects, except that it incorporates a safety factor of 50 times, so it is five times lower than the CE value.

C95.1 also has recommendations for spatial-peak SARs, where the local SAR is a small mass (1 gram) of tissue. Spatial-peak SARs are based upon the finding that SARs within models of man may be on the order of 20 times greater than the WBA-SAR. The combination of this factor and the WBA-SAR (20×0.4 W/kg) led to the derivation of the spatial-peak SAR for the CE, 8 W/kg in 1 g of tissue. The spatial-peak SAR for the UE was derived by the inclusion of an additional fivefold safety factor to the CE value, to yield 1.6 W/kg per g (see Table 101.6).

Table 101.6. Specific Absorption Rate (SAR) Recommendations in IEEE C95.1 (W/kg)[a]

Target Population	Whole body average	Spatial-peak[b] (partial body)	Extremities[c]
Occupational environment / controlled exposure	0.4	8.0	20.0
General population / uncontrolled exposure	0.08	1.6	4.0

[a] Applicable to the spectral region between 100 kHz and 6 GHz.

[b] Averaged in 1 g of tissue in the shape of a cube.

[c] Applicable to hands, wrists, feet, and ankles, averaged in 10 g of tissue in the shape of a cube.

Hence, the spatial-peak criterion for the CE is based on experimental observations and uncertainty factors. No biological effects have been directly linked to spatial-peak SARs, although it is possible that auditory perception of pulsed RFR may be associated with the spatial-peak dose rate delivered to the head. Hence, the biological significance of these values is not clear.

The U.S. Federal Communications Commission (FCC) has requirements for the broadcast and communications industries in 47 CFR 1.1307(b), 1.1310, 2.1019, and 2.1093. These are a combination of IEEE C95.1-1991 and recommendations made by the National Council on Radiation Protection and Measurements (NCRP) (229). The Occupational Safety and Health Administration (OSHA) addresses microwave radiation in the general industry standard in 29 CFR 1910.97 and 1910.268(p)(2) and (3) and in the construction industry standard in 29 CRF 1026.54(l). In general,

the 10-mW/cm^2 limit in 1910.97 is not enforceable, but OSHA inspectors may use consensus standards in enforcement activities based on the General Duty Clause, Section 5(a)(1) of the Occupational Safety and Health Act of 1970 (2).

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1 Introduction

Sir William Herschel's discovery of "obscure rays," extending beyond the red end of the visible spectrum, launched the exploration of the electromagnetic spectrum outside the visible range in the year 1800. The following year Johann Ritter demonstrated that invisible rays beyond the violet end of the spectrum are capable of chemical action. These three adjacent portions of the electromagnetic spectrum: infrared (IR), visible (vis), and ultraviolet (UV) are collectively known as optical radiation. Although infrared and ultraviolet radiations are invisible to the human eye, they are considered to be "optical" because they share some propagation and interaction characteristics with visible. As does the rest of the electromagnetic spectrum, optical radiation obeys the laws of electrodynamics and can be described both as electromagnetic waves and as energy corpuscles.

A wave is characterized by the distance between two successive peaks—its wavelength—or by the number of peaks passing a given point in space per unit time—its frequency. The wavelength l is measured in meters (m) or its multiples such as the kilometer (km) or nanometer (nm). The frequency n is measured in hertz (Hz) or its multiples such as kilohertz (kHz) or megahertz (MHz). One hertz is simply one cycle per second (s^{-1}). The propagating speed V of a wave of wavelength l (m) and frequency n (Hz) is measured in meters per second (m/s) and is given by the expression:

$$V = \lambda\nu \qquad (1)$$

Unlike waves on a pond or sound waves in air, electromagnetic waves do not need a physical medium to propagate. Electromagnetic waves are composed of mutually perpendicular electric and magnetic fields oscillating in phase and propagating at the speed of light in a direction perpendicular to both fields. The speed of light is a physical constant that depends only on the dielectric characteristics of the medium. In vacuum and in air, the speed of light, c, is approximately 3×10^8 m/s. Since the propagation speed of electromagnetic radiation is a constant, either the frequency or the wavelength can be used to describe any given radiation. The frequency is the physically invariant quantity, and the wavelength changes depending on the propagation medium. However, it has become customary to designate bands in the optical radiation range in terms of wavelength, usually in nanometers (1 nm = 1×10^{-9} m), micrometers (1 mm = 1×10^{-6} m), or angstroms (1 Å = 1×10^{-10} m) (Å is obsolete).

Electromagnetic radiation can also be described as energy corpuscles called *photons*. The energy of a photon is proportional to the wave's frequency, and thus, inversely proportional to the wavelength. The photon energy of electromagnetic radiation of frequency n and wavelength l is given by the equation:

$$E = h\nu = hc/\lambda \qquad (2)$$

where the energy E is expressed in joules (J) and h is Planck's constant (h = 6.63×10^{-34} joule second (J·s). In atomic physics and chemistry, it is customary to use an energy unit in the atomic-particle scale: the electron volt (eV). The electron volt is much smaller than the joule; the conversion factor is 1 eV = 1.6×10^{-19} J.

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2 Optical radiation and the electromagnetic spectrum
All known electromagnetic radiations are customarily arranged monotonically according to their energy in a continuum called the *electromagnetic spectrum*. The electromagnetic spectrum spans many orders of magnitude in energy and, correspondingly, in frequency and wavelength. As is

shown in the schematic representation of the electromagnetic spectrum in Figure 102.1, the optical radiation range is located between microwave radiation and X-rays. The optical radiation range is composed, in order of increasing energy, of infrared, visible, and ultraviolet radiation.

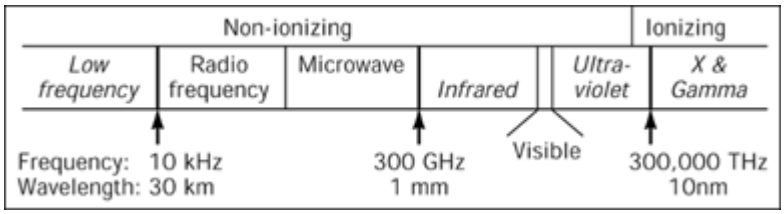

Figure 102.1. The electromagnetic spectrum. The frequency of electromagnetic fields is measured in *Hz* (hertz), or cycles per second. 1 kHz = 1000 cycles/second. 1 GHz (gigahertz) = 1000 million cycles/second. 1 THz (terahertz) = 1 million million cycles/second.

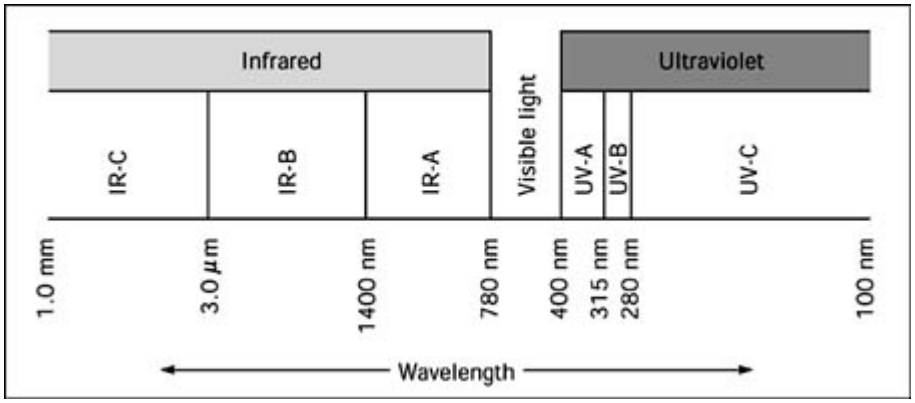

Figure 102.2. The optical spectrum. The wavelength of light, both visible and nonvisible, is typically measured in nanometers (nm) 1 nm = 0.001 mm = 0.000 001 mm = 0.000 000 001 m.

Although there are no sharp, well-defined boundaries in the electromagnetic spectrum, the optical radiation range is conventionally defined as extending from 1 mm at the bottom end of the infrared to 100 nm at the upper end of the ultraviolet. The optical range is divided as follows:

Ultraviolet: 100–400 nm
Light: 380–400 to 760–780 nm
Infrared: 760–780 nm to 1 mm

The reason for the "fuzzy" boundaries for the visible range is that they are defined by the physiological process of vision, which has some intrinsic variability.

The important boundary between ionizing and nonionizing radiation, marked in the electromagnetic spectrum in Figure 102.1, falls in the optical radiation range. When the energy of radiation incident on an atom or molecule exceeds the binding energy of the target's outer electrons (the ionization potential of the substance), the target is ionized (i.e., the outer electrons are separated from the rest of the atom or molecule). The chemical changes produced by ionization account for the serious health effects of ionizing radiation. When the energy of the incident radiation is below the ionization potential of the target, energy is transferred to the substance's electronic levels, leading to photochemical effects, or to its rotational, vibrational, or translational states, leading to increases in thermal energy of the molecules. Although there is no well-defined boundary between ionizing and nonionizing radiation (it depends on the ionization potential of the substance to be ionized), it is conventionally set at 100 nm, which corresponds to a frequency of 3 PHz (3×10^{15} Hz), and a

quantum energy of 12.4 eV. This value is very close to the ionization potential of atomic hydrogen, the most abundant element in the universe.

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3 The generation of optical radiation
The main mechanisms that produce optical radiation are incandescence, electrical discharge, and lasing. Incandescence is the emission of radiation by hot bodies. Large numbers of energy transitions in the material's molecules, excited by the increase in kinetic energy, emit radiation over a wide frequency range. All substances at temperatures above absolute zero (–273°C) emit radiation. At low temperatures most of the emitted radiation is in the infrared range. At temperatures greater than 500° C, many substances start to emit in the visible range. As the temperature increases, the wavelength of the most intense radiation shifts in color from the red toward the blue. This phenomenon is known as Wien's displacement law: "The wavelength of maximum intensity, l_{max}, is inversely proportional to the absolute temperature, *T*, of the emitting body."

$$\lambda_{\max} = 0.29(\text{cm K})/T(\text{K}) \qquad (3)$$

The total energy flux, integrated over all wavelengths, emitted per unit area by a body at absolute temperature *T* is given by the Stefan–Boltzmann law:

$$W(\text{W/m}^2) = \sigma T^4 \qquad (4)$$

where s = 5.67×10^{-8} (w/m^2) and the temperature, *T*, in kelvin.

In order to study the emission of incandescent bodies, the simplifying assumption of an idealized nonreflecting object, or "blackbody," is often made. The distribution of the intensity of the emitted radiation as a function of wavelength for a blackbody is given by Planck's radiation law. Both Wien's and Stefan–Boltzmann's laws can be deduced mathematically from Planck's law. Dense incandescent bodies approximate the behavior of the ideal blackbody. Examples of incandescent sources of optical radiation are filament lamps, molten metals, and the sun. The sun is the main source of optical radiation in the environment. Radiation from the sun fits closely the spectral emission of a blackbody at 5900°C (6173 K).

Unlike incandescence, which produces an emission continuum, electrical discharge in a gas results in the emission of optical radiation at discrete, characteristic wavelengths (emission lines). An electric current passing through a low-pressure gas ionizes the gas and excites the electrons. The radiative de-excitation of the electrons taking place between energy levels produces photons of specific wavelengths. Increasing the pressure of the gas broadens the emission lines. At high pressures, neighboring lines start to merge, emulating a continuum. Examples of electrical-discharge sources of optical radiation are fluorescent tubes and high- and low-pressure gas lamps. Electric arcs, such as welding arcs, are powerful sources of optical radiation. Electric arcs take place when the electric potential difference between two electrodes is high enough for the electrons to breach the dielectric separating them.

Laser (light amplification by stimulated emission of radiation) radiation is generated by when the radiative de-excitation of electrons is brought about by photons of the same energy. This process is called "stimulated emission" and requires that more electrons stay in an exited atomic state than in the ground state (population inversion) for a relatively long time (metastable levels). The photons produced by stimulated emission have the same frequency (and therefore the same wavelength) and

are in phase (the radiation is said to be coherent). By using a resonant cavity, the lasing is amplified and the photons are collimated in a very narrow beam that can propagate for a long distance with minimum divergence or spread. It is the low divergence and the coherence of the monochromatic laser light that creates the unique capabilities, and hazards, of laser radiation. Different lasers can produce radiation at many wavelengths over the optical range. A comprehensive treatment of laser radiation can be found in the Chapter 103.

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4 The interaction of optical radiation with matter
Electromagnetic radiation must be absorbed by a medium in order to take effect on it. Not all electromagnetic radiation incident on a surface is absorbed; a fraction of the radiation may be reflected, and some may be transmitted through the medium. The biologically relevant energy fraction absorbed by the target, E_a, is given by:

$$E_a = E_i - E_r - E_t \quad (5)$$

where E_i is incident energy; E_r, reflected energy; and E_t, transmitted energy. In addition to reflection, transmission, and absorption, electromagnetic energy interacting with matter can undergo refraction, diffraction, and scattering. The reflection of optical radiation at the interface between two media can be specular or diffuse. In specular reflection the interface acts like a mirror, and the reflected rays follow the familiar law of reflection (the angle of reflection is equal to the angle of incidence). Specular reflection requires that the reflecting surface be smooth compared to the size of the wavelength of the incident radiation. When the surface irregularities are greater in size than the wavelength, and are oriented randomly, the reflection is diffuse. A surface that reflects radiation equally in all directions is called a *Lambertian surface*. Refraction is the change in direction that light rays, and by extension other optical radiations, undergo when traveling from one medium to another with a different index of refraction. This process is frequency dependent (that is why a prism can be used to separate the colors in white light) and follows Snell's law, which states that the ratio of the sine of the angle of incidence to that of the angle of refraction is inversely proportional to the ratio of the indexes of refraction of the media.

Scattering takes place when energy from a radiation beam is removed and redirected by particles along its path. The intensity, direction, and spectral content of scattered radiation depend on the size, orientation, and dielectric properties of the particles and on the intensity and spectral content of the incident radiation. Rayleigh scattering of sunlight by air molecules is inversely proportional to the fourth power of the wavelength and thus removes preferentially blue light. This phenomenon accounts for the blue color of the sky and the red color of sunsets.

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5 Quantities and units of optical radiation
The measurement of optical radiation requires knowledge of the amount, rate, and spectral distribution of energy emitted by sources and impinging on surfaces. Two systems are used to measure optical radiation: the radiometric and the photometric systems. The radiometric system, used throughout the optical range, is based on absolute measurements that are independent of the

characteristics of any detector. In the visible range, however, the spectral response of the human eye is all-important, and a special system of photometric quantities, relative to the spectral response of the human eye, has been developed. The main radiometric and photometric quantities and units are listed in Table 102.1

Table 102.1. Radiometric and Photometric Quantities and Units

Radiometric System		Photometric System	
Quantity	**Unit**	**Quantity**	**Unit**
Radiant energy	J	Quantity of light	lm s
Radiant flux	W	Luminous flux	lm
Irradiance	W m^{-2}	Illuminance	lm m^{-2}
Radiant intensity	W sr^{-1}	Luminous intensity	lm sr^{-1}
Radiance	W m^{-2} sr^{-1}	Luminance	lm sr^{-1} m^{-2}
Radiant exposure	J m^{-2}	Light exposure	lx s

J, joule; W, watt; sr, steradian; lm, lumen; lx = lux = lm m^{-2}; cd = candela.

The prefix “spectral” indicates that the quantity refers to a unit wavelength. The spectral irradiance at the target (W m^{-2} nm^{-1}) and the source's spectral radiance (W m^{-2} sr^{-1} nm^{-1}) are the most useful quantities in UV hazard evaluations.

The relative luminous efficiency of the eye for photopic (day) vision peaks at about 555 nm. The efficiency falls off rapidly to less than 10% of the maximum in the blue and orange wavelengths and has decreased by about four orders of magnitude at 400 and 750 nm (1). Because of this variation in the luminous efficiency as a function of wavelength, the correspondence between the radiometric and photometric output of a visible radiation source is complex.

All the quantities and units shown in Table 102.1 conform to the International System of Units [Système International (SI) d'Unitès] (2). Irradiance and radiant exposure are specified frequently in units of mW/cm^2 and mJ/cm^2, respectively (1 W/m^2 = 0.1 mW/cm^2; 1 J/m^2 = 0.1 mJ/cm^2).

The term luminance *L* describes the brightness, or luminous intensity of an object per unit area. There are several different measures of luminance; the basic unit is the candela per square meter (cd/m^2). In the English system, the unit is the footlambert (ftL). The conversion is 1 ftL = 3.426 cd/m^2. Illuminance *E* is the luminous flux per unit area impinging upon a surface. The common unit is the lumen per square meter (lm/m^2) or lux (lx). The English unit is the footcandle (ftcd), which is 10.76 lx. The candela is the unit of luminous intensity *I*. The candela is equal to one lumen per unit solid angle [steradian (sr)]. One lumen is 0.00147 W at 555 nm. The relationship between the SI and English units is summarized as:

$$\begin{aligned} \text{illuminance} \quad &- \quad \text{lm/m}^2;\ \text{lm/cm}^2;\ \text{lux (lx)};\ \text{footcandle (ftcd)} \\ &\quad 1\,\text{lm/m}^2 = 10^{-4}\,\text{lm/cm}^2 = 1\,\text{lx} = 0.0929\,\text{ftcd} \\ \text{luminance} \quad &- \quad \text{cd/m}^2;\ \text{cd/cm}^2;\ \text{footlambert (ftL)} \\ &\quad 1\,\text{cd/m}^2 = 10^{-4}\,\text{cd/cm}^2 = 0.2919\,\text{ftL} \end{aligned}$$

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6 Characteristics of Optical Radiation Sources
Radiation sources are often classified as point or extended sources. Theoretically, no source is a point source because it has a finite size. Distant stars are treated as "point" sources, although the sun is certainly an extended source. The laser is the only man-made device that is treated as a point source. All other sources are extended sources.

The intensity of the radiation emitted by a point source varies with the distance from the source according to the inverse square law. The ratio of the irradiance (E_1) at distance r_1 to that (E_2) at distance r_2 is calculated as follows:

$$\frac{E_1}{E_2} = \frac{r_2^2}{r_1^2} \qquad (6)$$

This equation is a good approximation for extended sources at distances of >10 times the maximum dimension of the source. For lasers or other collimated sources, this law can be used only at very large distances from the source. The region in which the inverse square relationship applies is called the "far" field. It does not hold in the "near" field region at distances close to the source.

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7 The Biological effects of optical radiation
The wavelengths in the optical radiation range have limited penetration into the human body. Therefore, the main organs affected by optical radiation are the skin and the eyes, although systemic effects have also been identified. Evolving in an environment where the sun is the main source of optical radiation, humans have developed adaptive characteristics, such as skin pigmentation, a hairy scalp, receded eyes, and aversion responses to bright lights and to excessive heat. These characteristics, however, provide only partial protection against optical radiation.

Optical radiation can act on biological tissue through thermal and photochemical processes. The extent of damage depends on the intensity of the radiation, the wavelength, the exposure time, and the optical and physiological characteristics of the tissue exposed. The variability in biological effectiveness of different wavelengths (three orders of magnitude within the ultraviolet range) is particularly striking. This has led to the definition of "biologically effective" quantities, which are obtained by using a biological spectral effectiveness function. Both the eye and the skin are at risk of acute and chronic injury from optical radiation. The ocular media transmit visible and near-infrared radiation to the retina, but most ultraviolet and far-infrared radiation are absorbed in the cornea and the lens. The response of the skin depends strongly on its albedo and pigmentation.
7.0 Optical Radiation
Optical radiation extends between X-rays and microwave radiation in the electromagnetic spectrum and includes ultraviolet radiation (UVR), visible radiation or light, and infrared radiation (IR). These regions are further subdivided and receive various names.
7.1 Synonyms

Ultraviolet radiation, ultraviolet light (incorrect)
Visible radiation, light
Infrared radiation, radiant heat

7.2 Physical Properties
7.2.1 General Several schemes are used to divide the optical wavelengths into spectral bands, but that of greatest importance to the photobiologist and health professionals is that adopted by the Committee on Photobiology of the International Commission on Illumination (Commission International de l'Eclairage, CIE) (3, 4). Although sharp demarcation points have been given to the regions, there is no physical basis for these transition points. Rather they serve only as a convenient framework for discussing the biological effects and exposure hazards.

In the CIE classification, ultraviolet radiation extends between 100 and 400 nm and is subdivided into 3 bands: UV-A, UV-B, and UV-C:

Infrared, Visible and Ultraviolet Radiation

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Lasers

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1.1 Properties of Lasers

Laser light is produced from transitions between atomic or molecular energy levels. Generation of light requires two energy levels, E_1 and E_2, separated by the photon energy E_p of the light that is to be produced.

$$E_p = h\nu = hc/\lambda = E_2 - E_1 = \Delta E \qquad (1)$$

where h is Planck's constant, c is the velocity of light, and E_1 and E_2 are, respectively, the lower and higher energy levels. The relevant energy levels may be those of atoms or molecules in a gas, as in the case of the helium–neon laser, or of ions embedded in a solid host material, as in a ruby laser, or they may be energy levels that belong to a crystalline lattice as a whole, as in the aluminum gallium arsenide AlGaAs, semiconductor laser.

The light emitted by a laser has a number of unusual properties that distinguish it from light emitted by conventional light sources. Unusual properties include a high degree of collimation, a narrow spectral linewidth, good coherence, and the ability to focus to an extremely small spot. Because of these properties, there are many possible applications for which lasers are better suited than conventional light sources. For example, alignment applications utilize the collimation of laser light. Spectroscopic and photochemical applications depend on the narrow spectral linewidth of tunable laser sources. Interferometric and holographic applications require a high degree of coherence.

1.1.1 Collimation

One of the most important characteristics of laser radiation is its highly directional collimated beam. Although the beam divergence angle is very small, it is not zero.

1.1.2 Spectral Linewidth

Laser light is highly monochromatic; that is, it has a very narrow spectral linewidth. This linewidth is not zero, but is typically much less than that of conventional light sources. The discussion of linewidth is complicated by the presence of the resonant longitudinal cavity modes. The spacing between the longitudinal modes is given by $c/2D$, where c is the velocity of light and D is the length of the laser. Several longitudinal modes may be present simultaneously in the laser output.

1.1.3 Coherence

Coherence implies a regular, orderly progression of the vibrations of the electromagnetic radiation. Coherence can be understood only by reference to a considerable body of mathematical development, a detailed discussion of which can be found in the literature (9). Conventional light sources do not share the property of coherence; rather these sources have a certain amount of randomness or irregularity in the oscillations of the light waves. Radio waves exhibit coherence, or orderliness, and because of coherence properties information can be impressed on radio waves for communications applications. The advent of lasers made available coherent light sources of reasonably high intensity in the visible portion of the spectrum. Coherence is important in any application in which the laser beam is to be split into parts, such as interferometry and holography. Such applications rely on the high coherence of the laser beam.

The time period Dt in which the light wave undergoes random changes is called the *coherence time*. It is related to the linewidth Dn of the laser by the equation

$$\Delta t \simeq \frac{1}{\Delta \nu} \qquad (2)$$

1.1.4 Focusing Laser Light

One of the most important properties of laser radiation is the ability to collect all the radiation using a simple lens and to focus it to a spot. It is not possible to focus the laser beam down to a mathematical point; there is always a minimum spot size, set by the physical phenomenon of diffraction. A convenient equation is

$$D_m = F\theta \quad (3)$$

where D_m is the smallest focal diameter that can be obtained, F is the focal length of the lens, and q is the beam divergence angle of the laser beam.

1.1.5 Spatial Profiles

The cross sections of laser beams have certain well-defined spatial profiles called *transverse modes*. The word *mode* in this sense should not be confused with the same word as used to discuss the spectral linewidth of lasers. Transverse modes represent configurations of the electromagnetic field determined by the boundary conditions in the laser cavity.

1.1.6 Temporal Characteristics

Laser operation may be characterized as either pulsed or continuous. There are a number of distinctive types of pulsed laser operation having widely different pulse durations.

The earliest solid-state lasers, such as ruby lasers, were simply pulsed by discharging a capacitor through a flashlamp, without any attempt to control the duration of the laser output. Such lasers typically had durations around 1 ms. The pulses were called normal or free-running laser pulses.

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1.2 Production

The widespread interest in lasers is based on practical applications. Lasers are used to perform many useful functions in science, engineering, industry, and education. Additionally, many other applications are under development. An application such as welding depends on the collimation and focusing ability of the beam, which leads to high power density. A conventional light source, even one having higher total radiant power than a welding laser, cannot be focused well and thus is not useful for welding.

Most applications for which lasers are used were originally demonstrated using conventional light sources. In many cases, the application was only marginally successful using conventional sources and required the development of laser light sources to be practical.

1.2.1 Material Processing

Laser radiation can be used for a variety of material processing functions such as welding, cutting, shaping, marking, and drilling (10–12). Even a fairly modest pulsed laser can be focused to produce a power density greater than 10^9 W/cm^2; lasers can melt and vaporize materials. Spot welding using pulsed lasers was demonstrated in the 1960s (13). Seam welding is possible by overlapping pulses, or using continuous lasers. However, the penetration depth for such welding is limited. The energy is deposited at the surface of the workpiece. For complete penetration of the weld through the workpiece, thermal conduction has to carry heat energy through the entire thickness of the specimen. In practice, this factor limited maximum weld depths to perhaps 0.1 cm, depending on the thermal conductivity of the sample.

The advent of multikilowatt carbon dioxide lasers in the early 1970s eased the 0.1-cm restriction (14, 15). The beam can drill a hole into the workpiece, then, as the beam is translated, the hole moves through the material. Molten material flows into the region behind the moving hole and resolidifies. Thus a continuous seam is produced. Because the energy is deposited at the bottom of the hole, limitations because of slowness of thermal conduction do not apply. Welds having much greater depth can be produced by this technique, called deep-penetration laser welding. Welds as deep as 5 cm have been produced in stainless steel (16). Laser welding has become widely used in practical industrial processing (17–19).

High-power laser beams can vaporize material, leading to applications such as hole drilling and cutting. Higher power densities are used for these applications than for hardening and welding. Hole drilling in ceramic materials has become common. There is a need for small (less than 0.5-mm) holes in the alumina substrates used in many electronic applications. Holes drilled before the ceramic is fired tend to change dimension during firing. After firing, the material is very hard, brittle, and difficult to drill by conventional techniques. Laser drilling offers an improved technique for producing holes in the fired ceramic, and has become an important application for lasers in the electronics industry.

High-power lasers have impressive capabilities for cutting both metallic and nonmetallic materials. The cutting rates can be increased by the presence of gases. Typically oxygen is used but other gases have sometimes been employed. A jet of oxygen or air is blown on the workpiece at the position where the beam strikes it. The exothermic chemical reaction with the oxygen can greatly increase the cutting rate for reactive materials. Laser cutting is widely used in many practical applications, such as cutting titanium in the aerospace industry, cutting steel plates in the automotive industry, and cutting fabric in the garment industry.

Another important application involving material processing is trimming of resistors. Thick-film resistors used in many electronic circuits must be trimmed to the final desired value. This can be done by fabricating the resistor using a low value of resistance and then cutting part way through it with a laser. The resistance can be monitored as cutting proceeds. Trimming is terminated when the desired value is reached. Repetitively Q-switched Nd:YAG lasers are commonly used for resistor trimming. Laser trimming has become a standard procedure in the electronics industry.

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1.3 Use
1.3.1 Measurement Applications
Lasers have been used for measurement of many physical parameters. These include length and distance, velocity of fluid flow and of solid surfaces, dimensions of manufactured goods, and the quality of surfaces, including flaw detection and determination of surface finish.

Lasers are used in measurement of lengths in a variety of ways (20, 21). A very short pulse of high-power laser light may be directed toward a target the distance of which is desired. A photodetector viewing the target collects a signal resulting from light reflected by the target. The time t between the outgoing pulse and the detection of the reflected signal, that is, the time for the light to make a round trip from the laser to the target and back, is measured. Because the velocity of light is known, the range R to the target is

$$R = ct/2n \tag{4}$$

where n is the index of refraction of the air through which the pulse travels. Because the index of refraction depends on air temperature, pressure, altitude, and other factors, this method is subject to some uncertainties. It has been used for accurate measurement of the distance from the earth to the moon. Table 103.2 lists methods using lasers for measuring distances.

Table 103.2. Distance Measurement Using Lasers

Method	Laser type	Range	Typical application

Round-trip time-of-flight	Q-switched solid state	many km	Military ranging, satellite ranging
Phase comparison of amplitude-modulated beam	He–Ne, AlGaAs	km	Surveying
Interferometry	Frequency-stabilized He–Ne	few meters	Machine-tool control
Laser Doppler displacement	He–Ne	to 120 m	Machine-tool control

1.3.2 Holography

Holography, a photographic process that yields three-dimensional images, was invented in the prelaser era in 1948 (22). Light sources available at that time were not adequate for making good holograms and holography became practical only after the invention of the laser (23). The properties of coherence and monochromaticity offered by lasers are important for holography.

1.3.3 Medical Applications

Lasers have been used for a variety of medical applications. Perhaps the repair of tears and holes in the retina may be the best-known example.

Laser photocoagulation also has been widely used to treat diabetic retinopathy, one of the leading causes of blindness in the United States.

Laser removal of tattoos and of colored birthmarks has been widely studied. A high-power pulsed laser at a wavelength absorbed by the pigment is used to vaporize the pigment and to bleach the colored area. Ruby, Nd:YAG, and dye lasers are favored for this purpose.

High-power carbon dioxide lasers have been used for surgery. Absorption by tissue is very high at the 10-mm wavelength of the carbon dioxide laser. Laser surgery provides a possibility for simultaneous cutting and cauterization. Use of carbon dioxide lasers for bloodless surgery has been widely studied, especially for blood-rich organs such as the liver. Laser surgery has also been widely used for ear, nose, and throat procedures.

Laser angioplasty, a procedure in which laser energy is delivered through an optical fiber inserted into a blood vessel to a location of a blockage in the vessel and used to burn through the blockage, was studied extensively during the 1980s. Early enthusiasm for the procedure as a treatment for coronary disease seems to have waned because blockages can recur at the same locations.

The development of so-called photodynamic therapy uses lasers for treatment of cancer. The patient is injected with a substance called hematoporphyrin derivative, which is preferentially localized in cancerous tissues. The patient is later irradiated with laser light, often with a dye laser at a wavelength around 630 nm. The light energy catalytically photooxidizes the hematoporphyrin derivative, releasing materials that kill the nearby cancerous tissue. Normal tissue that did not retain the chemical is not harmed. Photodynamic therapy offers promise as a new form of cancer treatment.

1.3.4 Communications

The advent of the laser improved prospects for optical communications enormously. The coherence of the laser meant that techniques developed in the radio portion of the electromagnetic spectrum could be extended to the optical portion of the spectrum. Because lasers operate at frequencies near 10^{15} Hz, they offer a potentially wide bandwidth, equal to about 10^{7} television channels of width (ca. 10^{8} Hz). It has not proved possible to take advantage of this full bandwidth because devices such as modulators capable of operating at 10^{15} Hz are not available.

Laser communication systems based on free-space propagation through the atmosphere suffer drawbacks because of factors like atmospheric turbulence and attenuation by rain, snow, haze, or fog. Nevertheless, free-space laser communication systems were developed for many applications (24–26). They employ separate components, such as lasers, modulators, collimators and detectors. Some of the most promising applications are for space communications, because the problems of turbulence and opacity in the atmosphere are absent.

The most important application of fiber-optic laser-based communication is in long-distance telecommunications (27, 28). Fiber-optic systems offer very high capacity, low cost-per-channel, light weight, small size, and immunity to crosstalk and electrical interference.

Laser-based fiber-optic telecommunications has had a revolutionary impact on long-distance telephone communication and is now expanding into many new applications areas.

1.3.5 Consumer Products

Laser-based products have emerged from the laboratories and become familiar products used by many millions of people in everyday circumstances. Examples include the supermarket scanner, the laser printer, and the compact disk.

1.3.6 Spectroscopic Applications

Laser technology has led to a revolution in spectroscopic techniques. Absorption spectroscopy can be carried out at much higher resolution than is available from conventional spectrometers.

1.3.7 Laser Photochemistry

Photochemical applications of lasers generally employ tunable lasers that can be tuned to a specific absorption resonance of an atom or molecule. Examples include the tunable dye laser in the ultraviolet, visible, and near-infrared portions of the spectrum; the titanium-doped sapphire, Ti:sapphire, laser in the visible and near infrared; optical parametric oscillators in the visible and infrared; and line-tunable carbon dioxide lasers, which can be tuned with a wavelength-selective element to any of a large number of closely spaced lines in the infrared near 10 mm.

Other uses include purification of materials, deposition of thin films, isotope separation, and laser-assisted thermonuclear fusion.

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David H. Sliney, Ph.D.

1.4 Toxic Effects

Laser radiation can pose significant risks to vision when the eye is located within the beam (intrabeam viewing), and occupational Exposure Limits (ELs) have been developed for these conditions (1–10). Lasers pose a more significant optical radiation hazard than conventional light sources because lasers have a far greater brightness (radiance) and because a typical laser has a collimated beam, which can present a hazard to the eye at a significant distance. The potential hazards vary with wavelength, and this is particularly true for the eye, which is the more vulnerable organ because of its special optical properties. The eye is particularly vulnerable to injury in the retinal hazard region from 400 nm at the short-wavelength end of the visible spectrum to 1400 nm in the near-infrared part of the spectrum (29, 30). Within this spectral band, a collimated beam can be focused to a 15–20-mm-diameter retinal spot (i.e., much smaller than the diameter of a human hair). The gain in beam irradiance from cornea to retina is approximately 100,000 times in the visible spectrum. Hence, a corneal beam irradiance of 1 W/cm^2 becomes 100 kW/cm^2 at the retina. Vision loss can vary from temporary after-images to a permanent blind spot (scotoma) or even total loss of vision in an eye (29). Figure 103.1. illustrates that because of the great brightness of a laser, its radiant energy can be greatly concentrated when focused (e.g., upon the retina) as compared to the rays from conventional light sources, which are much less bright. This very high radiance can be

expressed as MW and TW cm^{-2} sr^{-1}, and this radiance is responsible for the laser's great value in material processing and laser surgery. When compared to a xenon arc or the sun, even a small He–Ne alignment laser or diode laser pointer is typically ten times brighter.

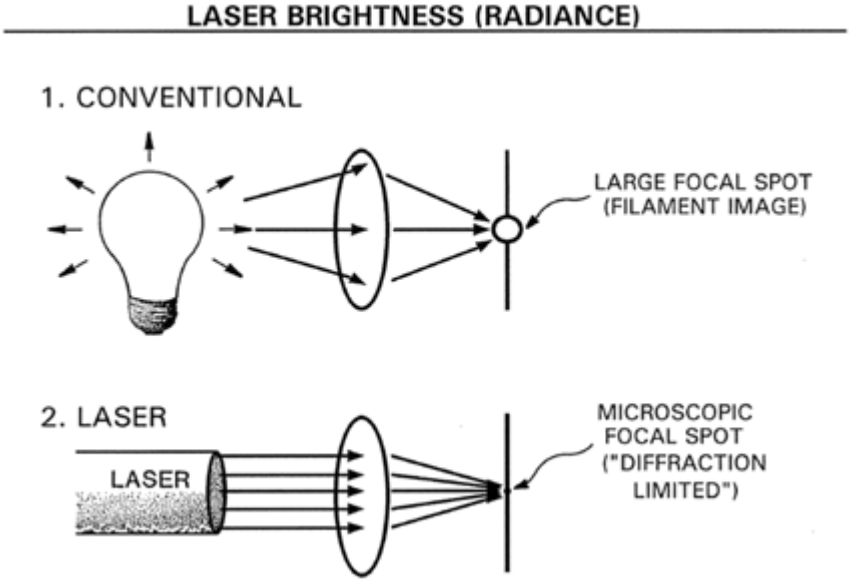

Figure 103.1. The great brightness (radiance) of a laser permits its beam to be greatly concentrated when focused as compared to the rays from conventional light sources, which are much less bright.

Although the laser focal image on the retina may cover only 20–30 cone cells, the retinal injury is always larger because of heat flow and acoustic transients (29). Even a small disturbance of the retina can be significant. This is particularly important in the region of central vision referred to by eye specialists as the *macula lutea* (Latin for "yellow spot"), or simply the "macula." The central region of the macula, the fovea centralis, is responsible for detailed "20/20" vision. Damage to this extremely small (about 150-mm-diameter) central region can result in severe vision loss even though 99% of the retina remains unscathed. The surrounding (peripheral) retina is useful for movement detection and other tasks but possesses little acuity. The eye moves across a line of print to read, because an individual's detailed vision covers only a very small angular subtense centered in the fovea. Outside the 400–1400-nm retinal hazard region the cornea—and even the lens—can be damaged by laser beam exposure (29, 30).

Diffuse reflections of laser beams are normally safe to view, since the energy is dissipated upon reflection into all directions and the resulting image on the retina is normally that of an extended source. However, under special conditions, it is a realistic possibility to produce a hazardous diffuse reflection. This can result from a diffuse reflection of a Q-switched (1–100-ns) laser in the retinal hazard region (29). This retinal injury hazard from diffuse reflections was one of the criteria for placing some pulsed lasers in the high-risk category known as Class 4 (29, 30).

The adverse effects associated with viewing lasers or other bright light sources such as the sun, arc lamps, and welding arcs have been studied for decades (31–35). Injury thresholds for acute injury in experimental animals for corneal, lenticular and retinal effects have been corroborated for the human eye from accident data.

1.4.1 Injury Mechanisms

For most exposure durations (t>1 s), laser-induced injury is dominated by either photochemically or thermally initiated events taking place during or immediately following the absorption of radiant energy. At nanosecond (1 ns = 10^{-9} s) or shorter durations, nonlinear mechanisms may play a role (29, 31, 36). Following the initial insult, biological repair responses may play a significant role in determining the final consequences of the event (38, 39). While inflammatory, repair responses are

intended to reduce the sequellae, in some instances, this response could result in events such as scarring, which could have an adverse impact upon biological function (40). Within the first several weeks, the inflammatory reaction itself (e.g., edema) may interfere with function (40, 41).

Laser damage thresholds vary with wavelength, duration, and spot size. However, photochemical and thermal effects vary differently depending on the wavelength, the exposure duration, and the size of the irradiated area. Indeed, experimental biological studies in humans and animals make use of these different relationships to distinguish between which of several competing mechanisms is playing a dominant role in observed injury (39). Photochemical injury is highly wavelength dependent, while thermal injury depends upon exposure duration. Each of these factors will be examined in the following.

1.4.1.1 Exposure Duration The Bunsen–Roscoe Law of photochemistry describes the *reciprocity* of exposure rate and duration of exposure. This law applies to any photochemical event. The product of the irradiance or dose rate (in watts per square centimeter) and the exposure duration (in seconds) equals the exposure dose (in joules per square centimeter at the site of absorption) to produce a threshold injury. Radiometrically this is expressed as: The irradiance E in W/cm^2 multiplied by the exposure duration t is the radiant exposure H in J/cm^2.

$$H = Et \tag{5}$$

Repair mechanisms and other biochemical changes over long periods (hours) and photon saturation for extremely short (submicrosecond) periods will lead to reciprocity failure. This reciprocity helps to distinguish photochemical injury mechanisms from thermal injury (burns). Because of heat conduction, thermal injury generally requires a very intense exposure within seconds to cause photocoagulation; otherwise, surrounding tissue conducts the heat away from the absorption site (e.g., a retinal image).

Thermal injury is a *rate process* dependent upon the volumic absorption of energy across the spectrum. The thermochemical reactions that produce coagulation of proteins and cell death require critical temperatures for detectable biological injury. The critical temperature for an injury gradually decreases with the lengthening of exposure duration. This approximate decrease in temperature varies over many orders of magnitude in time and deceases approximately as the exposure duration t raised to the – 0.25 power [i.e., $f(t^{-0.25})$].

1.4.1.2 Wavelength Action Spectrum As with any photochemical reaction, the *action spectrum* should be known (42). The action spectrum describes the relative effectiveness of different wavelengths in causing a photobiological effect. For most photobiological effects (whether beneficial or adverse), the full width at half-maximum of the action spectrum is less than 100 nm, and a long-wavelength “cutoff” exists where photon energy is insufficient to produce the effect. This is not at all characteristic of thermal effects, where the effect occurs over a wide range of wavelengths where optical penetration and tissue absorption occur. For example, significant radiant energy can penetrate the ocular media and be absorbed in the retina in the spectral region between 400 and nearly 1400 nm, and the absorbed energy can produce retinal thermal injury (29, 30).

Although the action spectra for acute photochemical effects upon the skin, cornea, lens, and retina have been published (43), the action spectra of some other effects appear to be quite imprecise or even unknown (35, 41, 43, 44).

1.4.1.3 Eye Movements Several physiological factors must be considered for CW exposures (generally thought of as greater than 0.25 s), where the person's visual task will limit the exposure duration and the retinal area illuminated. Physiological factors, such as pupillary activity, eye movements, breathing, heartbeat, blood flow, other bodily movements, and visual task behavior become important. In addition, at short visible wavelengths, another injury mechanism

(photochemical) plays an important role. All these factors were considered in setting the ELs for exposure durations greater than 10 s.

Eye-movement studies of Ness et al. (53) showed that the retinal image can remain remarkably still for a few seconds, but that within 30 s, the central retina (the fovea) must move to other points in space for cognition. Two viewing conditions were studied: with a stabilized head (as could occur with ophthalmic instrument applications of lasers), and without head restraint (normal conditions) while volunteers attempted to fixate on a small "point" light source. Results are evaluated in a variety of ways. The fixation history of the small retinal image diameter d_r (< 30 mm) can be plotted as a function of time to determine the integration of retinal exposure dose. The accumulated radiant exposure in the retinal image area directly predicts the extent and position of photochemical retinal injury, since retinal radiant exposure determines the risk of photoretinitis for a given wavelength. While these data permitted the determination of the photoretinitis ("blue-light hazard") EL value, the determination of the thermal hazard ELs was more complex, since thermal retinal injury thresholds decrease for increasing retinal spot size.

The determination of the potential for retinal thermal injury for long fixation times requires an examination of three factors:

1. The time-averaged retinal irradiance
2. The thermal effects that result from the way eye movements transform a fixed retinal image into the equivalent of a repetitive-pulse exposure
3. The manner in which image size affects the retinal thermal injury threshold due to radial heat flow during and after the exposure

The time-averaged retinal irradiance must not exceed the CW irradiance permitted for a fixed image. The thermal repetitive-pulse exposure obeys what is referred to as the $N^{-0.25}$ additivity rule, where the net effect is modified as the number of pulses N raised to the –0.25 power ($N^{-0.25}$).

Correction factors for eye movements are only important for viewing durations exceeding 10 s. Only the thermal mechanism is important at durations less than 1 s for small images. Although the physiological eye movements known as saccades do spread the absorbed energy in minimal retinal images (of the order of 25 mm or less) within the 0.1 to 10 s time regime, the limits recommended in these guidelines provide an added safety factor for this viewing condition. At 0.25 s with unrestrained head viewing, the mean retinal spot illuminated is spread out to approximately 50 mm. By 10 s, the illuminated retinal zone becomes approximately 75 mm, and the added safety factor for the minimal image condition becomes 1.7 over a stabilized eye, with the spot-size dependence taken into account. By 100 s, it is rare to achieve an illuminated zone (measured at 50% points) as small as 135 mm, and this means that there is, in effect, an additional safety factor of 2.3 or more above the minimal image condition. The data from eye-movement studies and retinal thermal injury studies were combined to derive a break-point in viewing time T_2 at which eye movements compensated for the increased theoretical risk of thermal injury for increased retinal exposure durations if the eye were immobilized.

The impact of eye movements is dramatic for minimal retinal spot sizes and permits a leveling of the thermal EL for a > 1.5 mrad to a constant irradiance of 1 mW/cm^2 in the visible spectrum (400–700 nm) for t > 10 s. However, as would be expected, there is only a small impact for a source size of 100 mrad, and the plateau of no further risk of retinal injury due to eye movements does not occur until 100 s. For photochemical injury, eye movements had already been incorporated into the visible laser limits for exposure durations between 10 and 100 s. Beyond 100 s, it is probably unreasonable to assume that fixation could realistically take place, and it was concluded that the limits for all but very large sources (greater than 100 mrad) should end there.

1.4.2 Acute Effects upon Vision

Accidental exposure of the eye to intense laser radiation can result in a range of visual effects. Three general effects upon vision are of particular importance. These three effects are: scotoma, visual disturbances, and acute injury to the cornea. Within the retinal hazard region, a scotoma, or blind spot can appear in the injured person's visual field. The scotoma will appear instantaneously if the injury from thermocoagulation and acoustic disruption of the retina is caused by a pulsed laser beam (approximately 420–1300 nm) focused on the retina. The result of this injury can be permanent functional loss depending upon the severity of the initial injury and whether scarring takes place in the retina which can produce a larger lesion than if biological repair is optimal. At levels below the MPE, temporary visual disturbances may occur. There are two sources of such a transient vision disturbance: (*1*) Veiling glare and (*2*) afterimages, or "flashblindness." Veiling glare from a CW laser is comparable to viewing oncoming automobile headlights while driving. While this glare can make it difficult to see (disability glare) or can be very uncomfortable (discomfort glare), it exists only as long as the laser illuminates the eyes. An afterimage (flashblindness) is most pronounced for low ambient illuminations. The duration of the afterimage is greatest for low ambient illumination (i.e., at night) and for the brightest sources. Although these transient effects are difficult to quantify, they may result in a transient, partial scotoma. The third category of visual effect results from acute injury to the cornea or lens. The effect may be immediate from thermal coagulation or thermal ablation, or it may be delayed for 9–24 h following UV photochemical injury. These injuries can cause the entire visual field to become cloudy due to light scatter.

1.4.3 Types of Injury

The human eye is actually quite well adapted to protect itself against the potential hazards from ambient environmental optical radiation (ultraviolet, visible, and infrared radiant energy) from sunlight unless ground reflections are unusually high, as when snow is on the ground, and reflected UV radiation can produce "snow blindness." Another exception to the general rule occurs during a solar eclipse, when some individuals stare directly at the solar disc for more than a couple of minutes without eye protection and incur an "eclipse burn" of the retina (photoretinitis) (29, 34). Lasers may injure the eye when the normal defense mechanisms of squinting, blinking, and aversion to bright light are overcome, as can occur when viewing pulsed lasers or when the eye is exposed to an invisible infrared or ultraviolet beam.

There are at least six separate types of injuries to the eye from lasers and other intense optical sources (listed with the approximate spectral region noted in parentheses):3

1. Ultraviolet photochemical injury to the cornea (photokeratitis)—also known as "welder's flash" or "snow blindness (180–400 nm) (41, 44) and erythema ("sunburn") of the skin (29, 43).
2. Ultraviolet photochemical injury to the crystalline lens (cataract) of the eye (295–325 nm, and perhaps to 400 nm) (29, 30, 44).
3. Blue-light photochemical injury to the retina of the eye (principally 400–550 nm; unless aphakic, 310–550 nm) (34, 35).
4. Thermal injury (photocoagulation) to the retina of the eye (400 to nearly 1400 nm), and thermoacoustic injury at very short laser exposure durations.
5. Near-infrared thermal hazards to the lens (approximately 800–3000 nm) (45, 46).
6. Thermal injury (burns) of the cornea of the eye (approximately 1400 nm to 1 mm) or to the skin (approx 320 nm to 1 mm) (29, 30).

The range of the aforementioned potential hazards to the eye and skin are illustrated in Figure 103.2, which shows how specific effects are generally dominant in certain CIE photobiological spectral bands, UV-A, -B and -C and infrared A, B, and C (47). Although these photobiological bands are useful shorthand notations, they do not define fine lines between no effect and an effect in accordance with changing wavelengths.

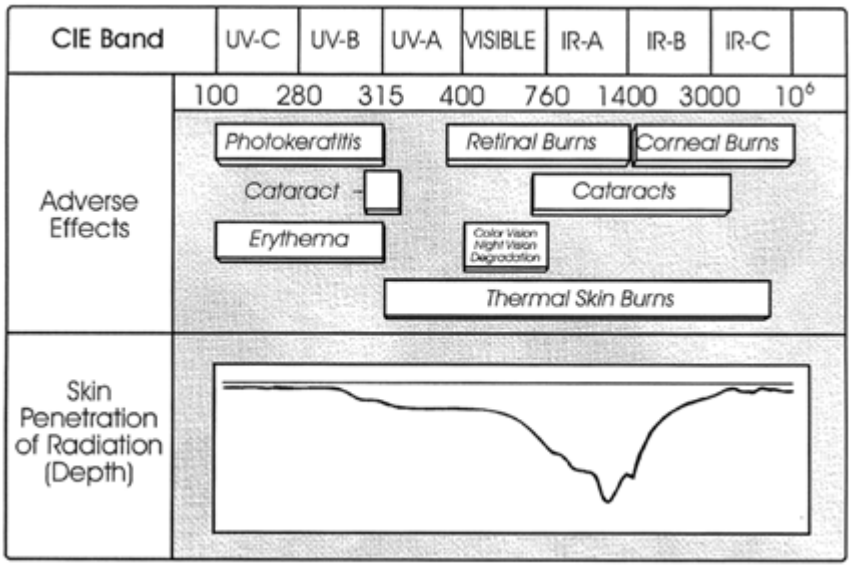

Figure 103.2. The potential hazards to the eye and skin as a function of wavelength. Certain effects are generally dominant in each CIE photobiological spectral band.

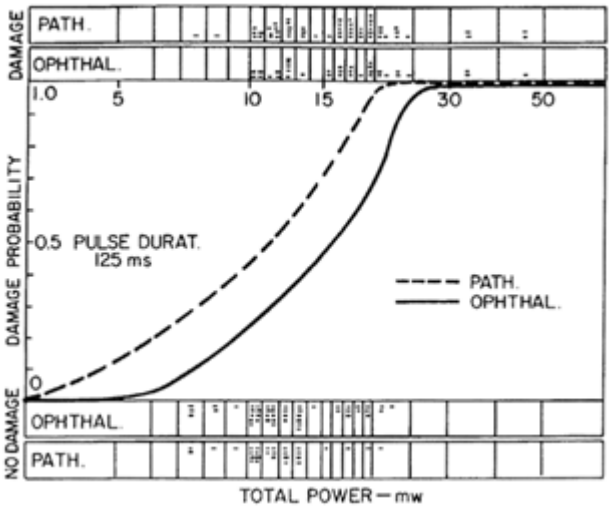

Figure 103.3. A typical probit presentation of experimental laser retinal threshold injury data where the ED_{50} has a probit value of 5.0. Strictly speaking, the probit value of 5.0 occurs at a 50% probability value.

1.4.3.1 Photokeratitis The relative position of the laser source and the degree of lid closure can greatly affect the proper calculation of this ultraviolet exposure dose low-level; scattered UV from excimer lasers has produced photokeratitis in workers. For assessing risk of photochemical injury, the laser wavelength is of great importance. Wavelengths between 260 and 280 nm are at the peak of the action spectrum and are the most dangerous (44).

1.4.3.2 Cataract Ultraviolet cataracts can be produced from exposure to UVR of wavelengths between 295 and 325 nm (and perhaps to 400 nm). Action spectra can only be obtained from animal studies, which have shown that cortical and anterior subcapsular cataract can be produced by intense exposure delivered over a period of days. Human cortical cataract has been linked to chronic, lifelong UV-B radiation exposure. Although the animal studies and some epidemiological studies suggest that it is primarily UV-B radiation in sunlight (44), and not UV-A, that is most injurious to the lens, biochemical studies suggest that UV-A radiation may also contribute to accelerated aging of

the lens. Since there is an earlier age of onset of cataract in equatorial zones, UVR exposure has frequently been one of the most appealing of a number of theories to explain this latitudinal dependence (35, 48). Laser exposure from the xenon–chloride laser at 308 nm is of particular concern, since this wavelength is in the narrow action spectrum for acute cataract. The ACGIH TLV and ICNIRP laser and noncoherent UVR guidelines are also intended to protect against cataracts (31, 36, 49, 50).

Since the only direct pathway of UVR to the inferior germinative area of the lens is from the extreme temporal direction, it has been speculated that side exposure is particularly hazardous. In the case of the lens, the germinative layer where lens fiber cell nuclei are located is of great importance. The DNA in these cells is normally well shielded by the parasol effect of the irises. However, Coroneo et al. have shown that the focusing of very a peripheral 308-nm beam by the temporal edge of the cornea can enter the pupil and focus in the equatorial region (48, 51). The Coroneo effect argues for assuring well-fitting side shields on UV laser eye protectors.

1.4.3.3 Photoretinitis The principal retinal hazard resulting from lengthy staring at bright CW light sources is photoretinitis. The best example is *solar retinitis* with an accompanying scotoma ("blind spot"), which results from staring at the sun. Solar retinitis was once referred to as "eclipse blindness" and associated "retinal burn." At one time, solar retinitis was thought to be a thermal injury, but it has been since shown conclusively to result from a photochemical injury related to exposure of the retina to shorter wavelengths in the visible spectrum, that is, violet and blue light (52). For this reason, it has frequently been referred to as the "blue-light" hazard. The action spectrum for photoretinitis peaks at about 445 nm in the normal phakic eye (34, 52). Laser exposure limits were revised to better characterize and quantify the risk from these blue laser wavelengths in 1999.

As a consequence of the Bunsen–Roscoe Law of photochemistry, blue-light retinal injury (photoretinitis) can result from viewing either an extremely bright blue laser reflection for a short time, or a less bright source for longer periods. The approximate retinal threshold for a helium–cadmium laser at 441.6 nm is approximately 22 J/cm^2; hence a retinal irradiance of 2.2 W/cm^2 delivered in 10 s, or 0.022 W/cm^2 delivered in 1000 s, will result in the same threshold retinal lesion (34). Eye movements will reduce the hazard, and this is particularly important for sources subtending an angle less than 11 mrad. Saccadic motion even during fixation is of the order of 11 mrad. In 1999 laser exposure limits were adjusted to provide for dual limits (photochemical or thermal) for retinal exposure and for the effect durations greater than 1–10 s (53).

1.4.3.4 Infrared Cataract Infrared cataract in industrial workers appears only after a lifetime of exposure to radiances of the order of 80–150 mW/cm^2 (29, 45). Although thermal cataracts were observed in glassblowers, steel workers, and others in metal industries at the turn of the century, they are rarely seen today (45). These irradiances are almost never exceeded in modern industry, where workers will be limited in exposure duration to brief periods above 10 mW/cm^2 or they will be wearing eye protectors. Good compliance in wearing eye protection occurs at higher irradiances if only because the worker desires comfort of the face. This is not a realistic exposure condition from infrared laser radiation. Laser heat treating of metal surfaces can produce reasonably high reflected irradiances, but levels of concern would be felt and considered quite uncomfortable. Thus a lengthy exposure of today's worker to such levels is unrealistic.

1.4.4 Experimental Studies

ELs for laser radiation are based largely upon experimental ocular injury studies. Most threshold data have been obtained from animal studies (primates and rabbits), although some limited human data exist for confirmation of the animal model.

W. T. Ham, Jr., and others studied (54) the effect of cumulative long-term exposure to pulsed laser on retinal injury in rhesus monkeys and cynomolgus monkeys. The main optical source was a continuous-wave argon/krypton laser (ArKrL) with emission lines at 647, 514.5, and 488 nm. The

pulses were produced at pulse repetition frequencies (PRFs) of 100, 200, 400, and 1600 Hz by chopping with a rotating disk. A helium/neon laser (HeNeL) was used to compare the ocular effects of 632.8-nm light width with the 647-nm line emitted by the ArKrL. The appearance of a visible minimal lesion in the paramacular area of the retina at 48 h postexposure was the biological threshold. The mean exposure damage level was determined by interpolation. A comparison of thresholds between wavelengths 632.8 and 647-nm for 500-mm-diameter retinal images at exposure times of 1, 16, 100, 1000, 3000, and 10,000 s showed that up to exposure times of 1000 s there was no significant difference between the thresholds for retinal damage from the krypton 647-nm and from the HeNeL 632.8-nm exposures. Beyond the 1000-s exposures the 632.8-nm wavelenght had a significantly lower threshold than the 647-nm line. The threshold for minimal retinal injury was always lower for the blue than for the red pluse trains. For 1000-s exposures at PRF of 1600 Hz the threshold was lower than for continuous-wave red light. The authors concluded that no ocular hazards exist in conventional application of nominal 1 mW HeNeL, such as those used in supermarket scanners.

W. T. Ham, Jr., and others also (55) exposed seven rhesus monkeys (14 eyes) to 1064-nm radiation in single pulses of 25 to 35 ps from a mode-locked Nd:YAG laser. Threshold injury resulted from single pluse with a mean energy of 13 mJ. Electron microscopy of the retina revealed that damage was highly localized in the photoreceptor and pigmented epithelial cells at the outer retina. Membrane disruption, distorted outer segments, and abnormal melanin granules resembling fetal premelanosomes were observed.

D. N. Farrer and others (56) conducted studies to evaluate retinal threshold burns and subthreshold exposures of the mammalian macula in terms of visual acuity. Rhesus monkeys (*Macaca mulatta*) were trained by a reward system to respond to the automated presentation of Landolt rings. After appropriate training, these animals were exposed to threshold and subthreshold levels of retinal energy density ranging from 3.2 to 10.7 J/cm^2, exposure time approximately 135 ms, spectral quality approximately that of color, a temperature of 6000 K with wavelength above 900 nm removed, and image sizes on the retina of about 1 nm in diameter, covering a major portion of the monkey macular area. Results, in terms of visual acuity decrement (monocular), indicated that energy densities on the retina below 5 J/cm^2 were not statistically significant, whereas energy densities greater than 5 J/cm^2 produced losses in visual acuity (monocular) that were significant. These results indicate that, at levels of energy density on the retina 80–50% below the threshold burn level, no loss in visual acuity can be detected in the rhesus monkey by the Landolt-ring testing system adopted for this investigation.

The ELs must be based upon an understanding of the mechanisms of laser/tissue interaction as well. A major point of discussion in the EL derivation process relates to the level of uncertainty of the threshold of injury. An indication of the level of uncertainty relates to the slope of the transformed dose-response curve, or the "probit plot" of the data. The most important point on the probit plot is the exposure which represents a 50% probability of injury: the ED_{50}. It is this value that is frequently referred to as the "threshold," even though some experimental damage points exist below this "threshold."

An analysis of any number of example data sets reveals that the slope in most experiments could not be explained by biological variation alone. This type of critical analysis is essential in deriving ELs. For example, if the slope is not very steep, as with some retinal injury studies, the probit curve may suggest that at one-tenth the ED_{50} energy value, there might be a 0.1% risk of injury—a risk generally

not acceptable in the laser safety community. Yet, from fundamental biophysical principles, this result could be shown clearly to be flawed. If the ED_{50} energy corresponds to a retinal temperature elevation of 150, an energy of 10% of the ED_{50} must correspond to 1.50 (10% of the ED_{50}

temperature elevation), which could not produce photocoagulation. This aptly illustrates that any derivation of human exposure limits for laser-induced injury requires one to estimate the true biological variation and separate this from the added experimental errors which reduces the probit slope.

Analysis of reported experimental data indicates that the thermal and thermoacoustic damage mechanisms apparently have an intrinsic slope of approximately 1.15 to 1.2. However, experimental threshold data from retinal studies give slopes that are often much greater (e.g., 1.5–1.7), which is really not surprising. The enormous difficulty of seeing a minimally visible lesion and focussing the laser beam to produce the nearly diffraction-limited image leads to this greater spread of data and shallower slopes. A probit curve applied to the derivation of exposure limits should have a slope of 1.2 or less with the ED_{50} point shifted to a lower value. The steepness of the probit curve is therefore not only related to the type of damage mechanism and variation among individual animals, but also indicates problems in conducting the experiment. Traditionally, all of these factors are assessed collectively in order to derive an appropriate "safety factor" for deriving the EL from the ED_{50}. The safety factor is not a true ratio between a true "threshold of injury" and the EL, but represents a committee judgement of uncertainties. Greater safety factors have been applied when uncertainties are greatest, and considerations of extrapolation from animal to human are also part of the process.

In an ideal experiment where the experimental errors introduced by the beam propagation through the ocular media were not present, the true spread of retinal threshold data would be much smaller than that obtained by current experimental methods aimed at determining the minimum visible lesion (MVL). The type of damage mechanism will affect the absolute spread of threshold data. Based upon the current understanding of the retinal injury mechanisms by short-pulsed lasers, thermal photocoagulation dominates for pulse durations of 10 ns to many milliseconds. Injury thresholds appear to vary little from 10 ns to about 18–50 ms. At longer durations, the thresholds increase because heat flow occurs during the exposure. At subnanosecond exposure durations, other nonlinear damage mechanisms come into play, such as self-focusing and laser-induced breakdown. The thermal and thermomechanical mechanisms have sharply defined thresholds in experiments where tissue is directly exposed without confounding factors, as in CO_2 laser-induced corneal injury. More stochastic effects appear in the subnanosecond regime (37, 40).

In the determination of thresholds of laser-induced injury, direct observation by ophthalmic instrument is most frequently used. For retinal studies, the ophthalmoscope or slit-lamp microscope is used by the experimentalist to observe the retinal location where the laser exposure takes place. In some cases the visibility of the laser-induced lesion can be improved by a technique known as *fluorescein angiography*, and some workers have even used light and electron microscopy to examine the exposed tissue. These measures claim to have greater sensitivity, but are more costly and less practical. Although fluorescein angiography is frequently used, the detailed histological studies with microscopic examination of thin slices of exposed tissue have only been carried out for specified laser wavelengths and exposure durations to quantify the reduction in the ophthalmoscopically determined ED_{50} by the more elaborate techniques.

The quantitative value of ED_{50} and the spread of data points can change by varying the experimental techniques. One of the most critical elements of the experimental protocol is the delay between laser exposure and time of examination, because biological changes undergo a time course following injury. Typical delays for examination range from 5 min to 48 h, with 1 and 24 h being the most frequently used. Depending upon damage mechanism (i.e., thermal, thermomechanical, photochemical, etc.), the optimum period to determine the ED_{50} changes as the time course varies for the biological response and amplification of the initial biophysical tissue insult.

Another factor that affects the ED_{50} value is the choice of experimental animal. One of the most

frequently used animals in ophthalmic research is the rabbit; it is used most often for corneal injury studies and in many early retinal studies. However, the optical quality of the rabbit eye is poor, leading to distorted retinal images and inaccurate threshold determinations (1–2). There have been studies employing ophthalmic contact lenses and careful optical alignment of the anesthetized rabbit to eliminate most corneal aberrations in the eye. These conditions produce nearly diffraction-limited retinal images and low threshold values; however, the required extrapolation to the human eye with its reduced optical performance leads to some level of uncertainty. Hence the currently most favored animal model has become the rhesus monkey for retinal studies by most investigators, and this has greatly increased the cost of the experiment, leading to fewer threshold determinations.

Still another factor, the retinal pigmentation, will determine the fraction of incident energy absorbed at each wavelength and thereby affect the resulting ED_{50}. Pigmentation in the retinal pigment epithelium (RPE) and choroid varies with the individual subject, the species, and the retinal location. Although the color of the rabbit retina appears to more closely resemble the human retina, it has been argued that the pigment density in the rhesus monkey is more similar to that of humans. In any case, these variables are accounted for in the derivation of MPEs and are considered in this report.

Another factor of concern is the refractive state of the experimental subject. As this refractive state determines whether the minimal retinal image size of a collimated laser beam is achieved, this is critical. A one-diopter error in the refractive state can result in an increase in the achieved retinal blur circle from approximately 25 mm to about 120 mm—a change in image area of 22 times. Investigators therefore normally attempt to correct the animal's state of refraction in the visible, but even this does not take into account the chromatic aberrations—also of the order of one diopter across the visible spectrum. Investigators are able to correct the refraction to within 0.25 D, which leads to an uncertainty in actually achieved minimal retinal image diameter of approximately 20–50 mm. Furthermore, during an investigative session, the animal's refractive state will vary slightly from exposure to exposure, the degree depending upon the level of anesthesia.

Eye movements during the experimental exposure will also affect the outcome. These eye movements will only be of concern for exposures lasting more than 10 ms. In the derivation of ELs, the impact of anesthetized animal exposures on the retinal injury threshold is measured (50, 53). This showed that laser energy was concentrated in a much smaller retinal area for exposures of several seconds, with the effect of eye movements considered in the derivation.

The actual site of retinal exposure will influence the ED_{50}. This occurs for two reasons. The optical quality of the eye for off-axis beams is somewhat less than for axial exposures to the fovea. Furthermore, the pigmentation and thickness of the neural retina vary from the center of the fovea, through the macula to the para-macular regions. As a general rule, the ED_{50} values will be less in the fovea than parafoveal or paramacular. This variation is of the order of twofold.

The state of the ocular media (cornea, aqueous, lens, and vitreous) influences the distribution of radiant energy at the retina. Intraocular scatter diffuses the beam, and depending upon the nature and size of the scattering centers in the ocular media, small-angle forward scatter and diffuse scatter will vary. The age of the eye, the care taken by the experimentalist to preserve corneal clarity by frequent irrigation of the cornea (or use of contact lens), and the potential for subtle lenticular opacities (early stages of cataractogenesis) all play a role in producing scatter.

The ability of the experimental investigator observing the retina to detect a just-perceptible minimum visible lesion (MVL) also influences the ED_{50} value. As investigators have more experience, the reported ED_{50} traditionally decreases. The visual contrast of the threshold injury is usually low, making the task of correct lesion detection difficult. Furthermore, the chance of scoring the presence of a very small lesion when an injury is actually not present (i.e., false positive) will increase if the retina appears mottled or otherwise exhibits abnormalities that could be mistaken for a laser-induced

lesion. It may also be difficult to discern the edges of some very large lesions, making positive identification difficult. Nevertheless, our review of the published threshold studies that provide dose-response slopes show a general trend for a steeper slope for larger images, suggesting the greater difficulty of executing the small-lesion experiments.

The optical quality of the incident laser beam influences the minimal retinal image size. In earlier studies, multimode lasers were frequently used, leading to a larger retinal image area and increased values of the ED_{50}. Today, most lasers used in these experiments have been carefully aligned to achieve a single transverse mode. The presence of apertures in the beam path can also alter the quality of the retinal image.

It is evident that aside from false positive identification of a lesion, all the other aforementioned sources of error will tend to increase the ED_{50} values and the spread of the data from which they are derived.

Lasers
David H. Sliney, Ph.D.

1.5 Standards, Regulations, or Guidelines of Exposure
A number of national and international groups have recommended occupational or public exposure limits (ELs) for laser radiation for wavelengths extending from 180 nm in the ultraviolet (UV) region, to 1000 mm (1 mm) in the far infrared (IR). These ELs apply for pulse durations from 100 fs (10^{-13} s) to 30 ks (8 h). In the United States, both the American Conference of Governmental Industrial Hygienists (ACGIH) and the American National Standards Institute (ANSI) have produced comprehensive sets of exposure limits (31, 49, 57). These ELs are virtually identical, although ELs are termed threshold limit values (TLVs) by ACGIH and maximum permissible exposure limits (MPEs) in the ANSI Standard Z-136.1. On the international scene, the International Commission on Non-Ionizing Radiation Protection (ICNIRP) publishes Guidelines on Limits of Exposure to Laser Radiation (36, 50). ICNIRP guidelines are developed through collaboration with the World Health Organization (WHO) by jointly publishing criteria documents that provide a scientific database for the exposure limits (30). The International Electrotechnical Commission (IEC) uses the ICNIRP guidelines (10). The ICNIRP ELs are essentially identical to the ACGIH, and ANSI limits (31, 32, 36, 40, 49, 50, 57). The ELs based in large part on ocular injury data from animal studies and from data from human retinal injuries resulting from viewing lasers, the sun, and welding arcs. All the guidelines have an underlying assumption that outdoor environmental exposures to visible radiant energy is normally not hazardous to the eye except in very unusual environments such as snow fields and deserts (29, 30).

The ACGIH ELs and ICNIRP ELs are generally applied to derive accessible emission limits (AELs) used in product safety standards of the International Electrotechnical Commission, the American National Standards Institute, and other technical standards groups. The U.S. Food and Drug Administration also uses these AELs in the Federal Laser Performance Standard (21 *CFR* 1040). These product safety standards must have carefully defined measurement conditions to simulate "worst-case" ocular exposure conditions (Tables 103.3–103.6).

Table 103.3. Intrabeam Laser Ocular Threshold Limit Values

Wave length l	Expos. *t* (s)	Threshold Limit Value EL (J/cm^2 or

(nm)	Duration t	W/cm^2)	Restrictions
		Ultraviolet	
180–302	1 ns–30 ks	3 mJ/cm^5	
303	1 ns–30 ks	4 mJ/cm^5	All ELs for l less than 315 nm must be $0.56t^{3/4}$ J/cm^5
304	1 ns–30 ks	6 mJ/cm^5	
305	1 ns–30 ks	10 mJ/cm^5	
306	1 ns–30 ks	16 mJ/cm^5	
307	1 ns–30 ks	25 mJ/cm^5	
308	1 ns–30 ks	40 mJ/cm^5	
309	1 ns–30 ks	63 mJ/cm^5	
310	1 ns–30 ks	0.1 J/cm^5	
311	1 ns–30 ks	0.16 J/cm^5	
312	1 ns–30 ks	0.25 J/cm^5	
313	1 ns–30 ks	0.40 J/cm^5	
314	1 ns–30 ks	0.63 J/cm^5	
315–400	1 ns–10 s	$0.56t^{3/4}$ J/cm^5	
315–400	10 s–30 ks	1.0 J/cm^5	
		Visible and IR-A	
400–700	1 ns–18 ms	0.5 mJ/cm^5	
400–700	18 ms–10 s	$1.8t^{3/4}$ mJ/cm^5	
400–550	10 s–10 ks	10 mJ/cm^5	
550–700	10–T_1 s	$1.8t^{3/4}$ mJ/cm^5	
550–700	T_1 s–10 ks	10 C_B mJ/cm^5	7 mm limiting aperture
400–700	10–30 ks	C_B mW/cm^5	
700–1050	1 ns–18 ms	0.5 C_AmJ/cm^5	
700–1050	18 ms–1 ks	1.8 $C_A t^{3/4}$ mJ/cm^5	
1051–1400	1 ns–50 ms	5 C_C mJ/cm^5	
1051–1400	50 ms–1 ks	9.0 $C_C t^{3/4}$ mJ/cm^5	
700–1400	1–30 ks	320 $C_A C_C$ m/cm^5	
		Far Infrared	
1400–1500 nm	1 ns–1.0 ms	0.1 J/cm^5	
1400–1500 nm	1.0 ms–10 s	$0.56t^{1/4}$ J/cm^5	
1500–1800 nm	1 ns–10 s	1.0 J/cm^5	
1801–2600 nm	1 ns–1.0 ms	0.1 J/cm^5	
1801–2600 nm	1.0 ms–10 s	$0.56t^{1/4}$ J/cm^5	
2601 nm–1 mm	1–100 ns	10 mJ/cm^5	3.5 mm limit. aperture

2601 nm–1 mm	100 ns–10 s	$0.56t^{1/4}$ J/cm^5
1400 nm–1 mm	1.0 s–30 ks	100 mW/cm^5

NOTES:

Time: All values of t in s; 1 ks = 1000 s, and 30 ks = 8 h. **spectral correction factors**: $C_A = 1$ for l = 400–700 nm; $C_A = 10^{[0.02(l-700)]}$ if l = 700–1050 nm

$C_B = 1$ for l = 550 nm; $C_B = 10^{[0.015(l-550)]}$ for l = 550–700 nm

$C_C = 1$ for l = 1150; $C_c = 10^{[0.0181(l-1150)]}$ for 1150 < l < 1200

$C_C = 8$ for 1200 ≤ l < 1400

$T_I = 10 \times 10^{[0.02(l-550)]}$ for l = 550–700 nm

Extended-source TLVs: For extended-source laser radiation (e.g., diffuse reflection) viewing at wavelengths between 400 and 1400 nm, the intrabeam viewing TLVs can be increased by the following correction factor C_E provided that the angular subtense of the source (measured at the viewer's eye) is greater than l_{min}, where l_{min} is: $l_{min} = 1.5$ mrad for $t < 0.7$ s

$l_{min} = 2\ t^{3/4}$ mrad for 0.7 ≤ t < 10 s

$l_{min} = 11$ mrad for t ≥ 10 s.

$C_E = l/l_{min}$ for $l_{min} < l < 100$ mrad

$C_E = l^2/(l_{min}l_{max})$ for l ≥ 100 mrad

$C_E = 10l^2/l_{min}$ for l ≥ 100 mrad for l expressed in rad

The angle of 100 mrad may also be referred to as l_{max}, at which point the extended source limits can be expressed as a constant radiance using the last equation written in terms of l_{max}.

$L_{TLV} = (8.5 \times 10^3)(TLV_{pt\ source})$ J/(cm^2 sr) for $t < 0.7$ s

$L_{TLV} = (6.4 \times 10^3\ t^{-3/4})(TLV_{pt\ source})$ J/(cm^2 sr) for 0.7 ≤ t < 10 s

$L_{TLV} = (1.2 \times 10^3)TLV_{pt\ source})$ J/(cm^2 sr)[a] for t ≥ 10 s

[a]or W/(cm^2@sr) for point-source limits expressed in W/cm^2

Terminology: The term *exposure limit* (EL) is used by IRPA. The same values are termed MPEs (maximum permissible exposure limits) by ANSI and TLVs (threshold limit values) by ACGIH. Essentially all groups have the same limit values.

Table 103.4. Laser Threshold Limit Values for Skin Exposure

Wave length l (nm)	Expos. t (s) Duration t	Threshold Limit Value EL (J/cm^2 or W/cm^2)	Restrictions
		Ultraviolet	
200–400	1 ns–30 ks	Same as eye EL[a]	
		Visible and IR-A	
400 nm–1 mm	1–100 ns	20 C_A mJ/cm^5	
400 nm–1 mm	100 ns–10 s	1.1 $C_A t^{1/4}$ J/cm^5	3.5 mm limit. aperture
400 nm–1 mm	10 s–30 ks	0.2 C_A W/cm^5	
		Far Infrared	
1400 nm–1 mm	1 ns–30 ks for 2601 nm–1 mm	Same as eye EL	

Note: See Notes, Table 103.3.

[a] Or W/(cm^2@sr) for point-source limits expressed in W/cm^2.

Table 103.5. Limiting Apertures Applicable to Laser TLVs (mm)

Spectral Region	Duration	Eye (mm)	Skin (mm)
180–400 nm	1 ns–0.25 s	1	3.5
180–400 nm	0.25 s–30 ks	3.5	3.5
400–1400 nm	1 ns–0.25 s	7	3.5
400–1400 nm	0.25 s–30 ks	7	3.5
1400 nm–0.1 mm	1 ns–0.25 s	1	3.5
1400 nm–0.1 mm	0.25 s–30 ks	3.5	3.5
0.1–1.0 mm	1 ns–30 ks	11	11

Table 103.6. Selected Occupational Threshold Limit Values (TLVs) for Some Common Lasers

Type of Laser	Wavelength	Threshold Limit Value
Argon–fluoride	193 nm	3.0 mJ/cm^2 over 8 h
Xenon–chloride	308 nm	40 mJ/cm^2 over 8 h
Argon ion	488,514.5 nm	3.2 mW/cm^2 for 0.1 s
		2.5 mW/cm^2 for 0.25 s
Helium–neon	632.8 nm	1.8 mW/cm^2 for 1.0 s
		1.0 mW/cm^2 for 10 s
Krypton ion	568,647 nm	
Helium–neon	632.8 nm	17 mW/cm^2 for 8 h
Neodymium–YAG	1064 nm	5.0 mJ/cm^2 for 1 ns to 100 ms
		5 mW/cm^2 for 10 s
Erbium glass	1540 nm	1.0 J/cm^2 for 1 ns–10 s
Erbium:YAG	2940 nm	10 mJ/cm^2 for 1–100 ns
Hydrogen fluoride	2.7–3.1 mm	10 mJ/cm^2 for 1–100 ns
Carbon dioxide	10.6 mm	100 mW/cm^2 for 10 s to 8 h, limited area
		10 mW/cm^2 for >10 s

Source: ACGIH TLVs.

Note: To convert TLVs in mW/cm^2, multiply by exposure time *t* in s; e.g., the He-Ne or argon TLV at 0.1 s is 0.32 mJ/cm^2.

1.5.1 Examples

Several representative exposure limits are shown in Table 103.4 for the most commonly available lasers. One should also remember that the way most of the laser safety standards are organized, one

makes use of a laser's hazard classification (initially based upon ELs) to perform a hazard evaluation, rather than to perform measurements of beam exposure for comparison with ELs. The ELs are actually used only in special instances where human exposure is intended and the laser beam irradiance or radiant exposure may actually be measured or calculated to determine if the EL will be exceeded.

1.5.2 Discussion

1.5.2.1 Exceeding the Exposure Limits In deriving the ELs for all optical radiations, the ACGIH and ICNIRP generally applied a factor of 10 to reduce the 50% probability of retinal injury by a factor of 10. This is not a true "safety factor" because there is a statistical distribution of damage and this factor was based upon several considerations. These included the difficulties in performing accurate measurements of source radiance or corneal irradiance; measurement of the source angular subtense; as well as histological studies showing retinal changes at the microscopic level at levels of approximately 2 below the ED_{50} value.3 In actual practice, this means that an exposure at 2–3 times the EL would not be expected to actually cause a physical retinal injury. At five times the EL, one would expect to find some injuries in a population of exposed subjects. As with other TLVs, the laser ELs are guidelines for controlling human exposure and should not be considered as fine lines between safe and hazardous exposure. With benefit versus risk considerations, it should therefore be considered appropriate to have some relaxed guidelines; however, to date, no standards group has seen the need to do this. This may apply to the development of safety standards for ophthalmic medical instruments.

1.5.2.2 Application of Limits in Laser Safety Standards Laser safety standards exist in the United States and worldwide. All the standards group manufactured laser products into four general hazard classes and provide safe measures for each hazard class (1 through 4) (36, 44). U.S. Federal regulations (21 *CFR* 1040) require all commercial laser products to have a label indicating the hazard class. The safety measures recommended in workplace safety standards are quite obvious (e.g., beam blocks, shields, baffles, eye protectors), once one understands and recognizes the hazards. The ocular hazards are generally of primary concern. Figure 103.4 illustrates the relative retinal hazard from intrabeam viewing of a laser in comparison with the hazard of viewing conventional light sources.

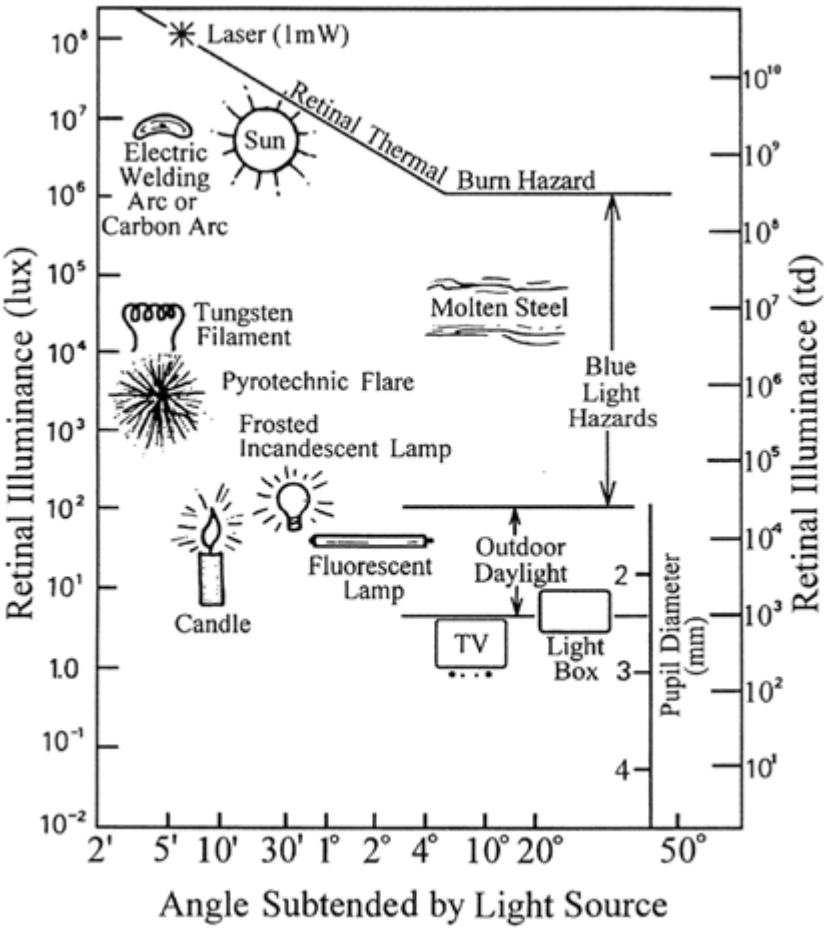

Figure 103.4. Relative retinal irradiances for staring directly at various light sources. Two retinal exposure risks are depicted: retinal thermal injury, which is image-size dependent, and photochemical injury, which depends on the degree of blue light in the source's spectrum. The horizontal scale indicates typical image sizes. Most intense sources are so small that eye movements and heat flow will spread the incident energy over a larger retinal area. The range of photoretinitis (the “blue-light hazard”) is shown to be extending from the normal outdoor light levels and above. The xenon arc lamp is clearly the most dangerous of nonlaser hazards.

The primary workplace safety standard in the United States is the American National Standard, ANSI Z136.1-2000, *The Safe Use of Lasers*. It is a national consensus standard for laser safety in the user environment. It has evolved through several editions since 1973. Although the ELs are termed maximum permissible exposure (MPE) limits by ANSI, they are all the same values. MPEs are provided for all wavelengths from 180 nm to 1 mm, and for exposure durations of 100 fs to 30 ks (8-h workday) the MPEs appear at the end of the safety standard. Since almost all control measures are based upon the laser's hazard class (1 through 4), the MPEs are seldom actually used. The MPEs did form the basis for deriving the hazard classifications. For example, the accessible emission limits (AELs) for class 1 are derived to prevent human access to levels above the MPE under reasonably foreseeable worst-case laser operating conditions. The Class 1 AELS are derived by multiplying the MPE for the longest foreseeable exposure duration by the area of the limiting aperture specified for that MPE. For example, the limiting aperture for visible lasers is 7 mm based upon a dark-adapted pupil. The resulting AEL has units of energy or power.

Nevertheless, health and safety specialists want the simplest expression of the limits, but some more mathematically inclined scientists and engineers on standards committees argue for sophisticated formulas to express the limits (which belie the real level of biological uncertainty) and the health and safety specialists at the same time demand greater simplification. These exposure limits (and the

identical ELs of ACGIH) formed the basis for the U.S. Federal Product Performance Standard (21 *CFR* 1040). The latter standard regulates only laser manufacturers. On the international scene, IEC standard 825-1 (1993) grew out of an amalgam of the ANSI standard for user control measures, the WHO-endorsed exposure limits of ICNIRP, ACGIH, and ANSI, and the CDRH product classification regulation. The International Commission on Nonionizing Radiation Protection (ICNIRP) has a special relationship with the World Health Organization in developing criteria documents on laser radiation and recommending exposure limits for laser radiation (ICNIRP, 1996). These standards are all basically in agreement.

1.5.2.3 Acute Exposure In realistic workplace settings, accidental and therefore exposures to a hazardous laser beam represent a low probability, but exposures can have severe consequences. This is illustrated by a typical accident in which a young investigator in a physical chemistry laboratory is aligning a short-pulse (10-ns) laser beam to direct it into a gas cell to study photodissociation parameters for a particular molecule. Leaning over a beam director, he glances down over an upward, secondary beam and approximately 80 mJ enters his left eye. The impact produces a microscopic hole in his retina, a small hemorrhage is produced over his central vision, and he sees only red in his left eye. Within an hour he is rushed to an eye clinic where an opthalmologist tells him he has only 20/400 vision (41). In a university laboratory, a physics graduate student attempts to realign the internal optics in a Q-switched Nd:YAG laser system—a procedure normally performed by a service representative that the student had witnessed several times before. A “weak” secondary beam reflected from a beam splitter enters the student's eye, producing a similar hemorrhagic retinal lesion with a severe loss of visual acuity (Fig. 103.5). Similar accidents occur each year, and frequently do not receive publicity because of litigation or for administrative reasons. Scientists and engineers working with open-beam lasers really need to realize that almost all such lasers pose a very severe hazard to the eye if eye protection is not worn or other safety measures are not observed.

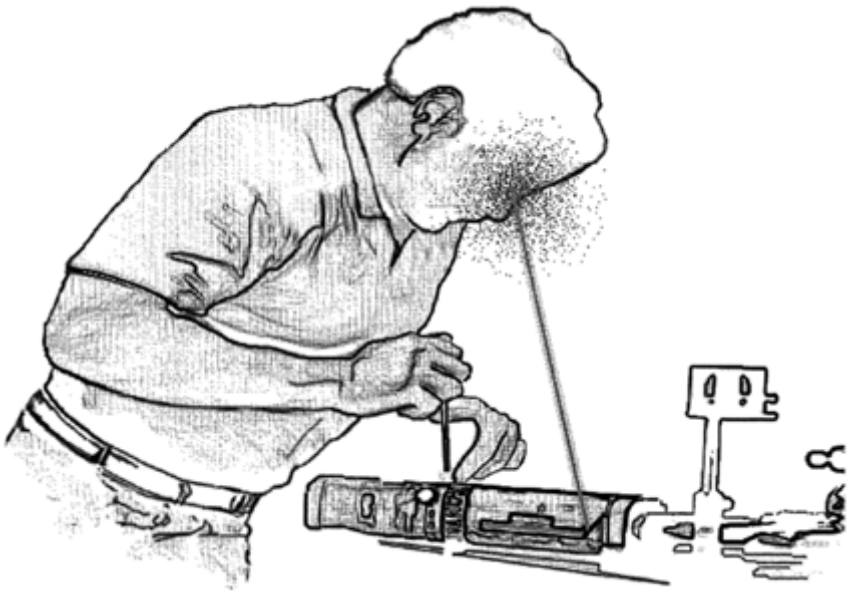

Figure 103.5. A “weak” secondary beam reflected from a beam splitter can enter the unprotected eye, as during laser alignment. An beam energy of only 0.1 mJ can produce a hemorrhagic retinal lesion with a severe loss of visual acuity.

In virtually all accidents, eye protectors were available but not worn. The probability that a small beam will intersect a 3–5-mm pupil of a person's eye is small to begin with, so injuries do not always happen when eye protectors are not worn.

1.6 Guidelines
The one area of TLV guidelines being considered for possible revision relates to further refinements of correction factors in the IR-B, that is, in C_D. Recently ELs for visible and near-infrared laser radiation in the subnanosecond pulse regime have been developed and have been published (37). Exposure limits for lengthy viewing have also just been modified. These changes would still not affect most applications. As in the past, the understanding of the basic interaction mechanisms is critical to setting limits.

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Occupational Ergonomics: Principles and Applications
Amit Bhattacharya, Ph.D., Nancy Talbott, MS, PT, Laurel Kincl, MS

1 Introduction

This chapter provides the basic principles that underlie the field of ergonomics and their application to some of the current issues of importance in the workplace. Sections 2 to 4 deal with the physiology of muscles; biomechanics; cellular responses to tissue, nerve, and joint injuries as they relate to cumulative trauma disorders; and common types of overuse syndromes. The remaining sections deal with applications of the principles to workplace ergonomic issues and proposed ergonomic regulations.

Occupational Ergonomics: Principles and Applications
Amit Bhattacharya, Ph.D., Nancy Talbott, MS, PT, Laurel Kincl, MS

2 Principles of Ergonomics

The word “ergonomics” is made up of two Greek words, “ergo” meaning work and “nomas” meaning laws. The field of ergonomics is highly interdisciplinary. It applies principles from engineering, physiology, medicine, and psychology to the understanding of the interaction of humans with their workplace. The interaction of humans with their workplace may consist of identifying the relationship between job physical risk factors and physiological responses. For example, a specific ergonomic problem of paramount importance in the occupational health and safety is the issue of work-related musculoskeletal disorders (WMD). Some of these issues are discussed further in this chapter. The specific areas of application relevant for the field of ergonomics are defined and briefly explained in the following.

2.1 Physiology of Muscle Contraction and Movements

2.1.1 Structure of Muscles and Contraction Characteristics The generation of forces and movements in living cells such as muscles requires special protein molecules and contractile proteins. These

types of proteins are available in great abundance in the muscle cell. These proteins can convert chemical energy such as adenosine triphosphate (ATP) into mechanical energy (1).

There are three major types of muscles in the human body: skeletal, smooth, and cardiac. Skeletal and cardiac muscles are striated muscles. Skeletal muscles such as muscles of the arms, legs, and back perform most of the voluntary actions, and smooth muscles such as muscles in the internal organs perform involuntary actions. The cardiac muscles also act autonomically (2). The major focus of this section is the skeletal muscle.

The skeletal muscle, the largest of the tissues in the human body, constitutes about 45% of the total body weight. The skeletal muscle is made up primarily of 75% water and the remaining 25% is protein, inorganic salts and high energy phosphates, urea, lactic acid, enzymes, minerals, etc (3). There are about 600 muscles in the human body. Each muscle is made up of many thousands of muscle fibers. Small muscles have only a few hundred fibers whereas larger muscles may contain several hundred thousand fibers. Each end of the whole muscle is attached to a bone by bundles of collagen fibers called tendons that can transmit forces from the muscles to the bones. Tendons have great strength, but unlike the muscle fibers, they cannot contract. Each muscle fiber is composed of thousands of myofibrils, the contractile element of the skeletal muscle. These myofibrils are about 1 micron (=1/1000 mm) in diameter. Each of these myofibrils has millions of filaments made up of two proteins, actin and myosin. Actin is known as the thin filament and myosin is called the thick filament. During electrical stimulation via nerve, attractive forces between the actin and myosin filaments cause muscle to contract. Table 104.1 gives a list of the major sequence of events between nerve action potential and contraction and relaxation of muscle fiber (2).

Table 104.1. Sequence of Events for Muscle Contraction

1	An action potential is generated in a motor axon.
2	Release of acetylcholine from the axon terminal at the neuromuscular junction known as muscle end plate.
3	A motor end plate potential is produced at the muscle end plate.
4	The motor end plate potential depolarizes the muscle membrane (to about–15 mV) causing it to generate a muscle action potential that travels along the surface of the muscle membrane. Acetylcholine-esterase (enzyme) immediately destroys acetylcholine so that the depolarized membrane returns to its resting potential of about–90 mV.
5	Depolarization of transverse tubules by the muscle action potential causes release of calcium ions from the sarcoplasmic reticulum around the myofibrils.
6	Calcium ions cause the actin-myosin filaments to slide, thereby producing contraction of the muscle fiber.
7	As the concentration of calcium ions falls, the actin-myosin sliding action reduces and the muscle relaxes.

2.1.2 Motor Neurons and Motor Units A neuron consists of the soma (main body), the dendrites, and the axon. The axon carries signals away from the neuron cell body, and dendrites bring signals from other neurons. However, one exception is the sensory nerve fiber, which is a single dendrite that transmits sensory signals from a peripheral receptor. Each neuron has many dendrites but only one axon. In the center of axon is a gel-like substance called axoplasm. Some nerve fibers have an additional layer surrounding their membranes called a myelin sheath. The myelin sheath is broken at

the nodes of Ranvier. The myelin sheath has insulating properties and is instrumental in propagating an electric signal along the axon by allowing it to jump from one node of Ranvier to the next. This process of impulse "jumping" decreases the amount of energy required for signal transmission.

A motor unit consists of a single motor neuron and all the muscle fibers controlled by it. Generally, large muscle fibers that perform strong body motions have more motor units than those for the smaller muscles. When excited, these motor units respond to activate all of the muscle fibers connected to them (4).

2.1.3 Energy Transform and Use The human body gets its energy from foodstuff (carbohydrates, fats, and proteins) it consumes. However, the foodstuffs have to be converted to a certain chemical form before the cells in the human body can use it as a supply of energy. This chemical compound is called adenosine triphosphate (ATP). This compound contains high-energy phosphate bonds. Each mole of ATP releases 8000 calories of energy each time a phosphate radical is broken away from ATP at the high-energy bond. This released energy is used as an immediate supply of energy for a variety of functions such as transport of glucose through the membrane, synthesis of chemical compounds inside the cell, muscle contraction, and neuronal activity. Once this ATP is used it becomes like a discharged battery known as adenosine diphosphate (ADP) which needs to be recharged with foodstuff via much slower chemical reactions with oxygen (5).

The formation of ATP within the cell uses carbohydrates, fats, and proteins. The absorption of carbohydrates forms glucose that is then used as an energy source by the cells. Two processes release energy from glucose; (*1*) glycolysis which does not require oxygen and (*2*) oxidation. The oxidative process releases much more energy than that released by glycolysis. For each molecule of glucose metabolized, the oxidative process produces thirty-four molecules of ATP whereas glycolysis produces only two molecules. The overall efficiency of energy transfer from glucose to ATP is about 39%; the remaining energy is lost as heat (of 686,000 calories of available energy in a mole of glucose, only 266,000 calories are stored in ATP). The 20% of total energy used by the cells is from the oxidation of glucose, and the remainder comes from fats and proteins (3).

In addition to ATP as an immediate source of energy, the cells have another source of energy, known as phosphocreatine, that contains high-energy phosphate bonds. Cells contain phosphocreatine in amounts much larger than that of ATP. The ATP and phosphocreatine help in each other's resynthesis to build up their presence in the cells. These reactions to resynthesize ATP and phosphocreatine are much more rapid than the oxidative process. Therefore, ATP and phosphocreatine serve as the rapid and immediate sources of energy in tasks such as the 100-yard dash and weight lifting.

2.1.4 Metabolism During Physical Exertion The source of energy varies depending upon the intensity and duration of physical exertion. For intense physical exertions that last less than one minute, the body relies primarily on the existing energy supplies of ATP and phosphocreatine in the muscles. The anaerobic glycolytic processes are used to provide energy for tasks of intense levels that last about 1–2 minutes. Once the physical exertion continues for several minutes, the primary source of energy becomes dependent on the aerobic process. In general, daily energy expenditure varies from 2700 to 3000 kcal for men and 2000 to 2100 kcal for women. Several factors such as age, level of physical activity, health status, and genetics can modify the daily expenditure. During physical exercise, skeletal muscle blood flow, mean arterial pressure, systolic arterial pressure, cardiac output, and heart rate may increase as much as 175%, 15%, 50%, 120% and 100%, respectively (2).

2.2 Skeletal System

The skeletal framework in the human body is needed to support its structure, muscles, nerves, organs, and blood vessels. This framework consists of "living girders," bones that can sustain the stresses and strains produced by the body's weight and the daily tasks of living. The performance of any task requires movement of body segments relative to each other. The skeletal joints that connect two adjacent bones allow articulating motion. Therefore, joints provide mobility to the

musculoskeletal system. There are three types of joints in the human skeletal system: (*1*) synarthrodial joints that do not allow any relative motion (skull bones), (*2*) amphiarthrodial joints that allow slight motion (vertebrae), and (*3*) diathrodial joints (knee, elbow, hip and shoulder) that allow much more relative motion than the other two. In general, joints that have a higher degree of mobility or relative motion suffer from reduced stability that makes them more prone to injuries.

2.3 Biomechanics

Biomechanics is the science of applying the laws of mechanics to understand the biology of work. The field of biomechanics relies on applying static and dynamic equilibrium conditions for calculating the forces experienced at the articulating bone surfaces (joints) during human body movements. When these forces appear repeatedly, they may cause trauma to the joint surfaces that gives rise to the development of musculoskeletal disorders.

2.3.1 Basic Concepts and Relevant Terminology (6)

2.3.1.1 Terms

- Center of mass: A point in an object about which the mass is equally distributed. Gravity acts upon it as though all mass was concentrated at that point.
- Moment of inertia ($kg \cdot m^2$ or $N \cdot msec^2$): The resistance to change in angular velocity depends upon the mass of the body and its distribution about the center of rotation. This resistance to change in angular velocity is called the moment of inertia (*I*).

$$M = I\alpha$$

  In angular motion, the moment of force (*M*) is proportional to the angular acceleration (a).
- Radius of gyration (r): In angular motion, the mass is not considered concentrated at the center of mass (or center of gravity). Therefore, the radius of gyration is defined as the radial distance from the axis of rotation at which the mass of the body could be concentrated without altering the moment of inertia of the body about that axis.
- Ground reaction force (Newton): Forces imposed upon the body due to direct contact with the ground.
- Center of pressure: The point at which the resultant force is applied.
- Impulse ($N \cdot sec$): The area under the force–time curve (or the integral of the force–time curve).
- Linear momentum ($kg \cdot m/sec$): Mass × linear velocity.
- Angular momentum ($kg \cdot m^2/sec$): Moment of inertia × angular velocity.
- Kinematics: The science of motion.
- Kinetics: The science of forces (and vectors) and torques associated with the motion of the body.

2.3.1.2 Types of Motion

The types of motion in joints include the following:

- Rotatory or angular: Few joints have pure rotational movement. The superior radioulnar joint moves in a spin-like movement, and the hip also makes an almost pure arc during flexion and extension.
- Translatory or linear (gliding): Compression, distraction, and gliding are most common. The lever arm moves towards the articulating surface, away from the surface, or in an anterior/posterior or medial/lateral direction.
- Curvilinear: This is the most common type of motion; the majority of joints move by a combination of rotation and compression. As rotation occurs, the lever arm also glides in one or more directions.

2.3.1.3 Laws Relevant to Biomechanics

- Law of inertia: Newton's first law of motion states that a body remains at rest or in uniform motion until acted upon by an unbalanced or outside set of forces. If the body is in equilibrium, then the

sum of all forces (F_{XYZ}) is zero.

For a body to be in static equilibrium, the following condition must be met:

$$\Sigma F_{x,y,z} = 0$$

- Law of acceleration: Newton's second law of motion states that the acceleration of a body is proportional to the unbalanced force acting upon it and inversely proportional to the mass of the body.

For a body to be in dynamic equilibrium, the following condition must be met:

$$\Sigma F_{x,y,z} = \text{mass} \times \text{acceleration}_{x,y,x} \rightarrow \text{Newton's second law of motion}$$

- Law of reaction: Newton's third law states that for every action there is an equal and opposite reaction. Forces come in pairs, and gravity exerts a force on all objects. Two objects in contact exert a force on each other.

2.3.1.4 Friction Friction is the resistance offered to the relative motion of two bodies in contact. As one body slides over another, the force that opposes the motion is called the force of friction. The magnitude depends on the kind of materials in contact with each other and how tightly the two surfaces are pressed together. Friction is a potential force that occurs only if movement is attempted.

- Static friction: The force that opposes a body at rest from being put into motion

$$f(s) = [(s)F(N)]$$

where $F(N)$ = the perpendicular force holding the two bodies in contact(s) = the coefficient of static friction of the material

- Kinetic friction: The force that opposes a body in motion from continuing that motion. Kinetic friction is always less than static friction.

$$f(k) = [(k)F(N)]$$

(k) = the coefficient of kinetic friction of the material

2.3.1.5 Torque Torque or moment is the ability of any force to cause rotation of a lever arm. The use of pulleys changes the direction of muscle force. Its use can also improve the ability of the muscle to generate torque by increasing the line of action of the muscle away from the axis of the joint. In the human anatomy, the patella serves as a pulley to transfer muscle force from the quadriceps to the ligament connecting to the tibia. The patella also increases the lever arm of the tibio-femoral muscle ligament providing an increased torque to flex and extend the knee joint.

2.3.1.6 Joint Reaction Forces Joint reaction forces are the forces applied by one segment on its

adjacent segment during joint compression. Joint reaction forces come in pairs. Forces between two joint surfaces in contact with each other can be resolved into components, contact or normal force and shear force. The contact or normal force is the component of the force that lies perpendicular to the contacting surfaces, and the shear force is the component of force that lies parallel to the contacting surfaces. Force applied perpendicular to a bony lever and parallel to the contacting joint surfaces will create a torque around the joint axis and a shear between the joint surfaces. A force applied parallel to a bony lever but not intersecting the joint axis will create compression or distraction and a small amount of rotation.

2.3.1.7 Stress and Strain

- Stress: Stress for a body that can be either stretched or compressed is the ratio of the applied force acting on the body to the cross-sectional area of the body.
- Strain: The ratio of the change in length to the original length of a body that can be either stretched or compressed, is called the strain.

The change in length (the strain) is directly proportional to the magnitude of the applied force, inversely proportional to the cross-sectional area of the body, and directly proportional to the original length:

$$L = \frac{1}{Y} \frac{F \cdot L_o}{\mathrm{A}}$$

Y Young's modulus of elasticity (material dependent)

F magnitude of the applied force

A cross-sectional area

L_o original length

L change in length

- Limits: The elastic limit is the point where the stress on a body becomes so great that the atoms of the body are pulled permanently away from their equilibrium position in the lattice structure. When stress exceeds the elastic limit, the material will not return to its original size or shape when the stress is removed.
- Shear: The elastic ability of a body to deform by changing shape when a stress is applied.

2.3.2 Application of Mechanical Lever System to Human Body Mechanical lever system laws are applicable to the human body. The bone, muscle, and joint are analogous to the mechanical lever system components, fulcrum, load, and effort.

2.3.2.1 Application of Lever Systems in Biomechanics

- Muscle moment or lever arm: The perpendicular distance from the action line of the muscle or tendon to the axis of rotation of the joint (fulcrum).
- Load moment or lever arm: The perpendicular distance between the center of gravity of the external load and the axis of rotation of the joint (fulcrum).

Load, force, lever arm, and fulcrum relationships:

$$\text{Force} \times \text{distance} = \text{load} \times \text{distance}$$

The three types of joints include the

- Hinge joint, such as the elbow
- Ball and socket joint, such as the hip
- Plate joint, such as the atlas joint in the neck

The mechanical laws of levers apply to each of these bone–muscle–joint systems. Each joint involves two bones that are in contact. A knowledge of the location, function, and limitations of anatomical levers involved in specific occupational movements is essential for ergonomic analysis and evaluation of operator-task systems.

The three bone–joint–muscle lever systems include the:

- First class lever: Fulcrum between load and force. Best suited for precision work.
- Second class lever: Load between fulcrum and force. Best suited for ballistic motion.
- Third class lever: Force between load and fulcrum. Best suite for heavy work.

Figure 104.1 gives examples of bone–joint–muscle lever systems from human anatomy.

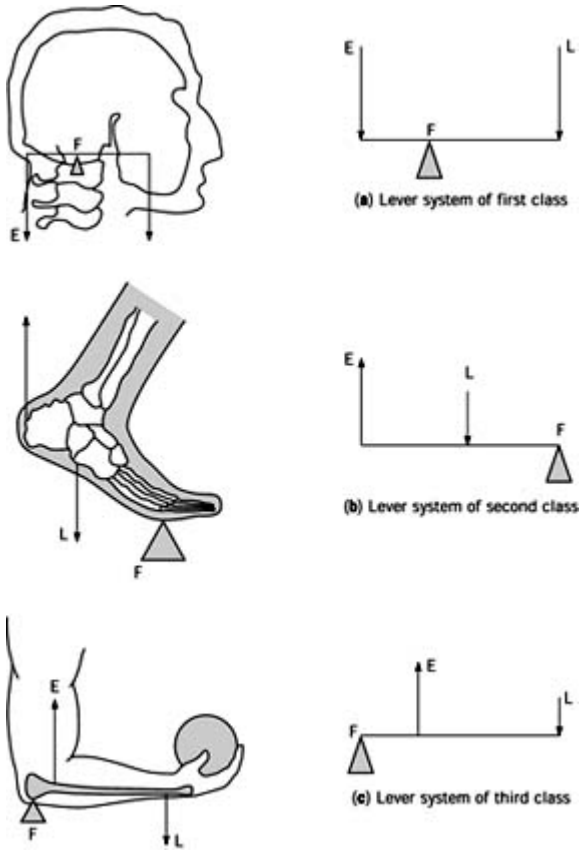

Figure 104.1. Three classes of lever systems. Examples from human anatomy (taken from Ref. 6).

Each class of levers is specifically suited to perform certain types of movements and postural adjustments efficiently without undue strain and risk of accidents. There is a potential of failure in a operator-task system if the

1. Degree of movement required exceeds that of the lever system employed.

2. Lever system performs at a mechanical disadvantage.
3. Muscles used are too small.
4. Blood supply to the muscles is impaired.
5. Sensory feedback is defective.

Example: Biomechanical Analysis of Holding an Object in Hand

[see Figure 104.2]

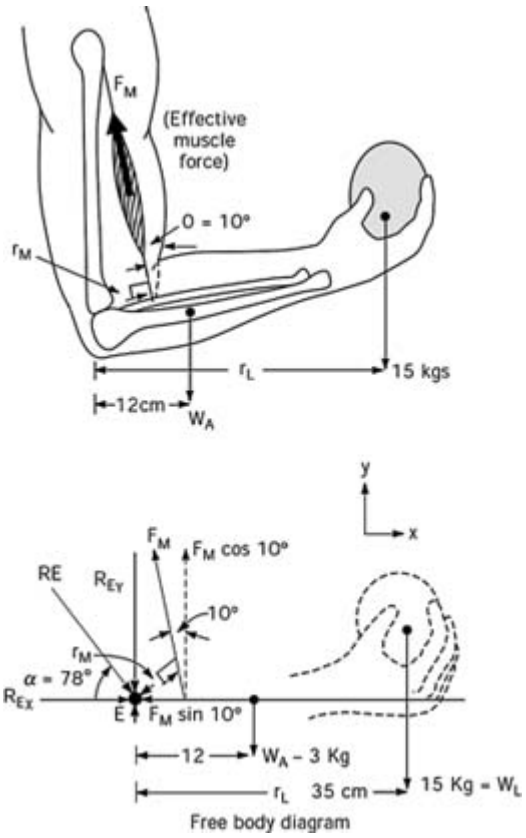

Figure 104.2. Biomechanical analysis of holding a weight in the hand.

Calculate the muscle force and the reaction force at the elbow joint (humerus against ulna).

$$Nomenclature: {}^{y}\uparrow is + ve \;\; and \;\; \rightarrow_{x} \;\; is \; + \; ve \; and \; (\; is - ve \; moment$$

Given:

$$\mathrm{WA} = \text{forearm weight} = 3\,\mathrm{kg} \text{ acting at } 12\,\mathrm{cm} \text{ from the elbow joint } \; W = \text{weight in hand} = 15\,\mathrm{kg}\text{Muscle mor} \tag{1}$$

Find:

$$F_{\mathrm{M}} = \text{Biceps muscle force} R_{\mathrm{E_{X,Y}}} = \text{Reaction force at the elbow joint} \Sigma F_{\mathrm{y}} = 0, \Sigma F_{\mathrm{x}} = 0, \text{ and } \Sigma M = 0 \text{ around} \tag{1}$$

Solution:

$$\text{For } \Sigma M = 0 - 15{\cdot}35 - 3{\cdot}12 + (F_M){\cdot}5 + R_E{\cdot}0 = 0 - 525 - 36 + F_M{\cdot}5 = 0 \text{ or } F_M = 112.2 \text{ kg For } \Sigma F_Y = 0 F_M \cos 10° - \quad (1)$$

Resultant reaction forces at the elbow joint:

$$R_E = \sqrt{R_{E_X}^2 + R_{E_Y}^2} = \sqrt{363.8 + 8456.6} \text{or } R_E = 93.9\, kg \qquad (1)$$

$$\text{Direction of } R_E = \tan\alpha = R_{E_Y}/R_{E_X} = 4.82 \text{ or } \alpha = 78.3° \text{ with respect to the horizontal}$$

Conclusion: It takes muscle force levels more than seven times the weight being held by the worker because the human lever system works at a mechanical disadvantage. For this reason, even holding small weights for a prolonged period or repetitively can cause muscle sprain and strain in a worker.

2.3.2.2 Biomechanical Loading of the Wrist Previous studies have shown that cumulative trauma disorders such as tenosynovitis, bursitis, and carpal tunnel syndrome are associated with repeated deviations (or extensions) and excessive use of force by the hand. Biomechanical studies (7, 8) have shown that tasks that require excessive and repeated use of force in nonneutral (deviation and flexion) wrist/hand postures produce stress concentrations on the tendons and tendon sheaths. The buildup of excessive strain might weaken the tendon and/or create inflammatory reactions. The following example illustrates the use of biomechanical models of wrist to estimate tendon force while holding a tool.

Example: Biomechanical Loading of the Wrist. Figure 104.3 shows the forces that act on the hand of a person who operates a screwdriver. Calculate the tendon force F_T and the reaction (or radial supporting) force F_R. For the purpose of this example, the grip force P acting at the finger may be assumed to be 1.5 newton. Assume a small hand in operation on a small grip size. Also assume that the subtended angle (wrist deviation or contact angle =) is 40°.

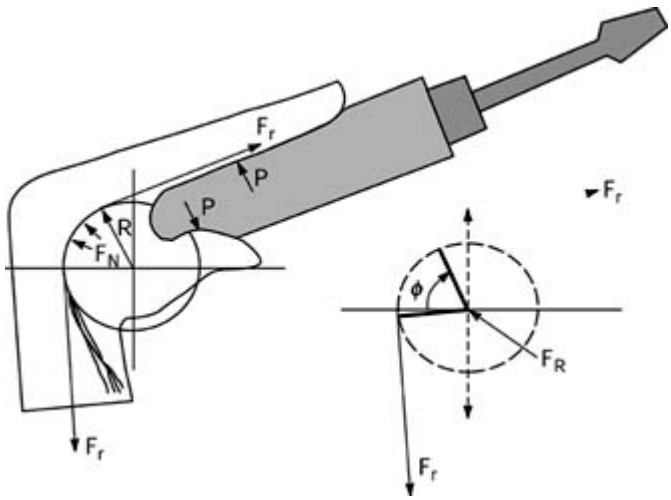

Figure 104.3. Internal forces acting on the wrist during flexion (taken from Ref. 6).

Solution: Using the equation for small object grasp (with a small hand) developed by Armstrong (9),

$$F_T = 2.8\, P = 2.8 \times 1.5 = 4.2 \text{ N} \quad (\text{Note : Foralargehanduse } F_T = 3.1\, P) \quad (1)$$

Using the simple pulley model of the wrist developed by Armstrong (10), the equation for F_R is

$$F_R = 2\,F_T \sin\phi/2 = 2 \times 4.2 \times \sin 40^\circ/2 \text{or } F_R = 2.87\text{N} \qquad (1)$$

2.3.3 Anthropometry Anthropometry is the science of measuring human body dimensions. Because people come in different sizes and shapes, it is critical to quantitate the characteristics of their body dimensions so that this information can be used to design workplaces. The major goal of anthropometry is to match the dimensions of workers' workstations with the appropriate body dimensions so that body postures used are neutral and exert minimal strain on the musculoskeletal systems. For example, people who have fifth percentile reach or short will be forced to extend their forearms excessively to reach for objects in workstations which are designed for a ninetieth percentile population or a population that has a longer reach. Therefore, it is critical to base workstation design on an anthropometric database that represents the user population well. The principles and practices of anthropometrics accommodate the diversity of human body size in designing equipment and workplace environments. In general, the anthropometric goal is to design a workplace so that 90% of the working population is accommodated.

The anthropometric parameters to be measured depend on the application. For example, workstation designs generally require measuring linear dimensions of body segments such as height, length, depth, and breadth. However, clothing design requires measures of body segment circumferences and contours. In biomechanical modeling, anthropometric measures of interest are the location of body joint centers of rotation, body segment centers of mass, interjoint link lengths, and radii of gyration. A detailed discussion of these issues can be found in the literature (11, 12).

2.3.4 Work Physiology The job or work demand should be matched or be comparable to the individual's work capacity, otherwise the potential for injury increases. The field of work physiology gives us tools to quantify the physiological work demand of a task. The individual work capacity or capability depends on a variety of factors such as genetics, training/adaptation, gender, age, body size, environmental (temperature, altitude, and air pollution), and attitude/motivation. The science of work physiology is essential for performing ergonomic evaluation of a task at the workplace. All physical work requires the use of muscles. Therefore, the foundation of work physiology is based on the principles of classical exercise physiology (1, 5). The ergonomic evaluation of work uses appropriate physiological measures that can directly or indirectly assess the workers' cardiopulmonary performance. It is a common practice in the classical exercise physiology literature, to measure whole body oxygen consumption as a direct indicator of physiological work done, but this measure may not be practical to obtain at a workplace. Therefore, ergonomists have used heart rate as a practical (yet scientifically acceptable) surrogate of whole body oxygen consumption during task performance at workplace. For example, it is a common practice to calculate “work pulse” to indicate the physiological workload of a task performed by a worker. “Work pulse” is defined as the average heart rate during task performance minus the workers' resting heart rate. The use of resting heart rate in the calculation of work pulse incorporates the fitness level effect (a fitter person generally has a lower resting heart rate) of the worker. Based on research studies where both oxygen consumption and heart rate were measured, ergonomic criteria for “acceptable” work pulses for men and women are 35 beats per min and 30 beats per minutes, respectively (13). Based on research studies by work physiologists in academia and NIOSH, physiological workload guidelines have been developed for task performance for various time periods without causing whole body fatigue (14, 15). NIOSH determined that any manual task, performed for an 8-hour period at a workload of more than 33% of the worker's maximum oxygen consumption capacity will produce unacceptable fatigue (13, 15). For occasional lifting tasks that last 1 hour or less, metabolic energy costs should not exceed 9 kcal/min for physically fit males and 6.6 kcal/min for physically fit females. Primary tasks variable that affect metabolic demand during a lifting task are the load lifted, the vertical location at the beginning of the lift, the vertical distance, and the frequency of the lift. Based on these metabolic cost criteria, one can then determine the need for appropriate rest periods during task performance.

2.3.5 Psychophysics The field of ergonomics relates workplace factors to human response, so it is reasonable to apply established principles of psychology to capture the subjective perception of the workers who perform a task. One such principle is Fechner's law (16), that relates physical stimulus intensity (*I*) to strength of sensation (*S*) logarithmically:

$$S = K \log I$$

where *k* is a constant. Stevens (17) further modified this as a power law in 1960 to accommodate a wider range of physical stimuli:

$$S = k I^n$$

where *k* is a constant of a particular unit of measurement and the exponent *n* depends on the type of physical intensity being tested. The values of *n* for muscular force, handgrip force, and light brightness are 1.6, 1.7, and 0.33, respectively.

Psychophysical methods are ideally suited for simultaneously assessing workers' subjective perceptions of exposure to a physical stimulus. For example, during a lifting task, the body is exposed to a physiological demand and a biomechanical stress in the low back area. The human brain does not evaluate this lifting task demand separately as physiological and biomechanical; rather it assesses the total demand simultaneously. The CNS performs the simultaneous evaluation, but modern day technology lacks methods for a directly and objectively measuring this simultaneous evaluation. Therefore, in the lifting task example, we have to rely on workers' perceptions of their CNS's assessment of the total (physiological and biomechanical) workload of the lifting task.

The ergonomic literature provides examples of psychophysical scales developed to capture whole body cardiopulmonary exertion (BORG's scale) (18), localized muscle fatigue, body part discomfort, perceived sense of slipperiness (19), and perceived sense of fall (20). These scales have been tested and validated by objective measures. Because these measures use only a paper and pencil questionnaire (usually one-page long) type of scale, they are ideally suited for epidemiological studies that generally use large cohorts.

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3 Physiological Effects
Injuries of any source are attributable to trauma. Whether the trauma is chemical, mechanical, thermal or due to some other agent, otherwise normal tissue must respond to a load that is either too large (macrotrauma) or repeated too often for recovery to occur (microtrauma). Macrotrauma usually involves insults that are sudden and direct and produce immediate symptoms. Microtrauma, the focus of the problem in most overuse syndromes, is the result of repeated loads in a physiological range. It is unlikely that one incident of exposure to the smaller loads involved in microtrauma will result in dysfunction. Instead, it is the longstanding and recurrent nature of the trauma that is responsible for tissue changes. It is also important to recognize that the extent of the repetitive microtrauma is likely to continue to affect the tissue that undergoes the load and also will result in abnormal effects on structures at secondary sites that are attempting to compensate for the impaired function. This propagation of the original insult can lead to microtrauma at the secondary site and further compensation at a more distal or proximal segment. An example of such a chain of events occurs with shoulder bursitis. Inflammation of the bursa due to repetitive stress from painting leads to pain and limited movement in the glenohumeral joint. The scapulothoracic joint substitutes for the

limited movement and increases the tension in the upward rotators of the scapula (upper and lower trapezius). Due to overuse during the substitution, the lower trapezius, fatigues and cannot maintain the depression of the scapula. The scapula elevates as it upwardly rotates and results in abnormal force, pain, and dysfunction of the trapezius. Cervical spine disorders may result.

As shown in Table 104.2, the sources of trauma are varied. The table summarizes some of the more common types of insults that can result in injury. The effects of these injuries can include decreased vascular supply, disruption of cells via direct force, damage by microorganism, or immunological responses that cause further harm to a wide range of tissues. If the initial insult is repeated, as in the case of overuse syndromes, further tissue reactions can perpetuate inflammation and result in changes in tissue size, cell size, cell function, and cell number. Most areas of the body consist of connective tissue along neurovascular bundles and muscle, and therefore a complex series of reactions occurs during the injury and repair process. Further complicating this scenario is the recognition that the effect of an insult on a group of cells is not always uniform. Cell injury is usually mild at the periphery of the application of a force. The damage to the cell can be reversible if it is limited in magnitude and short-lived. In such cases, the nucleus is preserved and continues to function. Cytoplasmic changes, however, occur. The injury produces an environment of decreased oxygen and energy and, under these conditions, the sodium pump cannot maintain the appropriate levels of ions. As Na^+ and Cl^- enter the cell, water follows and swelling occurs in the cytoplasm and in the mitochondria. Anaerobic glycolysis becomes the major source of energy production that results in higher levels of lactic acid. The lactic acid decreases pH slowing metabolism in the energy-deprived state. Protein synthesis decreases, and organelles may be damaged if lysosomal enzymes leak. Because the nucleus and the cell membrane are still intact, energy will slowly be restored. In time, the cell will return to the normal state. Changes, though, have occurred during the period of recovery, and cell function is altered. It follows that the ability of the cell to resist another insult is decreased and it is more susceptible to a lethal injury during this period.

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4 Common Upper Extremity Overuse Syndromes
Space does not permit a detailed description of all impingements or entrapments, but common upper extremity conditions are described following. Summaries include common signs, symptoms, methods of diagnosis, and treatment.
4.1 Thoracic Outlet Syndrome
Thoracic outlet syndrome (TOS) is a compressive neurovascular disorder of the upper extremity (78). Potential causes of this disorder include congenital abnormalities (cervical ribs), anatomic abnormalities of the anterior and middle scalene muscle, trauma, posture, tightness in the pectoralis minor muscle, and repetitive motion that involves continued abduction of the arms. Signs and symptoms are related to the compression of the nerves, arteries, and veins as they exit the cervical area and begin to transverse to the axilla (Fig. 104.10).

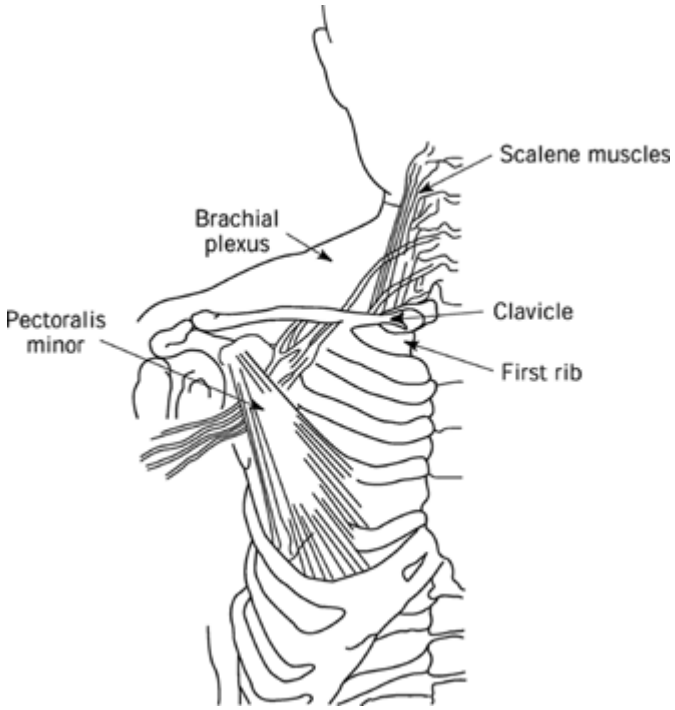


Figure 104.10. Thoracic outlet syndrome. The brachial plexus and related vascular structures can be compressed by the scalene muscles, the first rib, or the pectoralis minor muscle.

Signs and symptoms include pain or paresthesia in the upper limb, especially in the medial arm, forearm, and fifth digit. Pain is nocturnal but, unlike carpal tunnel syndrome, radial digits are not affected in TOS. Elevation above the shoulder increases symptoms as do provocative tests that include hyperabduction of the shoulder. Diagnosis can be made through X ray (cervical ribs), vascular tests (venous and arterial obstructions), provocative tests, and ruling out peripheral entrapments. Treatment depends on cause. Conservatively, physical therapy may be initiated to normalize posture and muscle lengths. Work situations may be modified to lower work positions of arms. Surgery may be indicated for cervical ribs or other entrapments of the neurovascular bundle (104).

4.2 High Median Nerve Entrapment

As the median nerve passes down the arm to the elbow, it travels anterior to the brachialis muscle and between the superficial and deep heads of the pronator teres muscle. It then traverses through the arch formed by the two heads of the flexor digitorum superficialis. Compression can occur as the nerve passes through the pronator teres or through the flexor digitorum superficialis. Signs and symptoms include pain in the proximal volar forearm and disturbances that may radiate proximally. Pain is increased with use of the upper extremity, especially forceful pronation and repeated pronation/supination. Unlike carpal tunnel syndrome, there is little nocturnal pain. Conservative treatment includes avoidance of aggravating activities, drugs, physical therapy, and splinting. Surgery may be indicated if motor and sensory symptoms persist (105).

4.3 Subacromial Impingement

Subacromial impingement is a painful condition that results from contact between the rotator cuff, the subacromial bursa, and the undersurface of the anterior acromion.

The supraspinatus tendon travels from the supraspinous fossa of the scapula underneath the coracoacromial arch to its attachment on the greater tuberosity of the humerus. In normal overhead elevation of the arm, the humerus must remain stable in a moving glenoid fossa. Kinematics involves complex dynamic stability of the rotators of the scapula, including a force couple that consists of the upper trapezius, the lower trapezius, and portions of the serratus anterior. These muscles contract throughout overhead movement of the humerus and cause upward rotation of the scapula without scapular elevation or depression. Stability is also needed to prevent superior movement of the

humeral head in the glenoid fossa. In a normal shoulder, the superior translatory force of the deltoid is opposed by the strong inferior and medial pull of the rotator cuff. The result is minimal superior movement of the humeral head as the arm flexes.

In a patient who has impingement syndrome, there is likely to be an increase superior movement of the humeral head during elevation of the arm (Fig. 104.11). As the humeral head moves up, the supraspinatus is compressed against the acromion. Individuals who have this problem usually have a history of overhead activity in which the arm is repetitively abducted or flexed above the shoulder level.

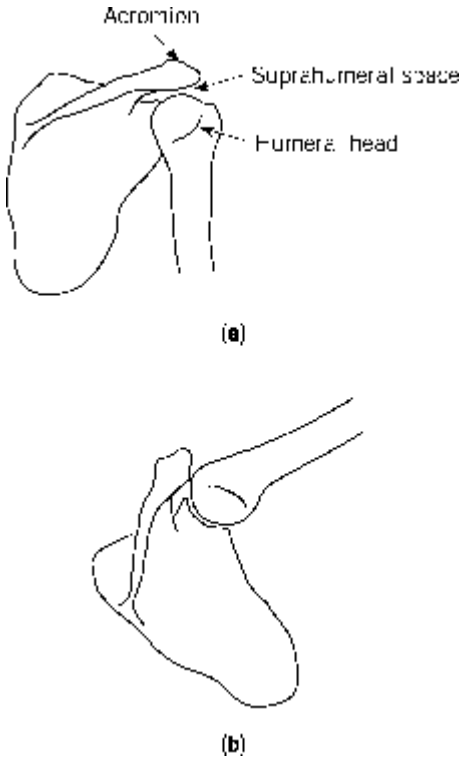


Figure 104.11. A. At rest, a space exists between the humeral head and the acromion. The suprasinatus tendon occupies this space. B. With humeral elevation, the scapula upwardly rotates and the humerus externally rotates. If the upward rotation is accompanied by elevation, the suprahumeral space can decrease. Impingement of the supraspinatus tendon can result.

Certain anatomical factors can also contribute to impingement. The presence of anterior acromial spurs, greater tuberosity spurs, inferior acromioclavicular osteophytes, or posteroglenoid rim spurs can narrow the outlet through which the supraspinatus tendon travels. It is expected that weakness in the rotator cuff that results in superior translation of the humeral head will be symptomatic earlier under these conditions.

The clinical picture of impingement begins with a history of overhead movement and pain. Initially, pain is present only with elevation. Without relief of the stress, pain develops with activities of daily living and progresses to pain at rest and then pain at night. Adhesive capsulitis and rotator cuff muscle weakness may occur secondary to pain. Examination shows a loss of internal rotation and localized weakness of rotator cuff muscles. Scapular muscles may also be weak. Impingement signs such as forced shoulder flexion and cross-body adduction can be positive. Magnetic resonance is the most objective test for accurately assessing the status of the supraspinatus tendon.

Conservative treatment of impingement includes modifying activities, physical therapy to restore rotator cuff and scapular strength, drugs, modifying the work position, and normalizing movement. If these are not successful, a range of surgical interventions can be considered.

4.4 Medial and Lateral Epicondylitis

Repetitive tension overload of the wrist extensors, lateral epicondylitis, or the wrist flexors, medial epicondylitis, results in a degenerative condition rather than a typical inflammatory tendinitis. Unorganized fibrotic tissue found in the tendons of individuals who have these syndromes indicates a failed healing response to low-grade reinjury. Inflammatory cells are absent which supports the belief that the process is not acute and repair is not being attempted. Tendon arrangement is disorganized as illustrated by abnormal collagen orientation and abnormal maturation of collagen. Cellular affects include alteration in the size and shape of mitochondria, decreases in mitochondrial enzymes, differences in RNA transcription, and changes in calcium release and uptake. Intracytoplasmic calcifications, longitudinal collagen fiber splitting, and abnormal fiber cross-links have also been documented. Evidence suggests that mechanical, tensile, and vascular hypoxic injuries have occurred. As changes progress in the tendons, muscles become weak and inflexible and can no longer resist normal loads. As stresses persist, effects are cumulative, and degeneration continues (106).

In lateral epicondylitis, the extensor carpi radialis brevis is involved in 100% of cases, the extensor digitorum in 30% (107). Medial epicondylitis usually involves the pronator teres and the flexor carpi radialis. Both result in aching pain in the tendon and muscle region and radiation of pain into the forearm. Symptoms increase with activity, with stretch, or with contraction of the involved muscles and decrease with rest. Lateral epicondylitis is accompanied by weak elbow extensors and posterior shoulder muscles. Medial epicondylitis is accompanied by weak elbow flexors and pronators.

Treatment for epicondylitis aims to reduce load on the muscles by avoiding identified activities that stress the muscles. Physical therapy, drugs, splinting, work modification, and cortisone injections may be used. Surgical intervention is not frequent and depends on the cause determined.

4.5 High Radial Nerve Compression

Compression of the radial nerve may occur proximal to the elbow as the nerve transverses the posterior aspect of the humerus. Trauma or pressure from crutches or support surfaces may be responsible. Strenuous muscular activity of elbow extensors may also contribute as the lateral head of the triceps constricts the radial nerve. Diagnosis is through EMG and nerve conduction studies. Therapy is conservative, although fractures may require surgical exploration.

4.6 Radial Tunnel Syndrome

Compression of the posterior interosseous nerve, the deep branch of the radial nerve, can occur 6 to 8 cm distal to the lateral epicondyle. Etiology can include overuse of extensor carpi radialis brevis or the possible calcification of the origin of the extensor muscles. More often, compression occurs after unreduced anterior dislocation or after excision of the radial head. Symptoms include motor weakness of the extensors of the wrist and fingers and sparing of the extensor carpi radialis longus and brevis. Diagnosis is confirmed via EMG, and denervation changes are seen in the muscles supplied by the posterior interosseous nerve. Treatment is usually surgical to remove compressive bands or structures (78).

4.7 Ulnar Nerve Entrapment

Ulnar nerve entrapment at the elbow is the second most frequently seen compression neuropathy. The ulnar nerve passes through the ulnar groove at the medial epicondyle and continues through the cubital tunnel. Compression can occur from hypertrophy of the origin of the flexor carpi ulnaris or from repeatedly resting the elbow on a flat surface. Fracture damage at the elbow and resultant scarring can also cause pressure on the ulnar nerve. Throwing can result in recurrent subluxation of the ulnar nerve over the medial epidoncyle and can also result in this type of neuropathy. Synovial cysts at the elbow and, more rarely, an abnormal insertion of the triceps brachii muscle may also cause symptoms in this part of the ulnar nerve. The cubital tunnel is 4 cm distal to medial epicondyle, and if the flexor-pronator aponeurosis tightens, symptoms may result. Common complaints that involve ulnar entrapment include symptoms of pain, numbness or tingling from elbow flexion, and weakness in finger abduction, thumb abduction, thumb and finger pinch, and power grip (78, 108).

Diagnosis is based on motor and sensory nerve conduction studies. Conservative treatment should be

considered for patients who have intermittent symptoms, mild neuropathy, or mild neuropathy that is from an occupational cause. Avoiding repetitive elbow extension and flexion, resting the elbow, splinting the elbow in extension, job modification, and patient education are included. Surgical techniques have mixed results.

4.8 Carpal Tunnel

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the United States. In 1988, the National Center for Health Statistics estimated that 1.89 million workers were affected with CTS. By 1995, that figure had increased to more than 5 million. Incidence was highest in women between the ages 35 and 55. More than 450,000 surgeries, it is estimated, are performed annually, usually in women in the 45–55 age group and in men over 65. It is estimated that up to 15% of workers in the high-risk industries are affected annually (109). In 1994, the Bureau of Labor and Statistics attributed 8.5% of the carpal tunnel cases to repetitive typing or key entry, 5.5% to repetitive use of tools, and 12% to repetitively grasping or moving objects (not tools) (110). Costs, including those for surgery, compensation, and expenses, can exceed $15,000 per worker (109).

4.8.1 Normal Anatomy of the Carpal Tunnel The carpal tunnel is an anatomic space in the anterior wrist that contains the median nerve and nine flexor tendons that pass from the forearm to the palm (Fig. 104.12). The floor is made up of the concave arch formed from the carpal bones and covered by intercarpal ligaments. The roof consists of the transverse carpal ligament as it extends from the scaphoid and trapezium bones to the pisiform and the hook of the hamate. The median nerve and its thirty to thirty-five fascicles are in line with the longitudinal axis of the third digit and contain sensory and motor fibers. The median nerve relays sensation from the thumb, index, middle, and the radial half of the fourth digit. Its motor fibers innervate the superficial head of the flexor pollicis brevis, the abductor pollicis brevis, the opponens pollicis, and the lumbricals of fingers one and two. The diameter of the carpal tunnel varies in the normal population, and changes with normal wrist movements. Wrist flexion decreases the cross-sectional area of the tunnel in the pisiform and hamate areas. Wrist extension also decreases tunnel size and alteration is noted only in the pisiform area. Normal pressures in the tunnel are approximately 2.5 mmHg at rest, 31 mmHg for wrist flexion, and 30 mmHg for wrist extension (111).

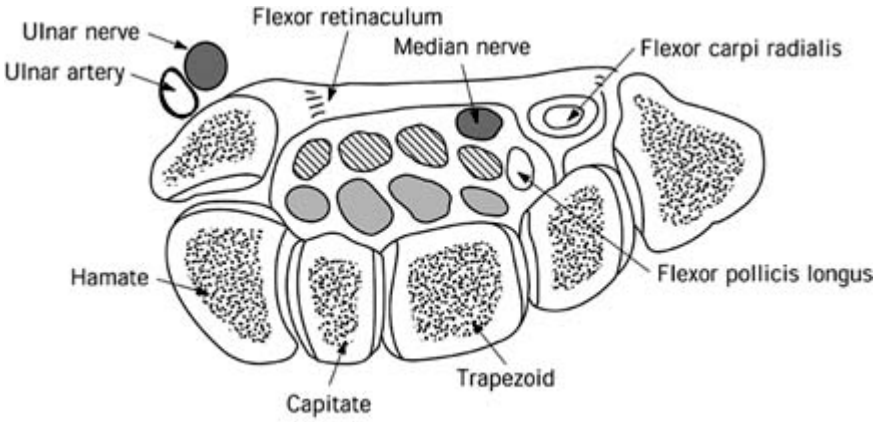


Figure 104.12. Carpal tunnel. A transverse view of the carpal tunnel. Flexor tendons and the median nerve travel under the flexor retinaculum.

4.8.2 Etiology of Carpal Tunnel Syndrome The major signs and symptoms of carpal tunnel syndrome are pain, tingling, numbness, paresthesia, and later, muscle weakness in the distribution of median nerve. Typically, symptoms are worse at night. All of these findings are considered the result of compression on the median nerve.

Theoretically, impingement on the median nerve could be due to any disorder that increases the volume of the contents of the carpal tunnel or that decreases the volume of the carpal tunnel. Rarely,

enlargement of the median nerve may result in compression. In addition, the prevalence of a decrease in the volume of the carpal tunnel due to rheumatic disease or bony deformities is unusual. The majority of symptoms are linked to increased content in the carpal tunnel that leads to tendonitis and/or tenosynovitis (89).

4.8.3 Risk Factors of Carpal Tunnel Syndrome Work factors are the most strongly associated risk factors of carpal tunnel syndrome. People who perform jobs with high repetition and high load have an increased risk of developing carpal tunnel (112). Risk is even higher if these high-repetition and high-load jobs also involve extreme wrist flexion, wrist extension, pinching, or ulnar deviation. Occupations that use high force and highly repetitive manual movements include meat packers, grocery store and assembly line workers, jackhammer operators, computer operators, and grinders. Vibration and awkward postures are additional stressors that increase the risk of carpal tunnel syndrome. Normal lumbrical muscle incursion into the tunnel may also contribute to work-related CTS (113, 114). Because the size of the tunnel may decrease, rheumatoid tenosynovitis, edema, pregnancy, and hypothyroidism have been identified as conditions that may contribute to the development of CTS.

4.8.4 Pathogenesis of Carpal Tunnel Syndrome The contents of the carpal tunnel, including the transverse ligament and the carpal bones are displaced against the walls of the carpal tunnel by flexion and extension. MRIs in normal persons have demonstrated changes in the size of the carpal tunnel, the shape of the tunnel, and the alignment of the contents with wrist flexion and extension (115, 116). The median nerve migrates during these movements, and the tendons slide over a curved surface. Friction occurs resulting in tendon edema and inflammation. As the tendon increases in size, it occupies a greater space in the carpal tunnel and increases the volume of the contents. The greater volume in the enclosed compartment results in more pressure on the median nerve. Signs and symptoms develop (90).

Studies confirm the differences in the pressure in the carpal tunnel between patients who have median nerve symptomatology and that in normal subjects. Pressures are lowest for both groups in the neutral position, increase significantly with wrist flexion, and increase even more with extension. Symptomatic patients exhibit significantly increased pressures in all positions. They also experience a prolonged recovery of pressures to baseline (117–120). Normal resting pressure in individuals without carpal tunnel syndrome is 2.5 mmHg; it is 32 mmHg in those who have carpal tunnel syndrome. Values for flexion and extension in the individual who have CTS range from 94–110 mmHg, significantly higher than normal range of 30–31 mmHg (111). This elevation of pressure leads to an ischemic compromise of the median nerve. The epineural venous blood flow is impaired and results in venous congestion, hyperemia, and circulatory slowing. Continued epineural edema leads to endoneural edema and alteration of the local ionic environment. Axonal transport is interrupted, and pathological changes occur. Ischemia and the presence of exudate promote fibroblastic activity and proliferation of fibroblasts. The epineurium and endoneurium are destroyed and replaced with dense, fibrous scar tissue that shows abnormal impulse generation and transmission, conduction delay, nerve block, and sheath enlargement (111). If repetitive flexion and extension continue, the coefficient of friction will increase and lead to further increases in the tenosynovitis. The volume of the content in the tunnel will become larger and lead to progressive entrapment. The unrelieved compression creates an initial neurapraxia and segmental demyelination of axons. Without relief, the pressure creates an axonotmesis in which axon continuity is lost and wallerian degeneration takes place.

4.8.5 Carpal Tunnel Syndrome, Clinical Manifestations Signs and symptoms reflect the median nerve distribution. Pain and paresthesia, especially nocturnal pain and numbness, are the hallmarks of carpal tunnel syndrome. Complaints usually involve the distal forearm and wrist and radiate into the thumb, index, and middle fingers. Symptomatic individuals are often awakened at night by painful numbness. Sensory complaints usually precede motor symptoms. Thenar weakness and atrophy can be seen in advanced cases. Half of the individuals who have carpal tunnel syndrome have bilateral symptoms. If untreated, pain will persist, the thenar musculature will atrophy, grip and

pinch strength will be lost, and further sensory impairment will lead to clumsiness.

4.8.6 Carpal Tunnel Syndrome, Diagnosis Provocation tests for carpal tunnel include the tethered median-nerve stress test, Phalen's test, Tinel's sign, and carpal compression. The tethered median-nerve stress test positions the forearm in supination with hyperextension of the index finger. As the median nerve becomes ischemic, pain will increase. Phalen's test involves bilateral wrist flexion to 90° for one minute. Pain will increase within that period if the test is positive. Percussion over the carpal tunnel (Tinel's) or pressure applied over the flexor retinaculum (carpal compression) are also positive if pain increases during application.

Diagnosis is confirmed by nerve conduction velocity studies of the median nerve. Changes in sensory conduction across the wrist are the most sensitive and most predictive (121). Magnetic resonance may be an aid, especially to rule out cervical radiculopathy.

4.8.7 Treatment of Carpal Tunnel Syndrome Early diagnosis and treatment are important because delay can result in irreversible median nerve damage, persistent symptoms, and permanent disability (78). Nonsurgical treatment is advised for patients who have mild symptoms, intermittent symptoms, or an acute flare-up from a specific condition. Conservative treatment includes steroid injection, oral steroids or nonsteroidal anti-inflammatory drugs, ergonomic measures, modification of occupation to avoid activities that precipitate the condition, wearing a splint that holds the wrist in the neutral position, patient education, and possible diuretics.

Surgical treatment is indicated if there has been no relief after 2–3 months of conservative treatment, if the symptoms have been present for more than one year with motor and sensory NCV involvement, or if denervation as evidenced by fibrillation potentials on EMG is documented. The most common surgical technique is the release of the transverse carpal ligament. Approaches to the release may vary. Newer techniques are performed through limited incisions and involve less exposure and less manipulation of the nerve (122). Seventy-six percent of surgical patients experience return of normal two-point discrimination, and up to 70% have normal muscle strength return (123). Prognosis depends on the severity of the nerve entrapment, the cause, and the mode of treatment. Recovery of impaired sensation and motor function may take several months; full recovery is not always the end result.

Occupational Ergonomics: Principles and Applications
Amit Bhattacharya, Ph.D., Nancy Talbott, MS, PT, Laurel Kincl, MS

5 Ergonomic Analysis of Low Back Loads and Pain
5.1 Specific Work-Related Injuries in the Low Back Region
5.1.1 Scope of Problem Low back pain and injuries among workers are major concerns of occupational safety and health personnel. Work-related back injuries continue to account for significant suffering, both physically and economically in the United States (124). Workers' compensation data support this. In the United States, approximately one-fourth of workers' compensation claims are filed for back injuries, and one-third of the costs are paid for back injury claims (125–127). The cost, however, is not only in the workers' compensation costs but in the loss of personal productivity, training of other workers to do the job, and medcal and supervisory time spent deciding the appropriateness of the injured worker's return to work and work restrictions (128).

The Occupational Health Supplement to the 1988 National Health Interview Survey (129) provides data on back injuries in the United States. Guo analyzed some of these data and reported that back pain is a major cause of morbidity and lost production for U.S. workers. This article also identified the risk of back injury as the highest among construction workers for males and among nursing aides

for females. Some previously unidentified high-risk occupations include carpenters, automobile mechanics, maids, janitors, and hairdressers (130). The National Safety Council released a report in 1990 (131) identifying overexertion as the most common cause of occupational injury and the back as the body part most frequently injured and most costly to workers' compensation systems.

Tables 104.3 and 104.4 show the incidence rates of nonfatal occupational injuries and illnesses according to industry and the number and percent distribution of days away from work for injuries to the neck, back, and shoulder (132). The transportation and public utilities industries have the highest incidence rates for neck, back, and shoulder injury. For the neck and back, 3–5 days away from work due to injury had the highest percentage distribution, and the shoulder had 31 days or more as the highest.

Table 104.3. The Incidence Rates for Nonfatal Occupational Injuries and Illnesses Involving Days Away from Work per 10,000 Full-Time Workers by Industry and Body Part Affected by Injury or Illness[a]

Industry	Neck	Back	Shoulder
Agriculture, forestry, and fishing	3.8	71.9	14.8
Construction	5.0	89.7	15.7
Manufacturing	3.7	56.8	13.6
Mining	5.9	56.5	10.3
Transportation and public utilities	10.1	108.2	25.3
Wholesale and retail trade	3.7	78.6	9.4
Finance, insurance, and real estate	1.4	14.8	2.8
Services	3.8	55.1	9.7

[a] Ref. 10.

Table 104.4. Number and Percentage Distribution of Nonfatal Occupational Injuries and Illnesses Involving Days Away from Work by Part of Body Affected by Injury or Illness and Number of Days Away from Work, 1996.

	Neck		Back		Shoulder	
Days away from work	Number	Percent	Number	Percent	Number	Percent
1 day	5,740	16.6	63,494	12.9	12,862	13.3
2 days	5,106	14.8	60,770	12.4	9,938	10.3
3–5 days	7,877	22.8	117,052	23.9	18,435	19.1
6–10 days	4,115	11.9	72,369	14.8	12,549	13.0
11–20 days	3,118	9.0	58,973	12.0	11,112	11.5
21–30 days	1,651	4.8	29,044	5.9	6,049	6.3
31 days or more	6,902	20.0	88,905	18.1	25,567	26.5

median days away	5	6	8

5.1.2 Biomechanics of Spinal (Vertebral) Column and Low Back Region The spinal unit is a complex structure that allows humans to perform a range of physiological motions such as flexion, extension, lateral bending, and rotation around its long axis. The spinal unit supports the attachments of internal organs, the head, and the extremities. It also provides mobility via a series of motion segments that consist of vertebral bodies (bony structure), intervertebral discs (soft tissue structures) sandwiched between each vertebra, and the surrounding ligaments (Fig. 104.13). This series of motion segments constitutes the entire spinal unit. The movement of the motion segment is controlled by active contraction of muscles and passive support provided by ligaments. This anatomical structure consists of thirty-three vertebrae. The major muscle groups that support the lower back are erector spinae muscles, hip flexor and extensor muscles, and abdominal muscles. Because of the short lever arm (2.5 cm) of the erectores spinae muscles, it has to generate a very high force to keep the body from falling forward during lifting or holding weight in the sagittal plane. The hip flexors and extensors are instrumental during forward, backward, and lateral bending. The abdominal muscles are instrumental in providing stabilizing force to the spine and because they are located anterior to the spinal unit, they provide an assistive torque that reduces the force needed by the erectores spinae muscle. The action of the trunk muscles converts the thoracic and abdominal cavities (chambers) into nearly rigid-walled cylinders of (1) air (thoracic cavity) and (2) liquid and semisolid material (abdominal cavity). Both of these cylinders can resist part of the force generated in loading the trunk and, thereby, relieve the load on the spine itself.

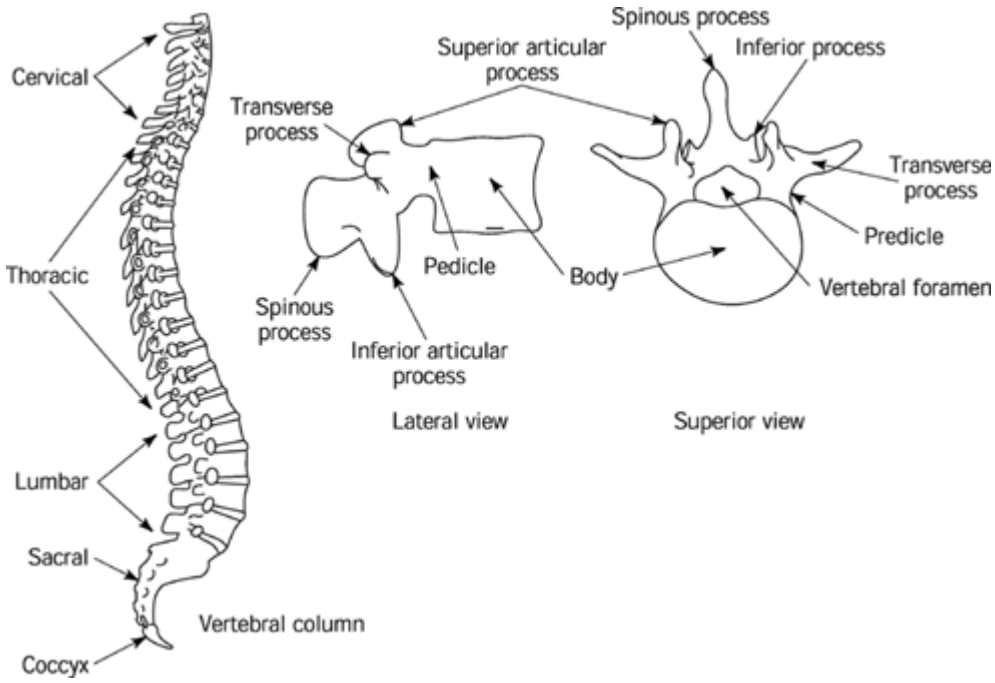


Figure 104.13. Spinal column.

The spinal unit also houses and protects the spinal cord and nerves along its entire length. The range of motion of the motion segments varies depending on their location in the spinal column and the mode of motion. The range of motion in the lumbosacral region is the largest for flexion/extension and the least for axial rotation. The range of motion in the lower thoracic region (T-10 to T-12) is the largest for flexion/extension and the least in axial rotation. Axial rotation in the cervical region is much larger than that available in the lumbar region (133, 134).

The literature provides data about the compressive strength of vertebrae at various levels of the spinal unit ranging from the cervical to the lumbar region (135, 136). In general, compressive strength is the smallest at the cervical level, and values increase for the thoracic and lumbar regions. Vertebral strength also decreases with age especially beyond 40 years. The rib cage provides strength and overall stability to the spinal column (137).

5.1.3 Intervertebral Disc About 20–30% of the entire height of the spinal column is made up of intervertebral discs. The disc has three components called nucleus pulposus, annulus fibrosus, and cartilaginous end plates. The intervertebral discs do not have a direct blood supply and do not carry any nerve endings. Upon the application of a load due to body segment weight associated with postures assumed, the fluid pressure within the nucleus pulposus (in a young healthy person, the inside of the disc is moist) pushes the surrounding annulus fibrosus and the end plates (Fig. 104.14). The orientations of the annulus fibers and the nucleus pulposus play a significant role in load transmission from one vertebra to the next.

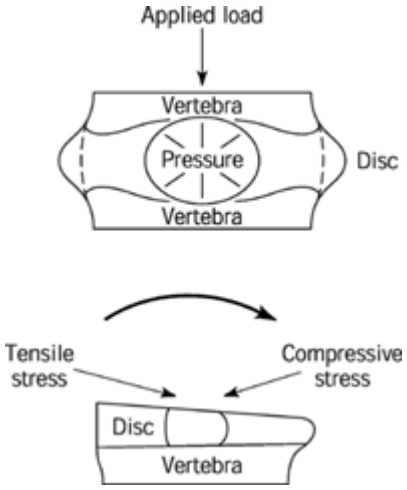


Figure 104.14. Spinal disc loading (Adapted from Ref. 133).

During normal physiological upright posture, the intervertebral disc along with facet joints is exposed primarily to compressive forces. However, during dynamic motions such as jumping and jogging, the disc loading may be severalfold higher than that observed in the static case. The types of stresses produced within the disc depend on the nature of physiological motion performed. For example, during bending (flexion, extension, and lateral bending), one side of the disc is subjected to compression and the opposite side experiences tensile load (Fig. 104.14). The compressive loading causes bulging of disc material which in the pathological case may impinge on the spinal nerve to cause back pain. Figures 104.15 and 104.16 show relative intradiscal pressure during various postures and the effect of various lumbar support on intradiscal pressure, respectively (138) (Fig. 106.17).

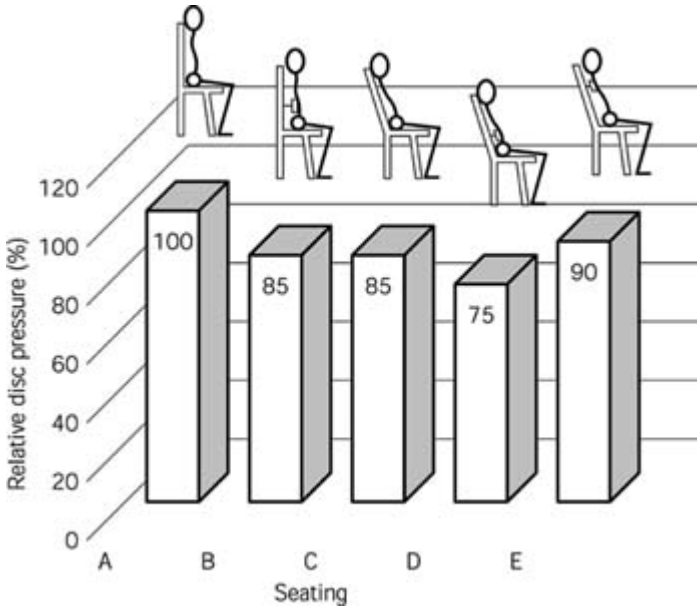


Figure 104.15. Effect of seat back inclinations on relative spinal disc pressure taken from Ref. 6.

Figure 104.16. Effect of body postures on relative spinal disc pressure taken from Ref. 6.

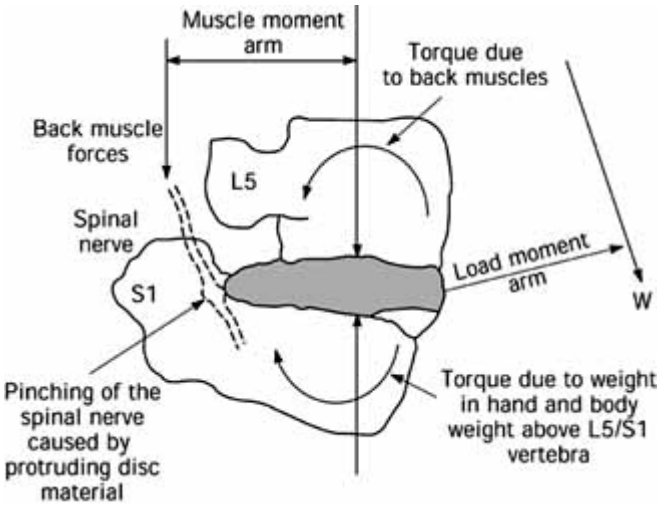


Figure 104.17. Potential pinching of spinal nerve during lifting weight taken from Ref. 6.

Axial rotation of the torso with respect to the pelvis causes *torsional* loads that result in *shear* stresses in the discs. Research studies have shown that bending and torsional loadings are more dangerous than compressive loads. Intervertebral discs have time-dependent properties such as fatigue and viscoelasticity characterized by hysteresis, creep, and relaxation. These properties determine disc failure due either to short-duration (high-amplitude load, i.e., jerk lifting) or long-duration (low-amplitude load) application of forces (11).

5.1.4 Biomechanical Aspects of Low Back Pain Low back pain symptoms can result from one of the following: disc degeneration, injuries and tumors of the spine, disc inflammation due to arthritis, and referred pain from abdominal or pelvic organs. A majority of low back pain cases (68%) fall into the category of disc degeneration (5).

A variety of factors such as physical, psychosomatic, biochemical, and anatomical can cause back pain. The biomechanical reason for back pain is explained in the following: Because disc materials do not have any nerve endings, simple compression forces do not create pain. Rather, during compression, the disc material can protrude outside and impinge upon the spinal nerves that surround the disc and the vertebral units. In the static spine, an increase in the lumbosacral angle can cause an increase in lumbar lordosis. This is called "swayback." About 75% of all postural low back pain is due to excessive lordosis. Pain caused is possibly due to facet impingement and irritation. See Fig. 104.17 (16, 139).

Kinetic low back pain is caused by abnormal body movement such as sudden movement or nonsymmetrical bending. Standing in a forward-flexed posture of 10–15° causes high loading of lumbar discs. This type of loading can also occur in a seated forward position.

These are common postures used in many industrial occupations that are responsible for occupational low back pain (5) (Table 104.5).

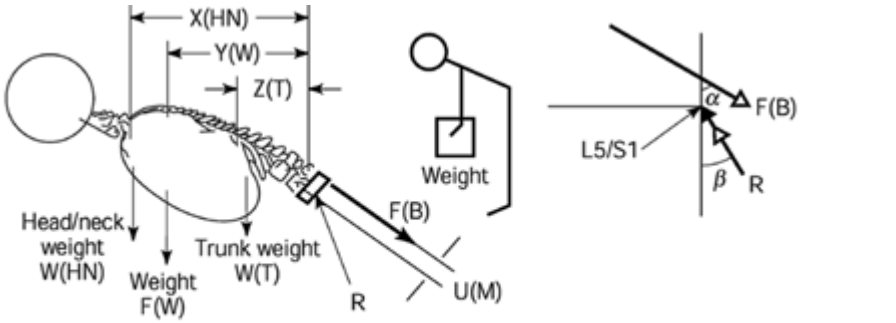
Table 104.5. List of Aggravators of Low Back Pain[a]

Descriptions of Tasks/Postures That Aggravate Low Back Pain
Constant standing and sitting
Low working height that makes worker bend
Extended reach to perform a task continuously for more than one minute
Turning and twisting of the trunk, such as lifting weights from the front to the side
Crouching posture for more than 1 minute
Repeated sustained work above the shoulder
Seats with improper low back support
Handling of loads with shifting weights of > 25 lb, such as liquids
Fixed work place height; frequent (one or more per minute) lifting or lowering of objects that weigh > 25 pounds
Handling of bulky loads whose physical dimensions are > 20 inches on any side of the box
Sustained (> 30-second period) pushing or pulling of loads in excess of 40 lb
Bending trunk below the waist for > 1 minute

[a] Ref. 5.

5.1.5 Analysis of Holding Weight in Hand and Its Effect on the Low Back Lumber-Sacral Joint The most common forces that determine the effect on the lower back during lifting in the sagittal plane are (1) gravity (BW, weight carried by the body) [external], (2) tension in the deep muscles of the back and in the muscles of the abdominal wall [internal], (3) pressure in the internal cavities of the trunk (intra-abdominal and intrathoracic) [internal], and (4) force transmitted by the spinal column [internal]. To determine the forces on the spine at a given level, say the L5/S1 point, it is necessary to consider the *external* (gravity) forces on the body above the L5/S1 level and the *internal* forces that resist or support the external forces. The stability of the spine depends largely on the action of the extrinsic support provided by the trunk muscles. The portion of the trunk above the L5/S1 is about 30% of body weight. The force of a weight lifted by the arms is transmitted to the spinal column by the shoulder-girdle muscles, principally the trapezius, and then to the abdominal cylinder and to the pelvis, partly through the spinal column but also through the rigid rib cage.

Example: The following data (Fig. 104.18) are given for a sagittal lifting activity (140). Calculate the back muscle force F(B) and the magnitude and direction of reaction force R at the L5/S1 joint. The person weighs 170 lb. Assume that F(B) is at an angle a = 40° to the vertical. Assume the right horizontal as the positive x-axis and vertical down as the positive y-axis (adapted from Ref. 18).



W(HN) = 17.7% of body weight; W(T) = 30% of body weight; F(W) = Lift weight = 200 lbs;
X(HN) =18 inches; Y(W) = 14 inches; Z(T) = 7 inches; U(M) = Back muscle moment arm = 2 inches.

Figure 104.18. Example of a biomechanical analysis of a lifting weight problem.

Solution:

$$\Sigma M = 0 \text{ around the L5/S1 joint } 30{\cdot}18{+}200{\cdot}14{+}51{\cdot}7 = F(\mathrm{B}){\cdot}2F(\mathrm{B}) = \frac{540+2800+357}{2} = \frac{3697}{2} = 1848.5\,\mathrm{l}$$
(1)

$$\Sigma F_{\mathrm{Y}} = 0 = F(\mathrm{W}){+}W(\mathrm{HN}){+}W(\mathrm{T}){+}F(\mathrm{B}){\cdot}\cos\alpha - R\cos\beta = R\cos\beta = 200{+}30{+}51{+}1848.5\cos 40^\circ = 281{+}18$$
(1)

$$\Sigma F_{\mathrm{x}} = 0 R\sin\beta = F(\mathrm{B})\sin\alpha = 1848.5 \cdot 0.642 = 1188.19\,\mathrm{lbs} \qquad (1) \qquad (2)$$

From Equations (1) and (2),

$$\tan\beta = \frac{1188.19}{1697} = 0.7 \therefore \beta = 35^\circ \therefore R\sin 35^\circ = 1188.19 \therefore R = \frac{1188.19}{0.573} = 2073.62\,\mathrm{lbs}$$
(1)

Conclusion: The back muscle force F(B) needed to sustain the posture and the 200-lb weight in the hand is about nine times that of the weight held because the body's lever system works at a

mechanical disadvantage.

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6 Job Analysis
Ergonomic job analysis is used to identify and measure potential hazards. From such an analysis, solutions for reducing or eliminating ergonomic risk factors can be developed. Potential ergonomic hazards include work conditions that cause fatigue, overexertion, injuries, and chronic musculoskeletal disorders (141). Physical, mental, and perceptual demands due to these hazards can be measured during a job analysis (142). The type of job analysis can vary according to the purpose and scope of the investigation but generally involves the following elements: (*1*) identifying the potential hazards, (*2*) preparing to conduct a job analysis, (*3*) conducting the job analysis, (*4*) interpreting the results, (*5*) developing solutions, and (*6*) documentation (143).
6.1 Identifying Potential Hazards
First a review of injury data should be completed. Statistics on injury, absenteeism, or a high turnover rate on specific jobs can be obtained from plant records and/or employee surveys. These jobs can then be ranked according to their severity. After this has been completed, jobs of the highest severity should be investigated further. Walk-through surveys can then be conducted for the selected jobs. Background information about the job, employee and supervisor interviews, checklists, and surveys can be used to collect information (143). Various checklists (144) that have been developed can be modified to analyze specific jobs as needed.
6.2 Preparing to Conduct a Job Analysis
Observation and direct measurements can be used to evaluate the ergonomic hazards identified. The equipment required will depend on the type of hazard and the specific type of job analysis to be evaluated. Table 104.6 displays some examples of measurements that may be quantified for physical, physiological, and mental work. Some items that are generally useful for job analysis are video cameras, tape measures, force gauges, and stopwatches. More sophisticated, equipment and techniques such as electromyography, accelerometers, finger force sensors, and electrogoniometers are available and have been applied in the field (143).

Table 104.6. Measurements for a Job Analysis[a]

Type of Measurement	Example of Measurement
Biomechanical	Reach height and distance
	Weight and dimension of material handled
	Forces and torques
Motions	Frequency
	Degree of rotation
	Duration
	Dexterity/coordination requirements
Timed activity analysis	Pattern of activities during shift
	Time to perform a task
	Frequency of more demanding tasks
Environmental	Temperature, humidity, air movement

	Noise
	Illumination
	Shift schedule
	Other physical or chemical factors (odors, work surface)
	Use of protective clothing or equipment
Mental and perceptual	Visual and auditory requirements
	Complexity
	Information handling/decision making requirements
	External pacing
	Productivity during shift (units/hour, interruptions, etc.)
	Quality of output (defects, incomplete work, etc)
Physiological	Heart rate
	Blood pressure
	Oxygen consumption
	Surface electromyography
	Psychophysical scaling (perceived exertion, comfort, stress)
	Minute ventilation
	Body temperature

[a] Ref. 142.

Methods and tools have been developed for analyzing a specific risk factor for some job tasks. For example, Waters et al. recently studied some methods for assessing manual materials handling (MMH) tasks (145). The review article provides information for selecting appropriate methods for a particular job/task and included the following:

1. The revised National of Institute for Occupational Safety and Health (NIOSH) lifting equation (146)
2. The University of Michigan 3D Static Strength Prediction Program (147)
3. The Oxylog portable consumption meter (148)
4. The Polar portable heart rate monitor
5. The University of Michigan Energy Expenditure Program (149)
6. The Chattanooga Corporation Lumbar Motion Monitor
7. The Ohio State University risk assessment model (150)
8. The Snook and Ciriello psychophysical approach for assessing manual lifting demands (151)

After equipment and/or an analysis tool are selected, a sampling strategy must be developed. A typical work period should be observed under normal conditions. At least three workers who perform the job and the entire work cycle should be observed at least three times. If the job does not have repetitive cycles or is an irregular task, the workers may need to be observed randomly during an extended period to capture all tasks.

6.3 Conducting the Job Analysis

For accuracy, the job should be disrupted as little as possible. A large part of the job analysis will be direct observation of the work tasks. Discussion with workers to obtain information on specific elements of the job and supervisors to obtain information on the broader view of the operations and the feasibility of future proposed changes can also be conducted. Finally, preliminary measurements of the worksite should be recorded, including a dimensioned sketch of the layout of the workstation

and tools. The specific measurements would depend on the type of analysis performed and the equipment used.

6.4 Interpreting the Results

To analyze the results, the job must be broken down in tasks or subtasks. Then, each task can be evaluated for such factors as force required, posture assumed, repetitiveness, duration of work and recovery periods, and other physical exposures such as vibration or cold temperatures. Factors such as these increase the risk of cumulative trauma disorders. However currently, there are no known limits for force and repetition that are safe for the working population. Estimates can be made from strength data, anthropometry, physiological data, psychosocial data, and integrated models.

6.5 Developing Solutions

The results from the ergonomic job analysis should include methods to eliminate, reduce, or control the ergonomic hazards identified. This can involve modifying equipment, workstation layout, work practices, and raw material packaging and administrative changes such as employee rotation, longer rest breaks, and reduced production rates. A follow-up job analysis should be conducted after the interventions are in place to ensure the feasibility and effectiveness of any changes made to the job.

6.6 Documentation

Finally, a report of the entire job analysis process should be written. It can include the reason that the analysis was done, what risk factors were identified, how they were evaluated, and recommendations for correcting the problem (143).

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7 Regulations and Recommendations

The Occupational Safety and Health Administration (OSHA) has issued guidelines for controlling ergonomic hazards in the meatpacking industry (152). OSHA is also developing a general ergonomic standard and will soon issue a draft of the proposed standard (153). California has a standard that regulates repetitive motion injuries (154). In addition, the American National Standards Institute's (ANSI) Z-365 (155) is another proposed general ergonomic standard for cumulative trauma disorders.

7.1 Occupational Safety and Health Administration's Meatpacking and Proposed Ergonomics Standards

The Occupational Safety and Health Act of 1970 states that it is the general duty of all employers to provide a workplace free of serious hazards. These hazards include ergonomic hazards. The management of worker safety and health protection includes all hazards even if they are not specified by a U.S. federal regulation. In 1990, OSHA issued general guidelines (OSHA 3123) for ergonomic management programs, specifically for the meatpacking industry. OSHA's proposed ergonomics standard, if passed, will be an enforceable regulation in the United States. A draft of the national standard is expected to become public in the near future.

7.1.1 Ergonomic Program Management Guidelines for Meatpacking Plants These guidelines are neither a standard nor a regulation but provide information on the approach that employers should take to determine if ergonomically-related problems exist in their workplaces, to identify the nature and location of these problems, and to implement measures to reduce or eliminate these problems. The guidelines are divided into three sections (1) management commitment and employee involvement, (2) program elements, and (3) detailed guidance and examples.

The *management commitment and employee involvement* section stresses the importance of management's commitment and a team approach to a successful program. It states that a written program should be developed and communicated to all employees. The importance of employee involvement in the program and in decision making is also stressed in this section. Finally, regular review and evaluation of the program by managers, supervisors, and employees is recommended.

The section on *program elements* includes four major elements: *worksite analysis, hazard prevention and control, medical management, and training and education*. The *worksite analysis* objectives described are to recognize, identify, and correct ergonomic hazards. The *hazard prevention and control* element includes guidelines for using engineering controls, work practice controls, personal protective equipment, and administrative controls. The third major element involves guidelines for implementing a *medical management* system that identifies, evaluates, treats signs and symptoms, and aids in preventing ergonomically related injuries and illnesses. Finally, the element that involves *training and education* presents information to inform employees about the ergonomic hazards to which they are exposed and their role in the ergonomics program.

The last section on *detailed guidance and examples* gives more specific information on an ergonomics program related to the meatpacking industry. A recommended worksite analysis for ergonomics is described in detail. It provides information on gathering information from available resources, conducting baseline screening surveys, performing ergonomic job hazard analyses both before and after controls are in place, and conducting periodic surveys and follow-ups to evaluate changes. This section also includes specific examples of engineering controls for hazard prevention and control and medical management programs to prevent and cumulative trauma disorders in the meatpacking industry (152).

7.1.2 OSHA's Ergonomics Standard The proposed standard includes the following sections: introduction, purpose, scope and application, identification of problem jobs, control of workplace risk factor exposures, ergonomic design and controls for new or changed jobs, training, medical management, recordkeeping, effective date and definitions. The standard can be found in 29 CFR 1910.500 or the OSHA homepage (http://www.OSHA.gov) on the internet. This standard is scheduled to go into effect, January 2001.

The *purpose* of this standard is to prevent and reduce the severity of musculoskeletal disorders by controlling the exposure to risk factors, medical management, information dissemination, technology, and management and employee participation in ergonomic programs. The *scope* covers employees who are exposed to risk factors that are measured in hours and employees who have recorded work-related musculoskeletal disorders. The *application* of this standard depends on the extent of workplace risk factors and work-related musculoskeletal disorders.

The *identification of problem jobs* includes sections on employee information, a workplace risk factor checklist, and start-up dates. An OSHA workplace risk factor checklist would be provided in an appendix. The *control of workplace risk factor exposures* describes the requirements for determining and implementing an appropriate strategy to control problem jobs by reducing or preventing employee exposure to workplace ergonomic risk factors. The *ergonomic design and controls for new or changed jobs* section includes ways to prevent or control problem jobs when changes are made in the workplace in the future. This includes information on eliminating workplace risk factors in job design and the employer's responsibilities when job changes introduce signal risk factors. The *training* section describes the training requirements for the employee. The *medical management* section describes the requirements for plans to assess and manage musculoskeletal disorders among employees. Such plans are proposed to provide for early assessment and treatment of work-related musculoskeletal disorders and to reduce their severity and prevent progression. The *recordkeeping* section details the maintenance of records according to the requirements of 29 *CFR* 1910.20. Finally, the effective date and definitions for the standard will be provided (153).
7.2 California's Repetitive Motion Injury Standard
This standard, Title 8, General Industry Safety Orders, Article 106, Ergonomics, Section 5110, Repetitive Motion Injuries, went into effect on July 3, 1997 in California. This standard is comprised of three sections, including scope and application, a repetitive motion injury program, and satisfaction of an employer's obligation.

The *Scope and Application* states that the standard applies to a job, process, or operation where at

least one employee has a repetitive motion injury (RMI) diagnosed by a licensed physician. This RMI must be work-related and must be reported by the employee within 12 months. Employers are exempt from this standard if they have fewer than nine employees.

The employer is required to develop an *RMI program*. This program is required to include a worksite evaluation, control of exposures that have caused RMIs and training of employees. The worksite evaluation involves evaluating jobs, processes, or operation for exposures that may cause RMIs. Control of exposures may include engineering controls and administrative controls and must eliminate the exposure or at least minimize it. The training must include an explanation of the employer's program, potential exposures, symptoms and consequences of injuries caused by repetitive motion, the importance of reporting RMIs and finally, the methods that are being implemented to minimize exposures.

Finally, the section on *satisfaction of an employer's obligation* states that the employer is obligated to take measures that would greatly reduce RMIs as long as they do not impose excessive costs (154).

7.3 ANSI Z-365

The ANSI Z-365 draft consensus standard for cumulative trauma disorders (CTDs) is a proposed voluntary standard, which means that it is not regulated and not enforceable. It is comprised of four sections, including purpose and scope, definitions, conformance, and the process.

The *Purpose and Scope* of the standard is divided into three sections. *The Purpose and Intended Audience* states the standard and describes the processes and principles for controlling work-related CTDs. A definition of CTDs is given, including their causes and their characteristics. The *Scope* states that the aim of the standard is to control work-related CTDs that arise from manual lifting, assembly, manipulation of tools, machinery and other devices, and other stresses on muscles, nerves, tendons, and associated soft tissues of the body. The *Scope* also describes the ergonomic considerations such as work postures, work layout, force requirements, vibration, work rates, tool design, and flexibility of workstations to accommodate individual variations. Finally, the *Standard Content* describes that the scope will be addressed through surveillance, job analysis and design, management of CTD cases, and training sections.

The *definition* section contains words relevant to understanding the standard. The section on *conformance* explains that the standards/guidelines in this document would be voluntary and, would be established by consensus. This section also discusses the wording used in the document. A section on the *process* includes background to explain how and why the standard came about. The *CTD Control Process* proposes a CTD control program that includes management responsibilities, training, employee involvement, surveillance, evaluation and management of CTD cases, job analysis and job design, and intervention. Finally the Program Implementation states that priorities will have to be established by individual employers to determine which component should be addressed first. This section also states that regular evaluations are required to determine if the evaluation and reduction of CTD risk factors is beneficial.

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Occupational Vibration
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1 Vibration Defined
1.1 Vibratory Motion
Vibration (2), by definition, is a vector quantity, consisting of both a magnitude (or intensity) and direction. Vibration motion measured at any one point is defined by a total of six vectors: three mutually perpendicular "linear vectors" and three corresponding "rotational vectors" called "pitch," "yaw," and "roll." Most occupational vibration measurements use only the three mutually linear vectors, ignoring the rotational vectors. Hand–arm vibration measurements use a special vector coordinate system, as shown in Figure 105.1. Whole-body vibration measurements use another special vector coordinate system, as shown in Figure 105.2.

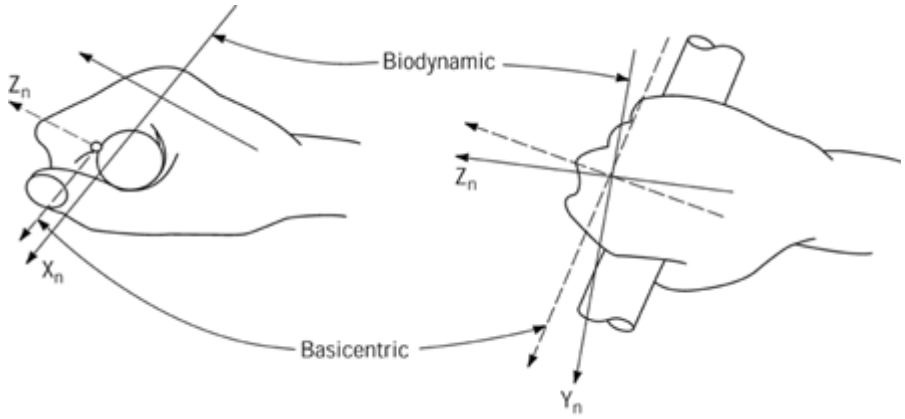

Figure 105.1. Coordinate system directions used to measure hand–arm vibration acceleration for use with ANSI S3.34 and ACGIH standards.

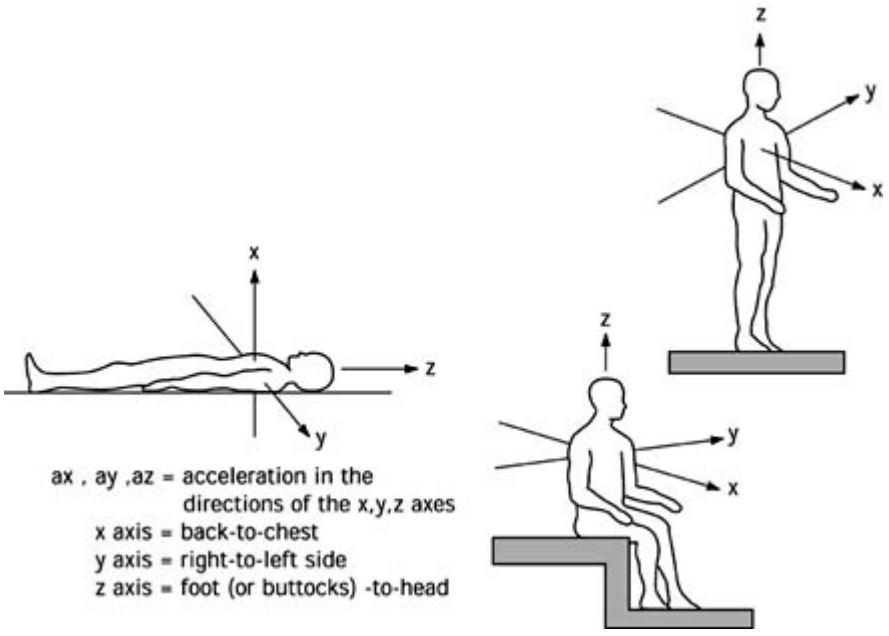

Figure 105.2. Coordinate system directions used to measure whole-body vibration acceleration for use with ANSI S3.18 and ACGIH standards.

1.1.1 Types of Vibratory Motion Vibratory motion can be: periodic or nonperiodic; continuous, impact, or random. The motion can be purely single sinusoidal (or pure tone, if it were audible) or a complex mixture containing many sinusoids. If sinusoidal motion is completed in one second, then the vibration frequency is one cycle/second or 1 hertz (Hz). If five complete cycles of sinusoidal motion occur in one second, then 5 Hz is the frequency; 1000 complete cycles in one second is 1 kHz (kilohertz), and so on.

1.2 Measures of Intensity

There are three interrelated descriptors of motion, which can be used as measures of intensity: displacement, velocity, or acceleration.

Displacement is motion measured away from some reference point. The units of displacement can be meters, feet, centimeters, inches, and so on.

Velocity is the time rate of change of displacement, or the speed of a moving object. The units of velocity are distance divided by time; feet per second, meters per second, and so forth.

Acceleration is the time rate of change of velocity. The units of acceleration are usually either in meters per second per second or in gravity *g* units, where 1 *g* = 9.81 meters per second per second. Acceleration is usually the measurement quantity of choice as the "intensity" descriptor for human vibration measurements.

Since displacement, velocity, and acceleration are all related mathematically, it is necessary to measure only one of these parameters, and the remaining two parameters can be mathematically obtained; for example, if acceleration is measured, mathematically integrating the acceleration function will yield velocity. Repeating the integration process on the velocity function will yield displacement.

1.3 Vibration Acceleration Intensity

Characterizing *vibration acceleration intensity*, as measured in the workplace, necessitates that the following issues be addressed:

- What is needed is a typical measure of the vibration acceleration intensity or "dose" impinging on the worker's body without collecting data over the entire workday.
- Workplace vibration is usually complex and time-varying and thus contains a mixture of vibration frequencies.

What parameter of acceleration intensity represents *vibration dose*? If we choose to measure only the "peak," or the largest value of acceleration occuring in a specific direction over a specific measurement time period, does this represent the vibration dose impinging on the worker? Probably not, since there is no guarantee that this motion will be repeated. The answer to these questions is to use a type of average vibration acceleration intensity measurement called *root-mean-squared* (rms) acceleration, which is more desirable than using peak measurements. If varying peak acceleration values do occur during measurements, then the rms mathematical process can account for these values. The Following equation defines RMS acceleration:

$$a_{\text{rms}} \sqrt{\frac{1}{T} \int_0^T a^2(t)\, dt} \qquad (1)$$

where: a = measured acceleration (m/s^2 or g value) t = time (s)T = measurement time period, (s)

In equation (1), acceleration values are first squared; thus negative values become positive. All such

values are summed or integrated over the measurement period; the sum is then divided by the total measurement time *T*; the square root of the resulting value yields the rms value. For pure sinusoidal motion the rms acceleration value is

$$a_{\text{rms}} = (0.707)\, A_{\text{peak}} \tag{2}$$

where *A* = peak acceleration, (m/s^2 or *g* values).

1.4 Using Fourier Spectrum Analysis to Calculate Workplace Vibration

Workplace vibration is rarely a single sinusoid, but is usually complex motion containing several vibration frequencies. A frequency separation method for data analysis known as *Fourier spectrum analysis* is needed and is used to

- Convert time-domain data to corresponding frequency domain data, thus forming a spectrum
- Determine the acceleration intensity contribution to the overall vibration spectrum for each frequency in the spectrum

Fourier spectrum analysis is analogus to chemical spectrophotometry, where the concentration of each element forming a compound is separated into its elements and graphically displayed as a *line spectrum*, in which position of each vertical spectral line denotes an element's wavelength in the spectrum and the corresponding height of each line represents the concentration that element contributes to the compound. In the 1800s a French mathematician, Jean-Baptiste Fourier (1768–1830), showed that a linear, complex waveform was composed of a mathematical series of sines and cosines of differing frequencies and amplitudes as given by equation 3:

$$\begin{aligned} F(t) = a_0 + a_1 \sin\omega t + a_2 \sin 2\omega t + a_3 \sin 3\omega t + \cdots + a_n \sin(n)\omega t + b_1 \cos\omega t \\ + b_2 \cos 2\omega t + b_3 \cos 3\omega t + \cdots + b_n \cos(n)\omega t \end{aligned} \tag{3}$$

where the *a* and *b* terms are intensity values for each sinusoid frequency that constitutes the spectrum. The a_0 term is the zero hertz [or DC] component and is seldom used.

The Fourier spectrum computer's output is a graphical line spectrum; the graph's abscissa is vibration frequency in hertz; the graph's ordinate is intensity in rms acceleration in m/s^2 or *g* units. Spectrum analysis is a very powerful analytical method for identifying the frequency/intensity characteristics of different vibration sources.

1.5 Vibration Transmissibility

Often many times it is necessary to determine how vibration entering and then exiting a structure is modified. An often used descriptive term is called *vibration transmissibility*, which is defined as the ratio of output acceleration exiting the structure divided by input acceleration entering the structure, as a function of vibration frequency, with both input and output vibration moving in the same direction. Transmissibility is a “transfer function” and is a dimensionless number; a transmissibility ratio equaling unity (one) means that there is no change between input and output; a ratio less than one (< 1) means that the structure internally reduces the input vibration; a ratio greater than one (> 1) means that the structure is internally amplifying the original vibration and may be “resonating,” which is an undesirable phenomenon, discussed next.

1.6 Resonance

Virtually all physical structures vibrate when mechanically excited, this is also true of the human body. There are certain preferred vibration frequencies (known as “natural” or *resonance frequencies*) where a structure will naturally vibrate with very little externally applied input excitation. Simply stated, resonance is the tendency of a mechanical system (or the human body) to act in concert with externally generated vibration and to internally amplify the input vibration and exacerbate its effects. Maximum vibration energy is transmitted from the source to the receiver at resonance. Resonance is undesirable, is uncontrollable, and can be very destructive (This is one reason why soldiers never march across a bridge); in rare instances, resonance can be managed and

controlled, and can even be desirable, such as in the construction of certain musical instruments (3). Undeniably, in the workplace situation, resonance is totally undesirable, because if a vibrating source such as a vehicle or powered handtool should emit frequencies corresponding to human resonances, and a worker's body comes in physical contact with that source, most likely the emitted vibration would be internally amplified by the worker's body. Resonance is the Achilles heal of human vulnerability to vibration and must be avoided.

1.7 Damping and Isolation

Finally, there are two main engineering methods for minimizing vibration: damping and isolation. Vibration *damping* is the conversion of mechanical vibratory motion into a corresponding small amount of heat, due to the deformation of the damping material as in a glove containing viscoelastic materials. Vibration *isolation* is the intentional design mismatch or alteration of the pathway(s) between the vibration source and the receiver; as, for example, in an automotive shock absorber.

Occupational Vibration
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2 Hand-Arm Vibration

2.1 Health Effects and Epidemiology

There are some 2 million workers (1) in the United States alone exposed to hand–arm vibration (HAV). These include workers using vibrating pneumatic, electric, and gasoline-powered handtools such as chippers, grinders, impact hammers, rachet hammers, jack-leg-type drills, demolition tools, jackhammers, chain saws, and brush removers. The negative health effects (4, 5) of this HAV exposure have been recognized since the very early 1900s. In 1911, Loriga in Italy reported white fingers in workers using pneumatic tools in mining (6). During 1918, in a study of cutters and carvers using vibrating pneumatic tools in the Oolitic limestone mines of Bedford, Indiana, the famous occupational physician, Dr. Alice Hamilton, first reported some 80% prevalence of a disease of their hands called white finger or *Raynaud's phenomenon* (7). Since those early times there have been numerous studies causally linking HAV exposure with disease of the fingers and hands (4, 5). Typically this condition's initial symptoms are attacks of tingling and/or numbness (paresthesia) in the fingers, followed by an initial attack of finger whitening (or blanching), usually of one finger, lasting a few minutes. As the vibration exposure continues, blanching attacks increase in number and severity, and include multiple fingers; cold temperatures often trigger these blanching attacks (4, 5), and smoking exacerbates this condition (8). Often the thumbs are the very last of the fingers to be affected. A small percentage of the population (mostly women) have naturally occurring *Raynaud's disease*, which is not an occupationally induced condition, but the symptoms of which are similar to the condition described above. Through the years occupationally induced Raynaud's has undergone several name changes from “dead fingers” to “white fingers,” to *Raynaud's phenomenon*, to “vibration white fingers” (VWF), and currently hand–arm vibration *syndrome* (HAVS). For the most part HAVS is an irreversible condition of the fingers and hands after the blanching process is well under way. *Calcium channel blockers* are the current medications used to relieve some signs and symptoms of HAVS; however, these agents are palliative and *not* a cure. The timespan from when a worker begins using a vibrating handtool to the appearance of the first white fingertip is called the *latent period* and has been used as the HAVS peripheral vascular time marker for many years. Depending on the type of tool used, worker exposure time and conditions, and attendent tool acceleration levels, the latent period can vary from as little as a few months to several years. Generally, higher tool acceleration levels result in shorter latent periods (4, 5, 9–11).

Patient diagnosis of HAVS consists of a vibrating toolwork and hobby history and a specialized battery of medical tests (4, 5), which include finger plethysmography and Doppler blood flow tests, finger systolic blood pressure, two-point discrimination, finger depth sense, vibrometry/frequency threshold measurements, and thermal hot/cold perception of the fingers.

In 1968 the Taylor–Pelmear medical classification system for scaling HAVS (11) was introduced and used successfully until 1986. Table 105.1 describes the Taylor–Pelmear system. The initial stages of tingling and/or whitening are noted as OT, ON, TN, followed by the initial blanching Stage 1, whose timespan is defined as the aforementioned latent period. With increased vibration exposure, overall finger blanching progresses, more fingers become involved, and the person's ability to perform work and overall quality of life steadily deteriorate in Stage 2, 3, and 4. If vibration exposure is allowed to continue beyond Stage 4, finger gangrene (tissue necrosis) can occur. In reality, in most cases the pain and suffering from HAVS is so extensive in these latter Stages that the worker is essentially forced to change jobs, thus avoiding any finger gangrene. Sadly, the white finger condition will persist despite removal of the vibration source. In 1986 the Taylor–Pelmear system was modified by the *Stockholm scale*, which separately grades each hand for peripheral vascular loss (Table 105.2) and sensorineural loss (Table 105.3). This modified system was requested by the international medical community because it was found that some HAVS patients never advanced to the finger blanching stages and only the early neurological stages occured with vibration exposure (12).

Table 105.1. Taylor–Pelmear Medical Classification System for HAV Syndrome[a]

Stage	Condition of Digits	Work and Social Interference
0	No blanching of digits	No complaints
OT, ON or TN	Intermittent tingling, numbness, or both	No interference with activities
1	Blanching of one or more fingertips with or without tingling and numbness	No interference with activities
2	Blanching of one or more fingers with numbness; usually confined to winter	Slight interference with home and social activities; no interference at work
3	Extensive blanching; frequent episodes, summer as well as winter	Definite interference at work, at home, and with social activities; restriction of hobbies
4	Extensive blanching; most fingers; frequent episodes, summer and winter	Occupation changed to avoid further vibration exposure because of severity of symptoms and signs

[a] Adapted from Ref. 9.

Table 105.2. Stockholm (Modified Taylor–Pelmear) Peripheral Vascular Classification System for HAV Syndrome[a]

Stage	Grade	Description
0		No attacks
1	Mild	Occasional attacks affecting only the tips of one or more fingers
2	Moderate	Occasional attacks affecting distal and middle (rarely also proximal) phalanges of one or more fingers

3	Severe	Frequent attacks affecting all phalanges of most fingers
4	Very severe	As in stage 3, with trophic skin changes in the fingertips

[a] Adapted from Ref. 4.

Table 105.3. Stockholm (Modified Taylor–Pelmear) Sensorineural Classification System for HAV Syndrome[a]

Stages[a]	Symptoms
0SN	Exposed to vibration but no symptoms
1SN	Intermittent numbness, with or without tingling
2SN	Intermittent or persistent numbness, reduced sensory perception
3SN	Intermittent or persistent numbness, reduced tactile discrimination and/or manipulative dexterity

[a] Adapted from Ref. 4.

Although the major components of HAVS are neurological and peripheral vascular, there are other conditions related to HAV exposure which are suspect but less documentated; these include some prevalence of elbow and wrist osteoarthritis and some damage to the articular cartilage due to impact tool vibration exposure (13) and a tonic vibration reflex that reduces tactile sensibility because the hand muscles are involuntarily contracting (14). The occurence of HAV-induced *carpal tunnel syndrome* (CTS), a compression syndrome, with or without HAVS (4, 5) can also occur. A combined medical treatment is needed for both CTS and HAVS.

Worldwide there have been numerous epidemiology studies of vibration-induced HAVS over the years. It is common to discover about a 50% prevalence of HAVS with relatively short latent periods of 1–2.5 years in foundry workers, for example, using vibrating pneumatic handtools (4, 5, 9–11, 15).

2.2 Hand–Arm Vibration Measurements (2, 4, 5)

Only the salient aspects of measuring both HAV and WBV in the workplace are discussed here. It is beyond the scope of this chapter to present the numerous details of this process, which are available elsewhere (2).

2.2.1 Premeasurement First, it is not advisable to attempt vibration measurements without careful planning; it is advisable to initially perform a “walk through” visit before conducting any vibration measurements, preferably with a portable videocamcorder, recording those vibration processes that are to be measured together with personal taped narration. Try to observe both new and experienced workers performing the same or similar vibration tasks. Later replay the video at normal speed and then in slow motion to observe how the worker(s) interact with the vibration process. Recognize that many work processes can be divided into a series of work, rest, vibration, and nonvibration steps; these steps and the vibration work cycle form the basis of the required measurements. Finally, plan how, when, and where the vibration measurements will be made for minimal disruption of production lines, and so on. When possible, test adjacent to, but not directly in, the actual production line area using experienced workers performing their regular tasks in a normal manner. Sometimes off-hour testing can be done, using experienced workers to avoid work disruptions. During testing it is advisable to maintain both written test logs and a videotape of the actual vibration measurements.

2.2.2 Workplace Vibration Testing Occupational vibration testing consists of the basic elements

shown in Figure 105.3. For a single HAV measurement, three axes (*viz.*, triaxial), mutually perpendicular, linear, rms acceleration measurements are required to quantify, record, and analyze the vibration impinging on a worker's hand. When both hands operate a tool, two triaxial simultaneous measurements are needed.

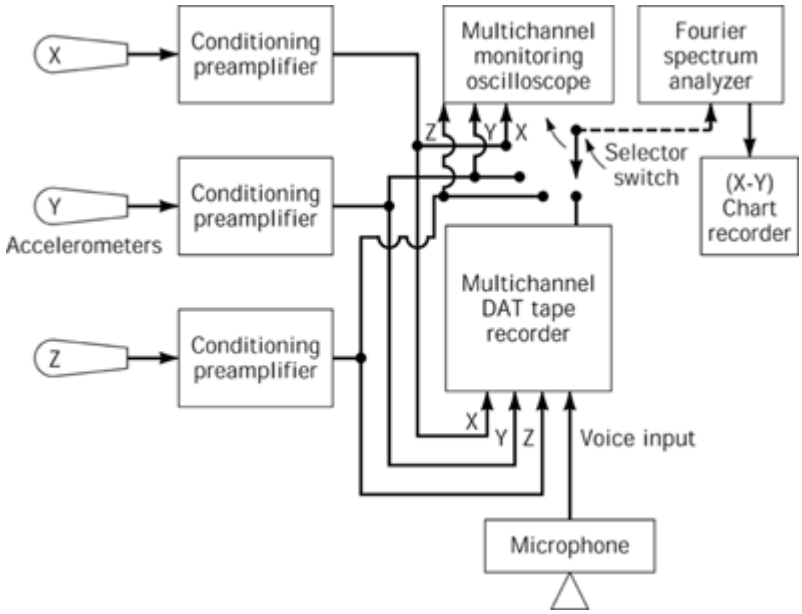

Figure 105.3. Typical equipment setup used to measure occupational hand–arm or whole-body vibration (adapted from Ref. 2).

All accelerometers used should be identical, very lightweight (<15 g each), piezoelectric/quartz crystal devices. Quartz crystal is a force transducer normally found in nature and is strongly *piezoelectric*, becoming electrically polarized with a negative charge on one end and a positive charge on its opposite end when subjected to mechanical force or pressure. The bonding of a small, light, mass to a quartz crystal transforms this natural force transducer into an accelerometer. An acceleration signal results when an external vibration force is applied to the accelerometer, and this small mass presses or accelerates against the crystal, resulting in a corresponding electrical charge; the effect is to simulate Newton's law, $F = ma$.

Finally, since the electrical impedance of an accelerometer is very high, it is difficult to directly extract and use this charge signal from the device; thus a *charge amplifier* is used with the accelerometer to both amplify and convert its charge into a corresponding useable electrical voltage.

Using this instrumentation, HAV testing basically consists of

- First, calibrating and recording each accelerometer to be used for testing, using a calibrator traceable to the National Bureau of Standards.
- For each hand position on the tool, mounting and orientating each triaxial accelerometer using the "basicentric coordinate system" shown in Fig. 105.1.
- The selection and mounting of each triaxial accelerometer and fixturing needs be done with care and must be tightly clamped to the tool to avoid internal resonances in the measurement system, which can result in incorrect results.
- A minimum collection time of one minute of continuous vibration data at each tool/hand position is needed. All three (or six) charge amplifier acceleration outputs are simultaneously recorded on a multitrack tape recorder called a *digital audio tape* or (DAT) for later analysis.
- Each recorded vibration data channel requires a separate spectrum analysis to be performed and each result separately compared to the HAV standards currently used in the United States.

- Most human standards contain *weighting functions* that must be taken into account when using these standards.
- There are a few commercially available portable, handheld, numerical readout, triaxial, vibration meters that contain HAV and/or WBV weighting functions in their software. They are primarily used as survey meters to assess whether a vibration problem may in fact exist. They are not Fourier spectrum analyzers and thus have limited use in clarifying and quantifying the problem once found.

2.2.3 Human Vibration Weighting Functions (2, 4, 5) Human response to vibration is not necessarily *linear*, which simply means that one unit of vibration impinging on the human body for a given time does not necessarily produce a corresponding one unit of biological damage. An example of nonlinearity is at resonant frequencies where the human body responds to a very small vibration excitation input, by internally amplifying and exacerbating the input vibration as much as twice, 3 times or more. Nonlinearity is not unusual for the human body; for example, it is well known that the human ear responds to sounds nonlinearly. Other body sensors most likely respond nonlinearly.

In human vibration, this nonlinearity has led to the development of *weighted human response functions*, which represent attempts to generate exposure-time-dependent dose–response relationships for HAV (and WBV). Thus weighting functions try to simulate how humans respond to impinging vibration; it is an evolving process as the scientific database improves with new knowledge. Most human vibration standards use weighting functions to help evaluate whether a given standard has been exceeded. The weighting function used for HAV is not the same as those used for WBV. Thus each weighting function is presented separately as the respective HAV and WBV standards are described individually.

2.3 Hand–Arm Vibration Standards and Guides Used in the United States

Currently three HAV standards and guides are used in the United States for occupational safety and health purposes:

- American Conference of Governmental Industrial Hygienists (ACGIH) standard for HAV (16), first issued in 1984.
- American National Standards Institute (ANSI) HAV standard (17), #S3.34, first issued in 1986.
- National Institute for Occupational Safety & Health (NIOSH) *Criteria for a Recommended Hand–Arm Vibration Standard* (18), #89–106, first issued in 1989.

At this writing the Occupational Safety and Health Administration (OSHA) has not issued any standard for HAV. The above ACGIH and ANSI documents listed above are *consensus standards*. There are two international HAV standards *not* used for safety and health purposes in the United States, issued by the International Standards Organization, ISO 5349 and ISO 8662. ISO 5349 provides some limited guidance for health and safety but provides no daily exposure limits for hand–arm vibration syndrome; rather, it defers to each country to determine such guidance. ISO 8662 is a multipart-tool-specific-limited measurement document used mainly by various tool manufacturers. This document clearly states that it is *not* intended for safety and health purposes. The European Community (EC) of nations has issued exposure limits for HAV and affects U.S. and other products sold in EC countries.

2.3.1 Hand–Arm Vibration Standards and Guides and the Weighting Function (*Caution*: It is imperative that a complete up-to-date copy of the applicable HAV standard be obtained, read, and understood by the user *before* attempting measurements or data evaluation, since descriptions given herein are for information only and are not exhaustive.)

Figure 105.4).X shows the graphical version of HAV weighting function used for both the ACGIH and ANSI standards; the shape of this function is defined by the family of parallel “elbow”-shaped HAV exposure-time-dependent curves and exposure zones ranging from 0.5 to 8 h/day. This same graph is used three separate times with the aforementioned results of the Fourier Spectrum analysis;

once with the tool spectrum for the *x*-axis acceleration, again with the spectrum for the *y*-axis acceleration, and finally again with the spectrum for the *z*-axis acceleration. The graph's abscissa shows the broad frequency range in $\frac{1}{3}$-octave bands extending from 5.6 to 1250 Hz, to accommodate the large number of different power tools that can be tested using these standards. Similarly, the graph's ordinate extends very high in rms acceleration intensity to 1000 m/s^2; corresponding to approximately 102 *g*.

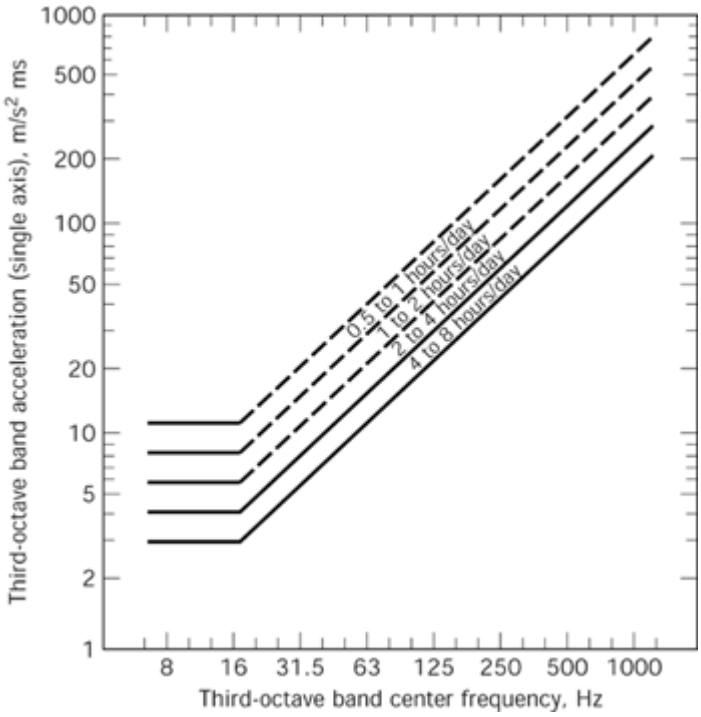

Figure 105.4. Hand–arm vibration weighted daily exposure zones used in the ANSI S3.34 standard.

In practice, for each measurement axis, a programmed Fourier computer automatically:

1. The computer calculates the entire unweighted vibration spectrum.
2. The computer compares and "overlays" this spectrum across the weighting graph (see example in Fig. 105.4
3. The computer numerically calculates the *overall weighted acceleration intensity* across this spectrum.
4. The interpretation of the *weighted* results are mainly based on the given HAV standard used as follows:

*ANSI S3.34*uses graphical evaluation criteria such that when no peak in the spectra either touches or pierces through any daily exposure zone in the family of weighted curves, that axis acceleration has passed the standard. Should one or more spectral peaks touch and/or pierce any of the exposure curves at any place(s) on these curves, the standard has been exceeded for that axis. The higher the peak(s) touching/piercing these curves, the higher the acceleration intensity and thus the shorter the allowable daily exposure time the worker is permitted to use the tool. Each of the three axes spectra is processed in the same manner. Usually the axis with the highest (acceleration intensity) peak(s) "dominates" over the other two axes. This dominant axis then determines the maximum permissible daily HAV exposure a worker can be subjected to when using the tested tool.

The *ACGIH standard* uses only the aforementioned weighted numerical *values* and separately assesses each of the computer's overall weighted rms values for each tested axis against those in

Table 105.4. Once again the largest overall weighted acceleration value dominates over the other two axes values. The dominant weighted value determines the daily permissible exposure levels for the tested tool. Both ANSI S3.34 and the ACGIH standards correlate well with each other, yielding similar, but not necessarily indentical, daily HAV exposure recommendations. It is important to note that these two standards try to minimize the potential of HAVS blanching in most workers, not necessarily the initial stages of finger tingling and/or numbness. Finally, a *time-weighted average* can be calculated for daily intermittent tool use and applied accordingly to the above two standards.

Table 105.4. ACGIH Threshold Limit Values®–Standard for Daily Exposure to HAV for Each Linear Vibration Axis[a]

Total Daily Exposure Duration (h)[b]	Values of the Dominant,[c] Frequency-Weighted, RMS, Component Acceleration, Which Shall Not be Exceeded[d] $a_{K'}$ (aK_{eg})	
	m/s^2	*g*
4–8	4	0.40
2–4	6	0.61
1–2	8	0.81
< 1	12	1.22

[a] Courtesy of ACGIH.
[c] Usually one axis of vibration is dominant over the remaining two axis. If one or more vibration axis exceeds the total daily exposure, then TLV has been exceeded.
[d] 1*g*=9.81 m/s^2.
[b] The total time vibration enters the hand per day; whether continously or intermittently.

The *European Community's* evaluation is also weighted numerically as a *vector sum*. This requires that *each* of the three axes overall weighted rms values be individually squared and then summed; the square root of this summed value is obtained, resulting in a vector sum value that is numerically compared to, and should not exceed, the EC "action level" of 2.5 m/s^2 (rms) acceleration for 8 h/day HAV exposure (19).

The *NIOSH HAV standard #89-106* does not contain permissible daily values for HAV workplace exposure (18). Administratively, NIOSH has chosen to issue an interim HAV document citing the need for a better dose–response relationship for HAVS, while agreeing that HAVS is a serious occupational health problem. The NIOSH document cites various administrative measures that can be taken in order to help minimize HAVS. This document also recommends collecting and analyzing both weighted and unweighted triaxial vibration data that have been extended in the upper frequency range to 5000 Hz. This extended frequency range, says NIOSH, is needed because of the recent introduction of some very high speed tools in selected industries. At this writing this NIOSH interim document appears to have limited value for HAVS and it has not been adopted by OSHA.

2.4 Hand–Arm Vibration Control in the Workplace

The control of hand–arm vibration (2, 4, 5) includes the following:

- Use power tools that are *both* anti vibration (A/V) *and* ergonomically designed. If a tool is only ergonomically designed without a corresponding reduction in its vibration levels, then most likely the potential of HAVS will be increased because of the better match between the hand and the tool handle. If a tool's acceleration levels have been reduced and the body and handle design are not ergonomically correct, then other cumulative trauma disorders, such as CTS, can be expected.
- Avoid the use of so-called vibration protective tool handle "wraps;" although inexpensive, many

are minimally effective at reducing vibration exposure, especially at low frequencies. These wraps also increase tool handle diameter and can lead to other cumulative trauma disorders.

- For personal protection, use only good-fitting *full-finger-protected* gloves. Since HAVS begins at the fingertips and then moves down toward the palm, gloves where only the palm is protected and the "fingers remain exposed" *do not* protect the worker from HAVS and are *not* recommended.
- In places where fixed workstations exist, use tool balancers and, where possible, antitorque devices. The former effectively removes the tool weight from the operator, the latter reduces some of the "twisting" or rotational tool motion.
- Comply with the aforementioned HAV standards.
- Workers should let the tool do the work using as light a grip strength as necessary to maintain safe tool operation; maintain the tools properly and replace as needed—operate tools at reduced speeds if possible; keep their hands and bodies dry and warm; avoid smoking, since cold, vibration, and nicotine all constrict blood vessels; see a physican immediately if signs and symptoms of HAVS occur, and adhere to manufacturer's vibration warnings on the tools and/or instruction books.

Occupational Vibration
Donald E. Wasserman, MSEE, MBA

3 Whole-Body Vibration
3.1 Epidemiology and Health Effects
Some 7 million workers (1) in the United States alone are exposed to head-to-toe whole-body vibration (WBV). These workers include truck, bus, forklift, heavy-equipment, farm vehicle, overhead crane, subway, locomotive, ship, fixed-wing aircraft, and helicopter drivers and operators. There are potential safety consequences and documented health effects of chronic occupational WBV exposure (2, 20–22). Historically, in the 1960s and 1970s, much of the initial and basic WBV research was conducted by U.S. Air Force, Navy, and Army laboratories in an effort to determine the ability of military personnel such as aircraft pilots, tank operators, and naval personnel to successfully execute their mission requirements. This experimental testing was conducted mostly under (acute) simulated or actual WBV military conditions. These studies were concerned primarily with human performance measures and not necessarily chronic health issues. The overall results of this military effort led to the following:

- The determination of WBV human resonances (23).
- The mathematical modeling of human mechanical response to WBV (23–25).
- The determination of the overall WBV human response weighting functions used in many standards today (26).
- The determination that under certain WBV conditions, human performance decrements can and do occur (26, 27).
- The issue of *chronic* WBV exposure effects was not addessed by these military studies; rather, it remained for other nonmilitary researchers to later investigate.

Relevant history shows that with the passage of the U.S. Occupational Safety & Health Act of 1970 and the subsequent creation of U.S. National Institute for Occupational Safety & Health, NIOSH chose to establish its first occupational vibration program (28). As part of this early NIOSH program, an extensive series of WBV epidemiological medical records studies, with control groups, were conducted of heavy-equipment operators (29, 30), and over-the-road truck (31) and bus drivers (32), all in an effort to help determine the *chronic effects* of occupational WBV exposure. The

summarized results of these early epidemiological medical records studies follows:

- The bus driver study showed a significant excess of venous, bowel, respiratory, muscular, and back disorders in a group of 1448 interstate bus drivers as compared to two control groups: office workers and the general population. This study concluded that the combined effects of body posture, postural fatigue, dietary habits, and WBV appear to contribute to the occurrence of these disorders.
- The truck driver study looked at 3205 long-haul truck drivers and a control group of air-traffic controllers. The results showed the truck drivers significantly suffered from the combined effects of forced body posture, handling cargo, WBV, and poor eating habits contributed to their vertebral pain, spinal deformities, sprains and strains, and hemorrhoids.
- There were two heavy equipment operators studies; the first study examined several hundred health claims of operators and showed they had elevated risks of certain musculoskeletal diseases, male genital diseases, ischemic heart disease, and obesity. The second study was a follow-up to determine whether these workers left their jobs due to WBV; the study results were equivocal.

These early epidemiology studies served to point the NIOSH vibration program in the direction of musculoskeletal and spinal disorders associated with WBV exposure. Some study results were confounded with similar spinal disorders in workers who both lifted cargo and were exposed to WBV (*i.e.*, while operating vehicles for long time periods in over-the-road bus and truck driving).

Subsequent WBV studies by other investigators, confirmed the thesis that chronic WBV exposure was and is associated with lumbar spine herniated disks and low-back pain (33, 34) and related degenerative spinal disks diseases (20–22). Laboratory studies of Wilder and Pope in the United States (35–37) and Dupuis, in Germany (22), and others began and continue to elucidate the biomechanical mechanisms of the human spine's response to WBV exposure. The summarized salient relationships of WBV exposure and the human spine are as follows:

- The (lumbar) spine has its own resonance at 4.5–5.5 Hz; located at L3–downward; in the vertical WBV direction; when the spinal dis pressure is at its maximum.
- When persons are seated, their lumbar spine vertebral facets normally disengage, leading to prestressing of the lumbar discs and limited rotation. When WBV occurs, for example, during the driving of a vehicle, this causes alternate stretching and rotation of these discs with maximum response occuring at the spinal resonance.
- During WBV exposure, lumbar discs can slide (prolapse); disks can tear; disk distortion, flattening, or increased height can occur; or herniation or a break in the disk can occur with a leaking out of its rubbery pulposus. Disk thinning can occur because of moisture reduction caused by WBV exposure.
- Vertically applied WBV creates an overload of the motion segments leading to disk buckling and instability; pelvic rocking can also result.

Thus, undeniably, the spine is a major target organ for WBV exposure.

3.1.1 Whole-Body Vibration and Work-Hardening (38) Inappropriately, medical rehabilitation specialists have begun to use WBV as part of “work hardening” simulation regimes used for the rehabilitation of vehicle drivers, many of whom have undergone back surgery and other medical procedures. WBV is *not* therapeutic and is definitely *not advised* in the work-hardening situations, since it could do serious harm to these patients! The reasons should be in part obvious:

1. As stated, WBV has been identified as one major cause of severe spinal problems.
2. The ability of the human spine, the autonomic nervous system, and the spinal musculature to respond to impinging (sudden-load) WBV is very limited, since it both lags and is out of phase with the input by as much as 120 ms; also, visual, proprioceptive, and vestibular responses

triggered by changes in posture take some 150 ms; and voluntary reaction time with latency take another 180 ms. Thus the human body cannot respond and adjust quickly enough to impinging WBV without potential damage.

3. Because the spine has its own resonant frequency of 4.5–5.5 Hz, should the source's impinging vibration contain these frequencies, the spine will amplify and exacerbate the effects of the input vibration.

In conclusion, because of the foregoing, WBV should *not* be used in work-hardening simulation regimes.

3.1.2 Other Medical Effects of Whole-Body Vibration Virtually all WBV epidemiology studies conducted to date have been of exposed male workers and not females (39–44). A major reason has been that until recently most of these WBV-exposed jobs were male dominated and suitable female study populations did not exist. Of growing concern, however, have been a number of reports of pregnant female vehicle drivers spontaneously aborting their fetuses as well as cases of other gynecological disorders in female drivers. These reports have prompted new and ongoing animal research studies in this area to determine the effects of WBV exposure on both the pregnant mother and the fetus.

3.2 Safety Aspects of Whole-Body Vibration

Many of the early studies of human subjects exposed to WBV were concerned with either "performance effects and/or comfort effects." The former was of primary concern to the military to ensure safe mission success; the latter was of concern to automobile and other vehicle manufacturers to design and sell comfortable products (21, 25, 45). Some of these first studies focused on the perception of magnitude (acceleration intensity), vibration frequency dependence, exposure time, and the effects of using seatbelt and other body restraint systems. These study results led in part to the early conclusions that a person's perceived endurance to WBV was both frequency-and magnitude-dependent, with the lowest tolerance occurring in the 4–8-Hz resonance band for seated subjects exposed to vertical WBV. This is a potential safety issue. Some early study designs consisted of various progressive multidimensional tracking tasks, memory and simple mathematical tasks, and pattern and visual monitoring (both of which appear to be minimally affected by WBV). Another related performance issue is of great safety concern: the "direct mechanical effects on performance." For those exposed to WBV while driving a vehicle, it is not always possible for a driver's hand(s) to safely control and grasp a steering wheel when a resonant frequency situation occurs, because of the involuntary "mechanical decoupling" between the hand and the steering wheel. Resonant vibration can potentially pose great difficulty in maintaining a safe grip on the steering wheel. Thus it is possible to envisage a situation where a truck driver, for example, encounters a resonant vibration condition through either the driver's seat and/or the steering wheel, which is triggered by driving off-road or over a series of potholes. The driver next loses control of the steering wheel, resulting in an accident or worse ... . a definite safety issue.

3.2.1 Whole-Body Vibration and the "Root Mean Quad" Discomfort Factor (21) Although discomfort is not in the forte of occupational health and safety, it is important that the reader appreciate the difficulty involved in assessing, in a simple measure, the numerous types of WBV motion encountered in various real-world situations. For example, in 1990, Griffin in Britain empirically determined that a reasonable measure of subjective discomfort due to WBV was related to the exposure time multiplied by the impinging acceleration raised to the Fourth power, using his *root-mean quad* (rmq) method, rather than the customary method of time multiplied by the acceleration square, or

$$a^4 t = \text{constant} \tag{4}$$

By introducing the Fourth-power concept, Griffin hoped that a wide variety of WBV motions "from individual bumps and repeated impacts to intermittent vibration and long-duration continuous vibration" (21) could all be simply taken into account by these rmq averaging proceedures. Although

his concept is now well known, it is not universally accepted; it appears to be of significant value when distinguishing between the comfort of various seating used in vehicles. Unfortunately, there have been attempts to use rmq methods to expand into the health aspects of WBV exposure. At this writing, there are *no* hard medical or epidemiological studies to justify the use of the rmq method to be used with medical assessments of WBV exposures. Work continues in this area.

3.3 Whole-Body Vibration Measurements

The basic elements shown in Figure 105.3 for HAV also apply to WBV measurements (2), but with differences in the actual hardware and software used for WBV measurements and data analysis.

3.3.1 The Piezoresistive Accelerometer WBV measurements usually require another different type of triaxial device known as a *piezoresistive accelerometer* rather than a *piezoelectric* accelerometer. The former accelerometer is suitable for very low frequency (WBV) use; the latter, for higher frequency (HAV) use. Refer to Figure 105.5, noting that

- Piezoresistive accelerometers are composed of four separate and identical pieces of the same type of semiconductor material, either P or N type (positive or negative).
- Each semiconductor element forms one “arm” of a classic four-arm Wheatstone electric bridge.
- Each bridge arm is physically arranged as side-by pair: one upper pair and one lower pair.
- One end of a small metal beam is next sandwiched and pinned between these two sets of semiconductor pairs, thus constraining the beam's movement at this pinned end. The opposite end of this metal beam protrudes outward beyond the constraining sandwich and is free to flex up and down when vibration is applied, similar to a flexible diving board pinned at one end.
- Vibration force applied to the free end of this beam moving in one direction causes it to bend, compressing one pair of the semiconductor devices, thus creating an “electrical unbalance” and a corresponding electrical signal voltage. A vibration force applied to this beam in the opposite direction compresses the opposite pair of semiconductor devices, creating another corresponding electrical voltage of the opposite polarity. A constant bending force (0 Hz) applied to the free end of the beam causes a constant output voltage to appear and remain until the force is removed. Thereupon the beam returns to its original neutral position, rebalancing the electrical bridge with zero output voltage.
- This device thus far is a classic force gauge, *not* an accelerometer. Placing and fixing a small mass at the free end of the beam transforms this force gauge into an accelerometer, using Newton's law, $F = ma$. When vibration is applied to the mass, it accelerates against the free end of the metal beam, causing it to bend and thus creating an output “acceleration” voltage.
- This accelerometer works well at low vibration frequencies down to 0 Hz. Since semiconductor materials are used as the bridge elements, the device is ambient-temperature-sensitive and must be purchased with a small external temperature-compensation module.
- Since this device is configured as a Wheatstone bridge, a single external DC voltage source is needed to power the bridge, usually a small stable battery. The bridge output voltage is measured “differentially” between two bridge arms using a differential voltage amplifier; *not* a charge amplifier as was used with HAV piezoelectric devices.

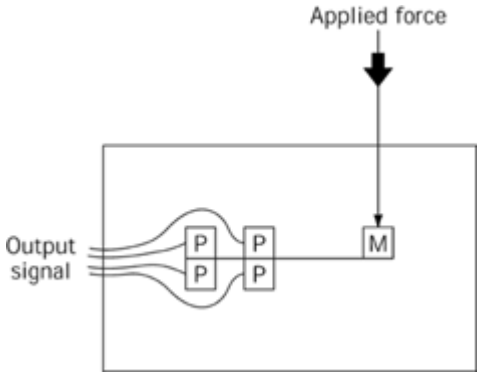

Figure 105.5. Operating principle and construction of piezoresistive accelerometers used for whole-body vibration measurements (adapted from Ref. 2).

3.3.2 WBV Mounting and Positioning The WBV measuring system usually consists of three piezoresistive accelerometers, each mounted mutually perpendicular (triaxially) to a metal cube. This cube and triaxial accelerometers are placed in the hollow center of a hard-rubber pie-plate-type disk (see Fig. 105.6). This instrumentated disk, in turn, can be used in many ways; frequently it is placed on a driver's seat cushion top with the driver actually sitting on the disk. The vibration so measured is the triaxial acceleration entering the lower spine. When a second instrumentated triaxial disk is mounted under the driver's seat, vibration transmissibility can be determined and the effectiveness of the seat as a vibration damper can be determined. If a worker is standing in a WBV situation, then the instrumentated disk can be appropriately placed near the feet. The axes orientation of the triaxial accelerometers and the disk is as shown in Figure 105.2.

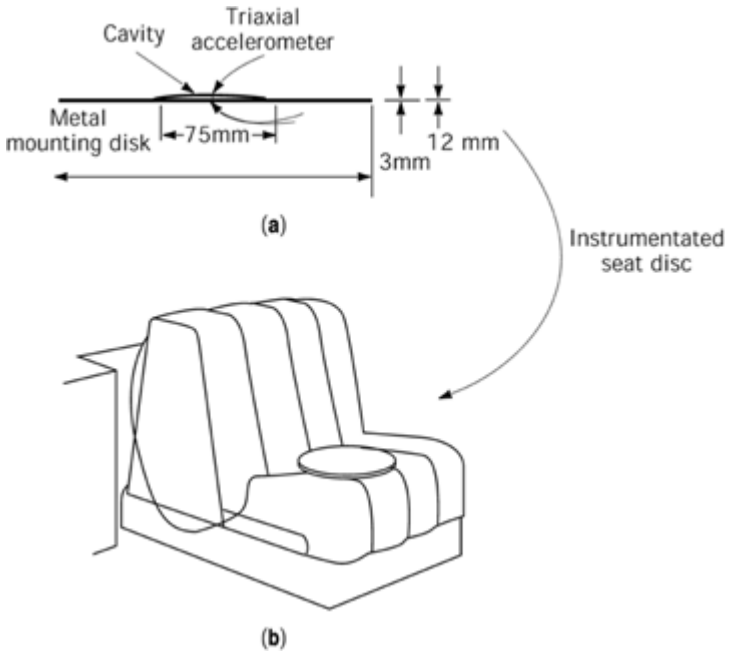

Figure 105.6. (**a**) Instrumentated triaxial accelerometer hard-rubber seat disk used for (**b**) whole-body vibration measurements (adapted from Ref. 2).

3.3.3 WBV Data Analysis WBV measurements first require triaxial calibrations to be performed and recorded; triaxial measurements are next all simultaneously recorded on separate data tracks using a DAT recorder for later Fourier spectrum analysis. The actual WBV measurement time depends to a great extent on the WBV task cycle time involved, since driving buses, trucks, trains, and other vehicles can easily extend from several minutes to hours. Measurements of as many complete work

cycles as feasible is desired. WBV data reduction analysis can therefore be a large task and must include calculations of *different* weighting functions for each vibration axis, as compared to HAV data analysis, which uses the *same* weighting function for each of the three measurement axes. Once data analysis is completed, the results need to be compared to the appropriate WBV standards.

3.4 Whole-Body Vibration Standards and Guides used in the United States

Currently there are two WBV standards/guides used in the United States for occupational safety and health:

- American National Standards Institute (ANSI) WBV standard (46), S3.18, first issued in 1979
- American Conference of Governmental Industrial Hygienists (ACGIH) standard for WBV (47), first issued in 1996

Note: At this writing neither OSHA nor NIOSH have issued any WBV standard. These ANSI and ACGIH documents are both "consensus standard." Salient parts of both the ANSI and ACGIH standards have been derived from international WBV standard (48), ISO 2631, which was first issued in 1972. Major changes to ISO 2631 were adopted in 1998 and are not reflected in either of the WBV standards listed above. There is a special ANSI standard for WBV exposure in buildings (49), ANSI S3.29, which in great part was derived from both ISO 2631 and ANSI S3.18. Also, The European Community (EC) has issued exposure limits for WBV and HAV (19); the former will be briefly discussed, the latter has already been discussed.

3.4.1 WBV Standards and Weighting Functions It is imperative that a complete up-to-date copy of the applicable WBV standard be obtained, read, and understood by the user *before* attempting measurements or data evaluation, since descriptions given herein are for information only and are not exhaustive.)

Figures 105.7Fig. 105.7 and 105.8 show the graphical versions of the two different WBV weighting functions shared by used in both the ANSI and ACGIH standards. Figure 105.7 is used only for the "vertical, or *z*-axis" vibration. Figure 105.8 is used twice: once for the "side-to-side or *y*-axis" vibration, then separately again for the "front-to-back or *x*-axis" vibration. In particular, the shape of the weighting functions shown in Figures 105.7 and 105.8 are each defined by their respective families of parallel WBV exposure-time-dependent curves ranging from 1 min per day up to 2 h/day exposures. In, for the vertical *z*-axis, the U-shaped family of curves acknowledge that WBV vertical resonance occurs at 4–8 Hz and that permitted time-dependent daily exposures are minimized at resonance more than at other non resonant frequencies. The same is true for Figure 105.8, where resonance occurs at 1–2 Hz for either the *x* or *y* axes. Beware that these "elbow"-shaped family of curves are based on WBV resonance data in the *x* and *y* axes; these curves should *not* be confused with similar shaped HAV weighting curves (Fig. 105.4) described previously. Refer to both Figures 105.7 and 105.8 and note that the graph's abscissa show a frequency range of 1–80 Hz divided into $\frac{1}{3}$-octave bands to accommodate the large number of vehicles, trains, buses, aircraft, and so on that can be tested using these standards. Similarly, the graph's ordinate extends in rms acceleration intensity to 20 m/s^2 or about 2*g*. Although ANSI S3.18 and the ACGIH WBV standard both use the same graphical evaluation criteria, each uses the criteria differently.

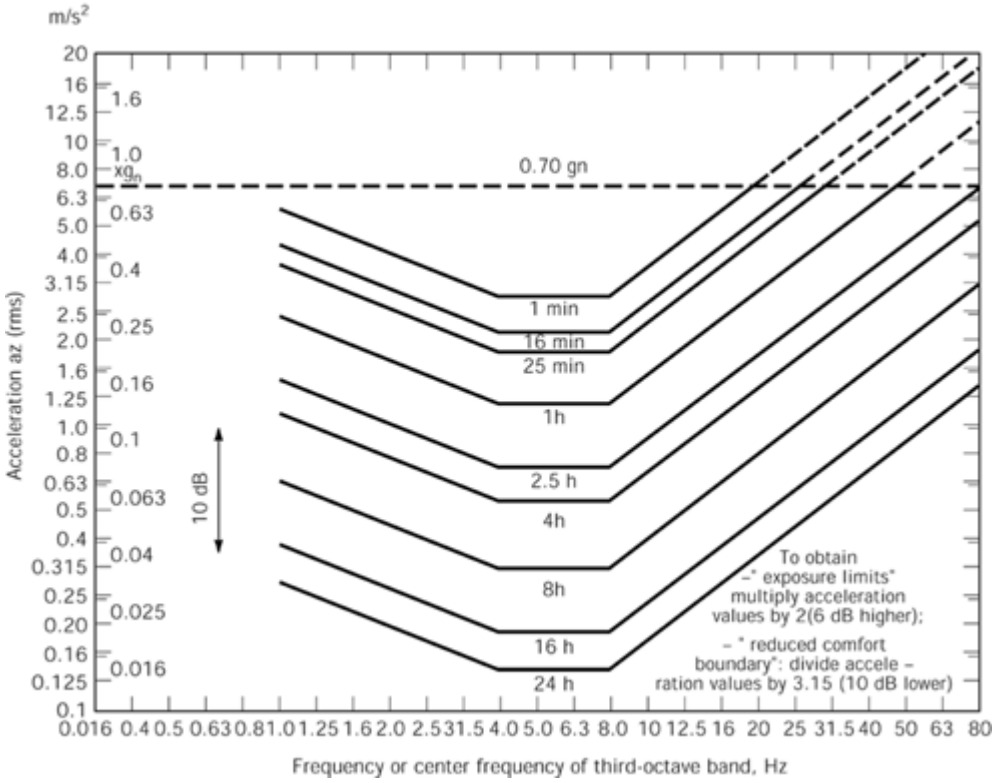

Figure 105.7. Whole-body vibration weighted *z* (vertical axis) daily exposure curves used by the ANSI S3.18 standard.

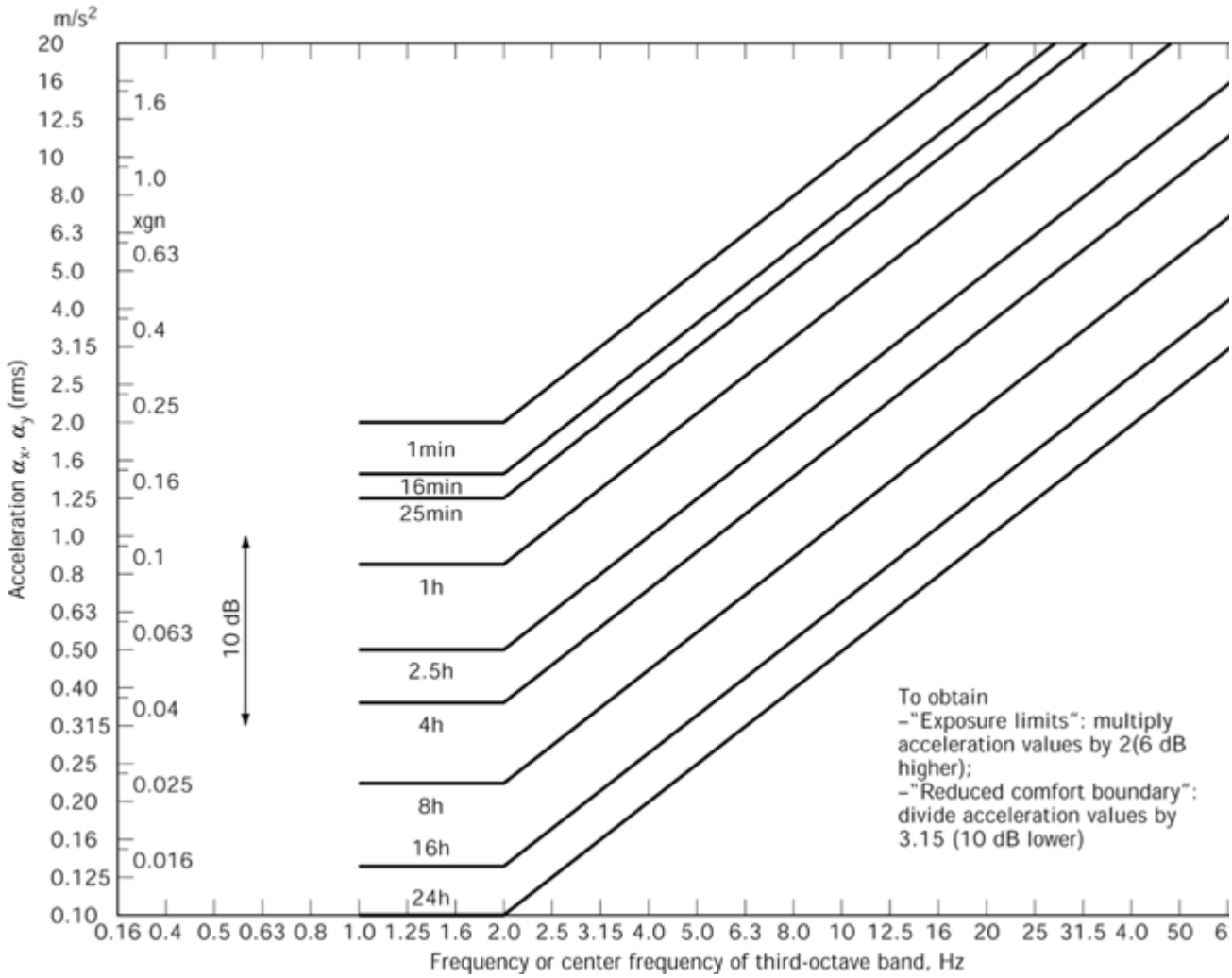

Figure 105.8. Whole-body vibration weighted *x* and *y* (transverse axes) daily exposure curves used in the ANSI S3.18 standard.

As adopted and used *only* in ANSI S3.18, in Figures 105.7 and 105.8 there are three distinct acceleration intensity criteria which can be evaluated depending on the study needs: fatigue-decreased proficiency (FDP); reduced comfort (RC), and exposure limits (EL). FDP curves are essentially concerned with performance effects of WBV. The RC curves are concerned with comfort. The EL curves are concerned with health effects of WBV. First, the FDP curves are directly shown in Figures 105.7 and 105.8. To determine the RC exposure boundaries, divide the FDP acceleration values by 3.15 (10 dB lower). The EL limits are obtained by multiplying the FDP acceleration by 2 (6 dB higher). In using this standard, it is important to inform you the reader that since the FDP, RC, and EL curves were developed in the early 1970s, experience has shown that the EL family of curves as used in ANSI S3.18 (and ISO 2631, before 1998) have been shown to be too permissive and *not* sufficiently worker-health-protective and thus the EL curves use is *not* advised by this author and others (2, 20). However, both the FDP and RC families of curves have been found effective and are recommended.

The *ACGIH standard* disregards all reference to the EL criteria, in all axes, and uses only the depicted FDP criteria shown in Figures 105.7 and 105.8 for both health and safety, without so naming these curves as FDP. Although useful, the RC curves are also unused in the ACGIH standard since it only addresses occupational health and safety issues and not comfort criteria.

3.4.2 Computer Analysis of WBV Data In practice, for each measurement axis, WBV triaxial data are simultaneosly collected and separately stored on a DAT recorder; a Fourier computer is then

used to analyze each data axis separately and automatically:

1. Calculates unweighted vibration spectra. For WBV, the spectral plots should first be determined by and subdivided into portions of the observed work cycle. Then all such spectral plots (for the same axis) are averaged into a single overall spectrum representing the entire work cycle in that axis. This process repeated separately for all three (*x,y,z*) axes. Using this method allows one to not only observe the overall spectrum over the entire work cycle by axis, but also to compare spectral plots by axis, over parts of the work cycle and thus determining the relative acceleration intensity in each part of the work cycle.
2. The computer next compares and "overlays" each spectrum across the appropriate (FDP) weighting graph; Figure 105.7 is used only for the vertical *z* axis; Figure 105.8 is used separately twice, once for the *x* axis and again for the *y* axis.
3. The computer numerically calculates the "overall weighted acceleration intensity" for each spectral plot.
4. The interpretation of the "weighted" results are based mainly on the given WBV standard used as described in the following paragraph.

ANSI S3.18 and ACGIH standards both use the same FDP graphical evaluation criteria shown in Figures 105.7 and 105.8 such that when no peak in the spectra either touches or pierces through any daily exposure curve in any family of weighted curves, that axis acceleration has passed the standard. Should one or more spectral peaks touch and/or pierce any of the exposure curves at any place(s) on these curves, the standard has been exceeded for that axis. The higher the peak(s) touching or piercing these curves, the higher the acceleration intensity and thus the shorter the allowable daily exposure time the worker can be exposed to WBV. Each of the three axes spectra is processed as described using the appropriate weighting functions given in Figures 105.7 and 105.8. Usually the axis with the highest (acceleration intensity) peak(s) "dominates" over the remaining two axes. This dominant axis then determines the maximum permissible daily WBV exposure a worker can be subjected to when using the tested WBV product.

Finally, it is important to know the validity for the above mentioned WBV standards as a function of the data collected in the time domain and as analyzed in the frequency domain for each vibration axis. This question is best answered by first recalling the term "crest factor," which is equal to the ratio of peak acceleration divided by rms acceleration, obtained over a one-minute period of WBV exposure time-domain data. By definition crest factor is a dimensionless number. The data collected and analyzed using the above WBV standards are valid for crest factors less or equal to the number 6. Crest factors exceeding the number 6 in the collected (time-domain) data, will result in an *underestimation* of the true results of the analyzed weighted WBV data. The higher the crest factor above 6, the less accurate the predictive are the standards presented above.

The *European Community's* WBV evaluation (19) is weighted numerically as a "modified vector sum" per the following equation:

$$a_{sum} = \sqrt{(1.4\,a_x)^2 + (1.4\,a_y)^2 + a_z^2} \qquad (5)$$

Equation (5) requires that first the numerical values for each axis' total weighted rms acceleration intensity value be determined. Next, only the *x* and *y* values are each multiplied by a constant value of 1.4, which represents the ratio of the values of the longitudinal and transverse curves of equal response in the most sensitive human response regions. The *z* axis has no multiplier. Next each of these axis values is squared and summed. Finally, the square root of this resultant value is obtained. This result is the "overall weighted total rms acceleration" and is compared to the EC 8-h "action level" of 0.5 m/s^2. In meeting this EC standard there are certain EC obligations and rules that must be followed should a product exceed the 0.5 m/s^2, 8-h WBV action level and be allowed to be used

in an EC country.

3.5 Control of WBV in the Workplace

Definitions of both vibration damping and isolation have been given previously. WBV control measures used in the workplace (2, 20, 21, 50) usually consist of protectively isolating the vibration source from the worker. For example, in common use are “air ride” isolated seats in many buses, trucks, heavy-equipment farm, and similar vehicles. These seats require a source of compressed air and operate effeciently to reduce 4–8 Hz WBV resonance vibration attempting to reach the spine. Air-ride seats with lumbar support, arm rests, and adjustable seat backs are highly recommended. In addition, many truck cabs use isolators and are suspended in addition to their use of air-ride seats. A properly tuned vehicle suspension and proper tire pressures will help reduce WBV.

Within plants, machines can be isolated from the floor and their vibration reduced; remote controls of machinery and processes using small videocameras can also be used to protect workers from WBV exposure. Using baloon tires in place of solid tires on forklift trucks can also help reduce WBV exposure. Contact the manufacturer first before doing so.

Finally, pregnant female operators should be especially careful to minimize WBV exposure (39, 51) and for all workers it is advisable to avoid lifting and bending immediately following WBV exposure (52, 53).

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4 Crossover and Combined Exposure to Hand–Arm and Whole-Body Vibration

As initially stated in this chapter, in most cases HAV exposure and WBV exposure are distinct and produce differing health consequences and require different control measures, but there are a few exceptions, such as using jackhammer-type tools, stand grinders, buffers, motorcycles, and water-powered skis.

It is important to appreciate that mechanical vibration must come into physical contact with the human body in order to produce the effects previously described in this chapter. Many times it is the *pathway into the body* that determines to a great extent the resulting health and safety effects workers experience from this stressor. When, for example, an operator uses a road ripper or jackhammer tool with arms extended away from the upper torso, one can expect potential HAVS; however, when the operator operates this same tool with the tool pressed against the abdomen and with arms close to the torso, nontraditionally vibration-induced medical problems can occur, such as a highly inflamed omentum (the veil-like sheath that covers the intestines) (54, 55). In a similar example using another powered tool, a male maintenance worker routinely operated a large vibrating floor-polishing-buffer machine “by holding it firmly against his lower abdomen. Ordinarily, hours of mechanical shaking of his abdomen caused no discomfort; however, on the night of his admission to the hospital, he had acute severe pain,” which was promptly diagnosed as a ruptured sigmoid colon and required surgery for correction (56). In both of these instances is the operators attempted to damp the power tool vibration using their abdomens and thus substituted HAV exposure for WBV exposure, causing *pathway changing* in the major vibration from entering the body via the hands to entering the body via the lower abdomen. The results were nontraditionally vibration-induced medical conditions because of the exposure “crossover” from HAV to WBV. Recall that these were normally hand-operated power tools. Another example, where many workers use floor-mounted “stand grinders” to remove outer metal flash from small castings (4, 5), one might expect WBV-related medical problems to develop because of the close whole-body coupling of this large machine to the worker's torso. Not so; instead, many of these workers routinely develop HAVS because the floor acts as a large reaction mass and damps the WBV but not HAV in contact with the hands. The vibration *pathway* into the worker's body is via the hands, which must firmly hold and press small castings

against the large grinder wheel to remove the excess metal flash.

Finally, a great pastime of many is to operate motor cycles, dirt bikes, water-powered skis, and similar, all of which represent significant exposures to *both* HAV and WBV (57).

In conclusion, observing the pathway vibration impinges on and then enters the human body is one key element to determining the potential destructive track vibration can leave in its wake, especially at resonance frequencies, which is the Achilles heal of human vulnerability to this insidious stressor.

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5 Summary
The salient aspects of recognition, measurement, evaluation, and control of both occupational hand–arm vibration and whole-body vibration have been presented. The physics of vibration is also given as the basis for and the interpretation of workplace vibration measurements, which are also described. Descriptions, interaction, and interpretation of the major occupational HAV and WBV standards and guides currently used in North America are presented. Comprehensive vibration control measures used to minimize worker exposure to both hand–arm and whole-body vibration are also discussed.

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Abnormal Pressures: Hyperbaric and Hypobaric
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1 The Universal Nature of Pressure

1.1 The Pressure Continuum—From Deep Sea to Space

This chapter deals with the interrelated physiological effects of the continuum of altered ambient pressure. These pressures may be both higher and lower than the sea level pressure to which we are accustomed and in which we have evolved.

The chapter first discusses what pressure is, and where and why alternative pressures are encountered by humans. It reviews the occupational, medical, and recreational incentives for forays into both environments, high and low. It points out the role of time in evaluating pressure exposures and the importance of transitions to and from higher and lower pressures. Then, it covers first the effects of elevated pressures, then the effects of lack of pressure, emphasizing the importance of breathing gases in most alternative pressures. Last, it pays particular attention to the main pressure-related disorder, decompression sickness, and its treatment.

This is a book on industrial hygiene and toxicology, so the chapter deals primarily with healthy individuals fit for the workplace, but does mention the special concerns about pressure needed for people who have various diseases.

1.2 Where Is Pressure Found, and What Is It All About

A physics book defines pressure as force per unit area. The important thing for our purposes here is how pressure is exerted on the human body. Normally this is as gas pressure, such as that of the atmosphere. Pressure may also be exerted by a column of liquid, such as the water pressure encountered in diving. Pressure, as a force, is due to the weight of the atmosphere above or of a column of liquid, or more usually, a combination of both. Gas pressure is due to the kinetic energy of the molecules of gas; increasing pressure is due to an increasing number of molecular collisions. The pressure of a column of gas or liquid is exerted in all directions.

Humans encounter elevated pressure when they are under water or in chambers used to simulated water pressure. Pressure chambers are also used in medicine and in various industrial situations. Low pressures are encountered on ascent to altitude. This may be by ascending mountains, in aviation or space activities, or in chambers used for simulating altitude or for other purposes.

High pressure is given before low, because the concept of pressure as such is more cogent in that direction. The chapter initially tells where these pressure environments are encountered, then later shows the effects.

1.2.1 Pressure: Atmospheric, Absolute, and Differential

Although pressure may vary substantially due to location and weather conditions, the average or typical barometric pressure (P_B) at sea level is considered “atmospheric pressure” or a pressure of 1 atmosphere. This is the weight of the atmospheric air above mean sea level; it is called the standard atmosphere. A universally recognized value is defined for atmospheric pressure, and it is expressed in various units. Many pressures such as those in pressure vessels (“gauge pressure”) or those due to water pressure in the sea (“depth”) may be referenced to atmospheric pressure. The barometric pressure at depth is a gauge pressure (pressure in excess of sea level pressure, the total of sea level atmospheric pressure plus the water pressure).

Abnormal Pressures: Hyperbaric and Hypobaric
R. W. (Bill) Hamilton Ph.D., R. D. Heimbach, MD, Ph.D., A. A. Bove, MD, Ph.D.

2 Effects of Pressure
2.1 Effects of Pressure Changes on Body Cavities That Contain Gas
This section discusses the effects of high pressures and of low pressures. It deals with a set of problems common to both environments, that of gas-filled spaces in the body. Because this is almost always the first thing to come to our attention when the ambient pressure changes, this section is first among the effects.

2.1.1 Expansion and Compression of Gas Spaces The body contains a number of gas-filled cavities that communicate in various degrees with the outside of the body. During changes in the ambient pressure, these spaces must equilibrate, or the individual will suffer adverse effects. The lungs, paranasal sinuses, and middle ears are semiclosed spaces, and the interior of the gut, as well as occasional spaces in teeth, are functionally closed (49). When pressure is reduced as a diver or aviator ascends, the volume of gas increases, and when pressure is increased or during descent, the reverse takes place. This is an effect of Boyle's law. Divers call an imbalance of pressure during descent a “squeeze.” Because these spaces are semiclosed and communicate with the ambient environment at various rates, the rate of change of pressure has a big impact on whether it causes problems.

2.1.1.1 Ears and Sinuses The middle-ear space is separated from the canal of the outer ear by the ear drum or tympanic membrane. The middle ears communicate with the nasopharynx by small tubes, the Eustachian tubes. The middle-ear portion of the Eustachian tube is lined with soft tissue so that the tube is not normally open. The outer pharyngeal end tends to form a one-way valve that allows gas to escape from the middle-ear when pressure is raised there, but prevents it from easily entering from the nasopharynx when pressure is lower in the middle ear (Figure 106.3).

Abnormal Pressures: Hyperbaric and Hypobaric

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Biological Rhythms, Shiftwork, and Occupational Health
Allene J. Scott MD, MPH,, Joseph LaDou, MD

A. Introduction

" ... and God divided the light from the darkness, and God called the light *day*, and the darkness He called *night*. And the evening and the morning were the first day" (Genesis 1:4–5, King James Version). Thus, as has been recognized for millennia, *Homo sapiens*, as well as all other living creatures on earth, are destined to live in a regular cycle of light and darkness, that is, the 24-h solar day. For diurnal species, such as human beings, the sunlight portion of the day is the time of activity and the dark, nighttime portion the time for sleeping. Periodicity is an integral part of life.

Although we are under the influence of environmental rhythms, such as the daylight–night cycle, we are also under the physiological influence of our own internal biological clock. Normally the synchronization of our biological rhythms with each other and with environmental rhythms (external time cues) maximizes our waking and sleeping performance and promotes overall well-being. Night work is opposed to the innate drive to sleep at night and work during the daytime. This unnatural mismatch of environmental and internal temporal influences is of concern for shiftworkers due to the often disruptive effect of schedule-related time shifts on the normal synchronization of individual biological rhythms with each other as well as with the external time cues.

This chapter reviews basic chronobiological principles as they relate to shiftworker safety and health. Studies dealing with the effects of time shifts on sleep and alertness are discussed as well as performance rhythms. Research exploring the consequences of shiftwork on physical and mental health is reviewed. Countermeasures for minimizing adverse health and safety effects of sleep deprivation and biological rhythm disruption are presented, including work scheduling considerations and medical surveillance. Industrial hygiene considerations related to control of worker exposure to potential toxins during extended and rotating shifts are presented. Finally, international and U.S. regulatory policy regarding shiftwork scheduling and special provisions for shiftworkers are reviewed.

Biological Rhythms, Shiftwork, and Occupational Health
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1.0 Circadian Rhythms
1.0.1 Definitions
There is considerable terminology peculiar to the study of biological rhythms. The necessity of developing a consistent definition of terms for researchers in this field was recognized in the 1970s, leading to the publication of the *Glossary of Chronobiology* in 1977 (1). The most commonly used terms are briefly defined here to assist the reader unfamiliar with the field. Readers who plan to review the primary chronobiology literature may benefit from first studying the referenced glossary, which contains extensive examples and in depth discussion of the terms.

Biorhythm, in the true scientific meaning of the term, refers to a repeating pattern of a quantifiable biological parameter, which persists as a fundamental property of a living cell or organism under varied conditions of constancy in environmental factors. The term should be reserved for cyclical biological phenomenon meeting testable criteria. However, the term biorhythm has been misused by nonscientific interests promoting the somewhat mystical "biorhythm theory" of forecasting times of optimal physical and cognitive functioning. The science of chronobiology does not support the biorhythm theory, and discussions of biological rhythms in this chapter have no relevance to that nonscientific school of thought (2). Due to the frequent misuse of the term biorhythm by proponents of the biorhythm theory, which became a fad in the 1970s, the term *biological rhythm* is used in this chapter, and in general in the chronobiological literature.

Chronobiology is that discipline which studies biological rhythms. It is the science of objectively studying and quantifying mechanisms of biologic time structure. Subspecialities of chronobiology include chronophysiology, chronopathology, and chronopharmacology, which includes chronotoxicology and chronotherapy.

Circadian rhythm: The primary category of biological rhythms of interest for shiftworkers and frequent transmeridian jet travelers are circadian rhythms. The term *circadian* (Latin: *circa*, about; *dies*, a day) was first used by Halberg and associates (3) to denote a periodicity of *about* 24h, specifically 20–28h. Thus a circadian rhythm is a biological rhythm with a frequency of 1 cycle in 24±4h. (Rhythms with periods less than 20h are referred to as *ultradian* and periods greater than 28 as *infradian*).

Desynchronization refers to the condition when two or more rhythms, which had previously been synchronized (having the same frequency) with each other, have different frequencies and no longer have the same phase relationship. When desynchronization has occurred between a biological rhythm and an environmental cycle, the term *external desynchronization* applies. *Internal desynchronization* occurs when two or more biological rhythms within the same organism become desynchronized from each other. *Forced desynchronization* of biological rhythms refers to a research

condition in which subjects are isolated from normal 24-h time information, and abnormally long or short days are artificially imposed by scheduling the sleep–wake cycle to a period length outside the bounds of the circadian entrainment of the temperature rhythm.

Diurnal refers to events or activity occurring during the daylight portion of the 24-h day. The opposite of diurnal is nocturnal, meaning the period of activity occurs between sunset and sunrise. Human beings are diurnal creatures with their natural awake, activity hours occurring primarily between sunrise and sunset.

Entrainment refers to the coupling of an endogenous biological rhythm with a synchronizing trigger such that they share the same frequency. Biological rhythms can be entrained with an external cycle, such as the 24-h day (external entrainment) in response to an environmental time cue. Entrainment with other biological rhythms (internal entrainment) is effected by response to an internal pacemaker.

Free-running refers to rhythms that are self-sustaining biological rhythms, desynchronized from the environmental time schedule, but continuing to exhibit a regular cycle that has a systematic, changing phase relationship to the external time period.

Nychthermal refers to occurring under the normal conditions of daytime activity and sleep during the night. Chronobiological observations made under nychthermal conditions, such as the timing of the peak and trough of a biological rhythm and the rhythm amplitude, cannot be assumed to be the same when the activity and sleep times are inverted.

Phase relation refers to the time relation between two rhythms.

Zeitgeber (German: *Zeit*, time; *Geber*, giver) refers to an external synchronizing trigger or time cue capable of entraining a biological rhythm. A zeitgeber is thus an entraining agent.

1.0.2 Overview of Biological Rhythms

The most obvious environmental periodicity is day and night. Although the earth's rotation on its axis takes 23h, 56min, and 4s (the sideral day), the solar day, which is the time interval between noon of successive days, takes about 24h and 4min. Since the earth's orbit is slightly elliptical, the time of the solar day varies, but not by more than 16min from its mean of 24h 3'57". Thus 24h is an approximation of the day–night cycle, but a reasonable one when studying its effects on living organisms (4).

Numerous psychological and physiological variables have been found to have a demonstrable 24-h rhythm, such as body temperature, the sleep–wake cycle, cardiovascular parameters, alertness and cognitive performance, endocrine and metabolic factors, therapeutic responsiveness to certain medications as well as sensitivity to toxic agents, and psychological variables of mood and anxiety. It should be noted that often there is not a simple two-state description of a parameter's rhythm with a maximum level and a minimum, but instead there is a continuous variation during the 24-h period, with a “peak” and “trough” usually coinciding with the natural light and darkness cycle (5). Some variables have rhythms that, when recorded with frequent measurements, are seen not to be smooth curves. For example, plasma cortisol normally has an episodic pattern with periods of large amounts of secretion.

Quantitative data for a physiological parameter can be most simply plotted on the vertical axis in reference to a horizontal time axis. Such a plot is properly referred to as a chronogram. However, in analyzing rhythms to demonstrate a 24-h pattern and to allow for quantitative descriptions, the wave form of the rhythm is often submitted to cosinor analysis to determine the best fitting cosine curve. In so doing, deviations in the data with respect to the curve are minimized in a fashion similar to linear regression analysis (6, 7). Descriptive terms may then be used to describe a rhythm presented by cosinor-analyzed data, including: the *acrophase* or crest of the curve; the *mesor* or overall 24-h mean value; the *amplitude*, which is the extent of variation between the trough and peak; and the

period of the oscillation (7–9). An example of a chronogram and cosinor analysis of the same data is presented in Figure 107.1.

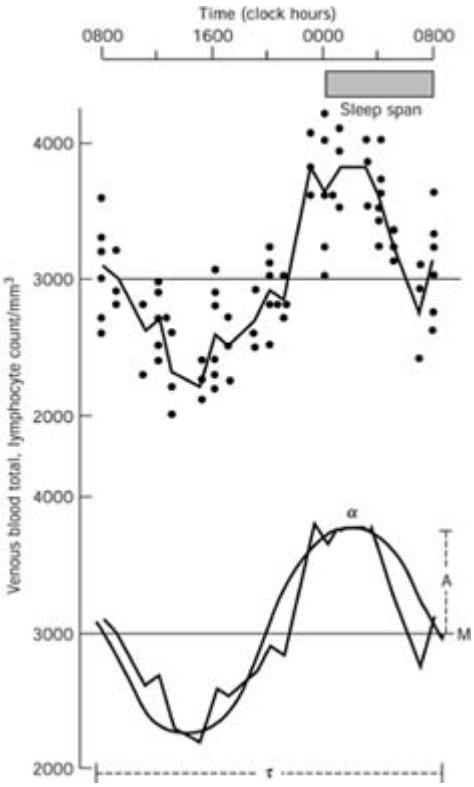

Figure 107.1. The circadian rhythm of the total lymphocyte count of venous blood is shown from samples from 12 subjects who were synchronized with respect to diurnal activity. The bottom panel is the best-fitting cosine curve approximating the raw data, by single cosinor analysis. Adapted with permission from Ref. 9a.

1.0.3 Endogenous Rhythms and the Biological Clock
The simple observation of a 24-h rhythm occurring under normal nychthermal conditions does not provide evidence for an endogenous biological rhythm. A rhythm such as this could be just a direct manifestation of an external 24-h influence. If biological rhythms merely reflected responses to external time cues, they would be of little consequence for the shiftworker. However, it has been well documented that most of the 24-h biological rhythms have an endogenous component. It is the desynchronization of endogenous biological rhythms with the external time cues and the associated disruption of the circadian system that are of great concern, when looking at the effects of work schedule-related time shifts on the workers.

1.0.3.1 Plant and Animal Studies One of the earliest demonstrated endogenous rhythms was that of the daily rhythm of a plant's leaf movements by de Mairan in 1729 (10). The opening and closing of the leaves, observed during daylight and darkness, respectively, had been assumed to represent a direct effect of sunlight and its absence during night hours. De Mairan, however, demonstrated that the rhythm of the opening and closing of the leaves continued when the plant was kept in total darkness for 24h. This finding indicated that the rhythm was not simply a response to the rhythmic presence and absence of sunlight.

Over two centuries later, Richter (11) did an elegant series of studies on over 900 rats which clearly demonstrated the existence of a “biological clock” in rodents. After characterizing the activity–rest cycles of the animals under conditions of 12-h periods of light and darkness, the rats were blinded. Almost immediately after blinding, the beginning and ending of the activity period began later each day, on a regular schedule. For example, in one of the rats, the activity period began 20min later each day, with the rhythm persisting for 7mo with great accuracy. The same phenomenon was observed in

60 other rats, with the same degree of regularity. However, the rhythm of an individual rat was not identical to the others. Some of the rats showed delays (up to 28min), and some advanced the period (up to 41min). Thus an independent "clock" was demonstrated, and because the different rats did not have exactly the same periodicities, a cosmic influence could not have been operating to produce the rhythm. The "clock" was also demonstrated to be inborn, by studying newborn rats blinded before their eyes had begun to function. Biological rhythms similar to those for rats blinded as adults were documented.

1.0.3.2 Human Studies The existence of a biological clock in humans was first demonstrated in temporal isolation studies in an underground cellar beneath a hospital in Munich (12). Three men and three women were isolated from all environmental and social time cues for 8–19d. All the subjects maintained a regular activity–rest cycle, free-running with a period slightly longer than 24h. The subjects consistently went to bed about an hour later each day and awoke an hour later than the previous day. This precise, regular delay in bedtime and spontaneous awakening has been demonstrated in numerous, subsequent temporal isolation studies, suggesting that the biological clock runs slow with respect to the 24-h solar day. For example, Wever (13, 14) compiled data from 156 subjects studied in temporal isolation which consistently demonstrated a slow biological clock with free-running periods of 25±0.5h for the body temperature and the sleep–wake cycle.

In order to determine if the sleep–wake cycle was maintaining the observed 24-h biological rhythms of physiological parameters, sleep deprivation studies were conducted (15, 16). In these studies, subjects were sleep deprived for 72h in temporal isolation (i.e., without 24-h cues). Again, persistent circadian rhythms were documented for several variables. Examination of the alertness rhythm revealed that subjects were found to be more alert after 58h of sleep deprivation than after 40h, providing further evidence for endogenous biological rhythms. These and several other classic studies demonstrating the endogenous nature of circadian rhythms in humans are summarized in Table 107.1.

Table 107.1. Studies Demonstrating Endogenous Circadian Rhythms in Humans

Type of Study	Findings	Reference
Temporal isolation, 3 male and 3 female subjects	All subjects maintained free-running rest/activity cycle	12
N=29, 72h sleep deprivation in temporal isolation; subjects aware of 3-h intervals between urine collections	Persistent diurnal rhythm in several parameters, e.g., fatigue, urinary adrenalin	15
Several temporal isolation studies (*N*=156)	Free-running period of 25.00±0.5h for temperature and sleep–wake cycle	13, 14
Temporal isolation, 72h sleep deprivation; 16 female subjects unaware of timing of collection intervals	Circadian rhythms in temperature, alertness, performance variables	16
Temporal isolation, polygraphic sleep recordings, blood cortisol and growth hormone sampled every 20 minutes,	During free-running conditions, timing and duration of sleep occurred at specific phase of temperature rhythm; 2 components of cortisol curve relative to phase of temperature curve; growth	145

continuous temperature readings, N=10	hormone related to first 2 hrs of sleep onset	
23 year old male subject, 2 weeks temporal isolation, choosing own sleep and meal times	Circadian rhythm of sleep/wake cycle free-ran at 24.7hrs	145a
Reviewed results of previous studies on same individuals at 1 to 5yr intervals	Rhythm patterns could be used as individual markers; Intra individual differences smaller than interindividual	14a
Temporal isolation, subjects' estimation of 1-hr time intervals recorded, N=14	Bimodal circadian rhythms	12a

Very recent studies continue to confirm the existence of the biological clock, but have presented evidence that the average length of the intrinsic circadian period may be closer to 24h than to 25h (17–19). In the recent widely publicized study by Czeisler et al. (19) the average intrinsic period of the temperature rhythm was determined to be 24.18±0.04h. In this study 24 subjects were placed into 20- and 28-h forced-desynchrony protocols (see Section 1.1.5) lasting 3½wk. The study protocols were carried out in conjunction with maintaining constant low light levels (15 lux, which is much lower than ordinary room lighting) during the scheduled wake time. In addition, sleeping was allowed only during the scheduled sleep time. Core body temperature was measured continuously, and plasma melatonin and cortisol were frequently sampled during the protocol. Several subjects were, in addition, tested during a standard temporal isolation, free-running protocol. During the free-running protocol these subjects, who had been shown to have temperature rhythms with periods just slightly longer than 24h under the forced-desynchrony protocol, had temperature rhythms with periods averaging slightly longer than 25h. The results of this study are consistent with several animal studies demonstrating a circadian pacemaker running very close to 24h with little intersubject variability (20–22).

Czeisler and his associates19 have suggested that the longer and more variable pacemaker period reported in the earlier classical free-running protocols reflected the subjects preferentially choosing exposure to room light prior to the circadian temperature nadir and to darkness following the minimum temperature. They have hypothesized that this behavior elicits light-induced phase delays and an overestimation of the circadian period. On the other hand, the Czeisler et al. (19) strict, forced-desynchrony protocol has been criticized as being too artificial, and may therefore somewhat underestimate the length of the intrinsic period.

1.0.3.3 Neuroanatomical Studies The first evidence of a neuroanatomic site of an endogenous pacemaker was uncovered by Richter (11) in a series of experiments conducted on over 900 rats. After demonstrating the existence of a biological clock by the persistence of a regular free-running endogenous activity rhythm after blinding the rats, the effect of the removal of various glands including the gonads, pancreas, adrenals, pituitary, thyroid, and pineal was determined. The circadian pacemaker was not disrupted by the removal of any of these tissues. Neither was it disturbed by a variety of insults including electric shock, anaesthesia, alcohol, or induced convulsions. However, lesions of the hypothalamus, specifically the ventral hypothalamus, did lead to a loss of circadian organization of activity, feeding, and drinking.

Later, as reviewed by Moore-Ede et al. (23) the suprachiasmatic nuclei (SCN) was identified as the specific pacemaker cite in the hypothalamus. This was accomplished by tracing tritiated amino acids injected into the vitreous humor of the eyes, reaching retinal ganglion cells, and subsequently

reaching the suprachiasmatic nuclei (24). Recently neural transplantation of the SCN in rodents has also demonstrated the pacemaker role of this group of neural cells. SCN grafts from mutant hamsters exhibiting an abnormally short circadian timing system were transplanted into normal hamsters that had undergone SCN ablation. The graft recipients had circadian rhythmicity restored, but with a period matching the mutant donors' (25). Additional evidence for the pacemaker function of the SCN are laboratory studies of rats, which have demonstrated circadian rhythms in electrical discharges from isolated SCN tissue *in vitro* (26, 27).

The complexity of the pacemaker role of the SCN precludes a complete discussion of the large amount of recent research addressing this topic. An entire journal supplement has very recently been devoted to a review of the nature of the SCN and its critical role in the maintaining of the circadian system (28). This supplement addresses entrainment mechanisms, including not only the principal photic mechanisms, but also the more recent research exploring nonphotic entrainment mechanisms. The multioscillator organization of the SCN is also scrutinized, as well as findings dealing with the communication pathways between the SCN and the circadian effector systems.

1.0.3.4 Molecular Genetic Studies The requirement for protein synthesis for circadian timing systems to function implies that gene expression directing circadian protein transcription/translation underlies the molecular control of the circadian system. It has been demonstrated that the existence of circadian rhythms in the fruit fly (*Drosophila melanogaster*) requires the interaction of certain proteins, involving gene transcription feedback loops. In *Drosophila*, several clock genes, including the *dbt* (double-time) gene, have been found to regulate molecular cycles underlying circadian rhythms. The *dbt* gene has been identified as the regulator of synthesis of two “clock” proteins (PER and TIM). In addition, two other clock proteins, CLOCK and BMAL1, have been demonstrated to interact with PER and TIM, producing periodicity in the fly and in mammals. Specifically, a negative feedback loop has been found with CLOCK and BMAL1, driving expression of PER and TIM until the latter two proteins accumulate sufficiently and inhibit the CLOCK and BMAL1 proteins. Evidence also exists for the conservation of PER gene homologs in the suprachiasmatic nucleus of mammals. Cloning of genes involved in abnormal circadian activity has also identified other clock genes in the fruit fly, including one named *dClock*. Isolation of a mouse mutation that changed the intrinsic period length and the persistence of rhythmicity has recently provided evidence for an analogous mammalian gene, named *Clock*, and its role in controlling the circadian timing system at the molecular level (20, 29–34).

A detailed discussion of research on the molecular basis of circadian regulation is beyond the scope of this chapter. However, the reader is alerted to this topic because research findings in this area will likely have implications for predicting genetic vulnerability to circadian rhythm dysfunction and shiftwork tolerance. In addition, doors are being opened for the development of molecular-level therapeutic interventions. In depth reviews of this area of research have recently been provided by Dunlap (35, 36) Herzog and Block (37), and Edery (38).

1.0.3.5 The Temperature Rhythm The body temperature rhythm is the most studied human rhythm. It is the rhythm most commonly used as the marker of the circadian pacemaker's phase and amplitude. For over a century it has been known to be, under nychthermal conditions, highest near evening and lowest in the early morning hours (39). Under these conditions the relationship of the temperature rhythm to the sleep–wake cycle is very predictable. The temperature peaks during the second half of the wake episode. More specifically, there is a pronounced rise upon awakening with a more gradual rise to the early evening peak. The temperature rhythm trough occurs during the last part of sleep in the early morning around 0500. The amplitude of the temperature rhythm averages 0.5°C (40, 41).

The relationship between the body temperature rhythm and other variables has been extensively studied. Examples of other rhythms that parallel the temperature rhythm with their nadir being during the night include adrenaline, alertness, cortisol, and blood pressure (15, 16, 42, 43). The normal relationship of the temperature rhythms to several other physiological parameters as well as to the sleep–wake cycle is demonstrated in Figure 107.2.

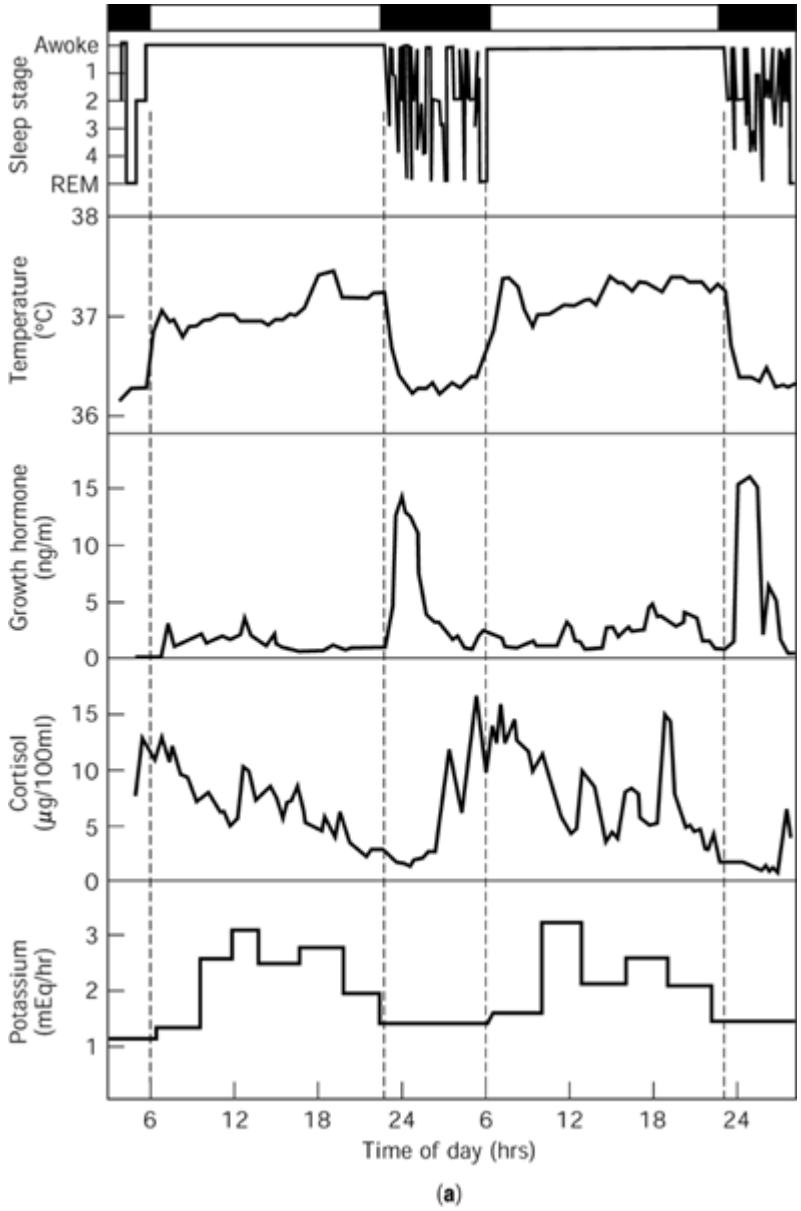

Figure 107.2. The circadian rhythms of five physiological parameters are plotted for a 48-h period. The rhythms for sleep stages, body temperature, plasma concentrations of growth hormone and cortisol, and urinary potassium concentration are shown in relation to each other and to the phase of the sleep–wake cycle. Adapted with permission from Ref. 42.

1.1 Adjustment to Time Shifts

1.1.1 Zeitgebers Although it has been shown that there is an endogenous circadian time-keeper active in humans, the fact that under normal nychthermal conditions the biological rhythms are synchronized with the 24-h day points to the presence of external triggers to which the biological clock is responsive. These time cues, which are capable of entraining the biological rhythms to an external periodicity, have been termed *zeitgebers*. Zeitgebers allow the biological clock to be reset and entrained to the 24-h day (39).

Various agents have been shown to act as zeitgebers including light, natural noises, social factors, awareness of the time of day, and behavioral patterns such as eating schedules, and sleep–wake schedules (44–47). Even electromagnetic fields appear to be able to act as zeitgebers (48).

1.1.2 Light as a Zeitgeber In the 1970s social cues and the sleep–wake schedule were generally considered the most important zeitgebers for humans, and light, a strong synchronizer in other

species, was considered to played a minor role (47, 49, 50). However, as the relationship of the hormone melatonin to sleep and light became recognized (51–53), the question of the importance of sunlight in entraining biological rhythms was again raised. Melatonin was shown to be a strong sleep inducer, and light was shown to affect the activity of the pineal gland where melatonin was known to be produced (53). A circadian rhythm was demonstrated in urinary melatonin excretion (52). Czeisler (54) demonstrated that an absolute light–dark cycle could entrain human circadian rhythms. Moore-Ede and Richardson (55) suggested that earlier experimental conditions did not allow dismissal of the light–dark cycle as an important zeitgeber for humans, because in those previous studies subjects were allowed to use auxiliary lighting such as desk lamps during the "dark" phase of the experiment.

Lewy et al. (56) demonstrated a dose–response effect of light on melatonin secretion. Bright light of about 2500 lux suppressed human melatonin secretion, while levels of 500 lux had no such effect, and light around 1500 lux had an intermediate effect. Successful clinical treatment of depressed patients was accomplished with bright-light exposure in the morning with an associated phase advance of night-time melatonin production (57). Broadway and Arendt (58) observed a subject living in the Antarctic during the 24-h darkness of winter (light level never over 500 lux) and during the spring time. A more rapid recovery from night-watch-induced sleep disturbance occurred during the spring (1wk for recovery) versus the winter (3-wk recovery time). A concurrent shift in the 6-hydroxymelatonin sulfate rhythm was also observed.

Based on animal experiments demonstrating a phase response to timed bright-light exposure, Daan and Lewy (59) successfully used sunlight exposure to hasten entrainment after transmeridian flights. Other researchers reported bright light exposure could expand the normal (approximately 22–27h) range of entrainment of the human circadian system. Wever and colleagues (60) found bright light (4000 lux) could synchronize the human circadian rhythm to over 29h. Lewy (61) observed that under the near-constant conditions of sunlight during the Arctic summer, humans could entrain to a 21-h period, which is normally below the entrainment range. Other studies demonstrated that bright light is a synchronizer of the human circadian clock (62). Recent studies have demonstrated that social cues, the sleep–wake schedule, and the rest–activity cycle are weak zeitgebers in comparison to the light–dark cycle (63), and sunlight and bright electrical lighting (7,000–13,000 lux) are now recognized to be a strong zeitgeber for humans. Recently, even low light exposure (typical indoor lighting of 50–300 lux) has been shown to effect phase shifts of the human biological clock (64).

1.1.3 Entrainment and Time Shifts There are two important limitations on the circadian timing system with respect to internal and external entrainment. Because of these limitations, time shifts experienced by shiftworkers can result in internal desynchronization between endogenous biological rhythms and in external desynchronization with the 24-h day.

One of the limitations is the range of entrainment of the circadian pacemaker. Wever (65) used the technique of "fractional desynchronization" to determine this range. Gradual lengthening or shortening (by 5–10min) of a zeitgeber-determined period was carried out and the limits of different overt rhythms observed. When the limit was reached, the variables began to free-run. The phenomenon of internal desynchronization was seen as different rhythms reached their limits of entrainment at different times. The range of entrainment for body temperature was found to have an upper limit of approximately 27h and a lower limit of about 22h.

Internal desynchronization had been observed prior to this study, and should be discussed a bit further because its occurrence is important when considering the body's response to time changes. Spontaneous desynchronization has been observed in some individuals, most often at the end of studies of regular free-running periods. Aschoff (39) studied human subjects isolated from temporal cues in underground bunkers for up to 4wk, allowing them to choose their own times for sleeping and eating. Continuous measurements of rectal temperature and activity (and analysis of urine volume, calcium, and potassium from specimens collected at self-chosen times) were carried out. Free-running periods of about 25h were noted for all variables. However, one subject was noted to

develop an extremely slow sleep rhythm of 32.6h while the body temperature and urine variables ran at 24.7h. The activity rhythm regained its original phase with respect to the other variables every third to fourth day. (When all rhythms were in phase, the subject noted in his diary that he felt especially good.)

Wever (48), in reviewing his many isolation studies, has noted internal desynchronization in almost 30% of subjects during the first month of free-running experiments and in almost all his subjects participating in longer experiments. Internal desynchronization was also seen in a sleep study where 6 out of 12 subjects in free-running conditions demonstrated an extremely long duration of sleep–wake cycles (up to 50h) with the circadian body temperature rhythm persisting (66).

It should be noted here that internal desynchronization can be induced in any person by imposing artificial zeitgebers such as a sleep–wake schedule or light–dark cycle outside the range of entrainment range of the body temperature rhythm, that is, less than 22 or greater than 27h (13, 19). Such study designs are referred to as forced-desynchronization protocols.

The second limitation of entrainment is the rate at which the circadian clock can be phase-shifted to match an imposed time-shift such as occurs with working night shifts, or with transmeridian jet travel. In addition, different individual biological rhythms have been shown to re-entrain to time shifts at different rates, reflecting different relative strengths of endogenous and exogenous rhythm components. For example, sodium and potassium excretion are closely linked in a stable rhythmic environment, but have significant differences in their re-entrainment to phase shifts (67). Adjustment of rhythms of urinary volume and potassium excretion in full-time night nurses required 4d for temporal phasing after returning to work after their days off (68). Urinary 17-hydroxycorticosteroid excretory rhythm did not fully reverse itself until the second week after sleep–wake reversal in a study of 5 healthy males (69).

Another study demonstrating desynchrony of rhythms due to different rates of adjustment after time shifts was done by Wever (70). Rhythms of rectal temperature and computation speed were seen to need more time than the 2d required for the sleep–wakefulness rhythm to adjust in this isolation experiment. Weitzman (71) has shown in several studies that the body temperature curve takes 2–3wk to adjust completely to sleep–wake reversal.

In phase-shift studies designed to simulate transmeridian flights (6-h time shift), Wever (70) also found that rhythms of different variables adapt at different rates to shifted zeitgebers, and that the sleep–wake rhythm adjusts faster than the body temperature rhythm. For both advance and delay time shifts, the activity rhythm adjusted in about 2d. More time was needed for adjustment of the temperature and performance speed.

When subjects entrained to an artificial day have been studied, it has been observed that when the phase of the artificial day is shifted, different rhythms entrain at different rates, with activity always adjusting faster than physiologic functions (72). Differences in the rate of phase adjustment of performance rhythms for various tasks to shiftwork and transmeridian flights have also been documented (73).

Mechanisms of reentrainment have also been studied. Mills et al. (74), observed subjects in isolation units under 24h of constant routine (continuous light and sedentary activity) and after time shifts of 8–12h. The direction of reentrainment of the circadian rhythms of temperature and urinary constituents was by phase delay. Again it was found that, under these controlled conditions, different variables reentrained at different rates. “Reentrainment by partition” was been observed in some subjects who were observed to have their circadian system split into the components of activity and temperature rhythms. After a 6-h advance in artificial zeitgebers, the temperature reentrained by an 18-h phase delay, while the activity rhythm shifted in the same direction as the zeitgeber shift. This phenomenon has also been observed in studies of eastbound transmeridian flights summarized by Ashcoff (75).

1.1.4 Light, Melatonin, and Photoreceptors For almost two decades, timed light exposure and administration of oral melatonin have been a focus of research directed towards helping jet travelers and shiftworkers adjust to time shifts. Therefore, some detailed discussion of the mechanism of action of these zeitgebers is necessary.

The phase-shifting effect of light on the circadian timing system is secondary to its suppressing action on the secretion of melatonin by the pineal gland. Melatonin is an internal signal to the circadian system that it is night time. This hormone, which is normally produced only during darkness, induces sleep and depresses the core body temperature. The normal relationship of the melatonin rhythm to the temperature rhythm and the time of day is shown in Figure 107.3 (76–78).

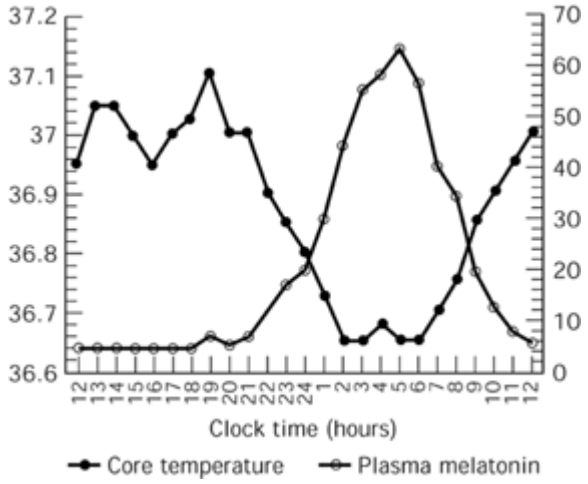

Figure 107.3. Graph of human plasma melatonin (pg/mL) and rectal temperature (°C) plotting real data from a 24-h constant routine condition. Under these entrained conditions the peak of the melatonin secretion is shown to correspond to the radir in core body temperature. Used with permission from Ref. 78a.

The mechanism of the chronobiological action of light has long been believed to require stimulation of retinal photoreceptors (79). Transmission of this information received by the retina is via the retinohypothalamic neuronal tract to the suprachiasmatic nucleus (SCN), which in turn suppresses the pineal gland secretion of melatonin. Melatonin in turn activates melatonin receptors in the SCN, which inhibit SCN metabolic activity (80, 81). This traditional pathway is diagrammatically illustrated in Figure 107.4.

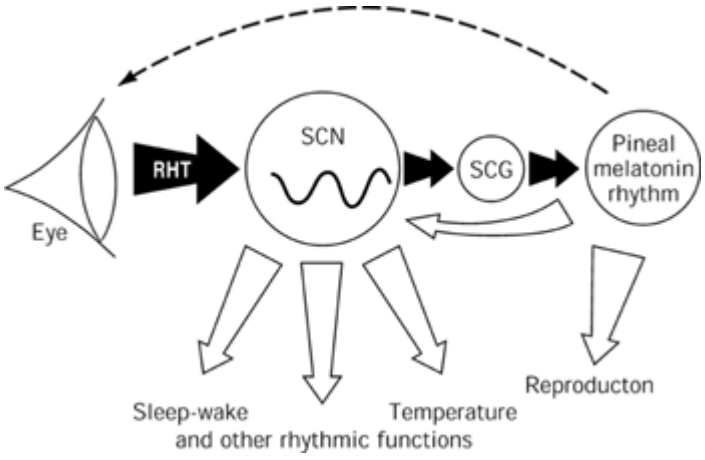

Figure 107.4. Generalized diagram of the circadian system central rhythm-generating system in the suprachiasmatic nucleus (SCN). Melatonin is shown to feed back at the level of the SCN to shift

circadian phase and also to influence rhythmicity at the retinal level. RHT, retinohypothaolamic tract; SCG, superior cervical ganglion. Used with permission from Ref. 78a.

In mammals, the retina of the eyes has long been considered the exclusive site for the chronobiological effects of light exposure. Evidence for the role of the eye as the receptor for the zeitgeber action of light includes studies of the effect of preventing light from reaching the retina. Shielding sighted individuals from the normal 24-h light–dark cycle in temporal isolation results in free-running endogenous circadian rhythms, including melatonin and the body temperature rhythm. It has also been observed that many blind persons have free-running circadian rhythms despite maintaining a regular 24-h sleep–wake schedule, and that these individuals often have cyclic disturbances of sleep quality due to phase changes in the circadian pacemaker (82–85). In addition, timed ocular light exposure had been successfully used to treat sleep–wake disorders and symptoms of seasonal affective disorder (winter depression), but exposure to light while the skin and eyes were shielded had been reported to be ineffective (86). Also several studies of rodents had failed to demonstrate entrainment to light after total enucleation of the eyes (87).

There is now an accumulation of findings from several studies providing evidence for a nonretinal circadian photoreceptor. First of all, some nonsighted persons do sustain a 24-h sleep–wake cycle without difficulty and maintain synchrony of biological rhythms including melatonin and core body temperature (83, 88, 89). The observation that some completely blind persons with no pupillary light reflex do have a positive melatonin suppression test (suppression of melatonin by ocular exposure to light) suggests that the photoreceptors that are involved with the entrainment of the biological clock by light are not the same as the visual light receptors. That is, the retinal projections that send information about light exposure to the visual and the circadian centers of the brain may not be the same, as had long been assumed to be the case (83, 90, 91). Rodent studies have demonstrated that genetic loss of the known mammalian retinal photoreceptors (i.e., the rods and cones) does not interfere with the normal light-induced suppression of melatonin secretion nor with normal light-induced phase shifting of behavioral responses (92, 93). Perhaps the most convincing evidence is from a recent study by Campbell and Murphy (94). These researchers showed a response to light in human subjects using extraocular light exposure. At varying times with respect to the baseline circadian phase, 3-h light exposures were directed over the popliteal area (posterior area of the leg at the knee joint) of 15 healthy subjects. Body temperature and salivary melatonin were monitored and used to determine the subjects' pre-light exposure circadian phase. Significant phase shifts were documented following the light exposures. Depending on the time of the light exposure, a phase-delay or a phase-advance response occurred.

Oren (95) has proposed a mechanism for this nonocular response, suggesting that there is a blood-borne circadian photoreceptor, such as hemoglobin, able to receive light stimulation through superficial vasculature. Hemoglobin is a likely candidate for the photoreceptor function as the tetrapyrrole-based heme pigment portions of its molecular structure are very similar to the plant photoreceptor pigment chlorophyll. This theory of “humoral phototransduction” is supported by other studies demonstrating light-induced release of the neuroactive gases carbon monoxide and nitric oxide from heme moieties (96). Two other classes of pigments, in addition to heme pigments, are potential candidates for having circadian photoreceptor properties. These additional pigments are opsin/retinal-based photopigments and pterin/flavin-containing crytochrome blue-light photoreceptors (97, 98).

1.1.5 Shiftwork Applications The studies reviewed in the preceding sections demonstrate that a major function of the circadian system is the internal sequencing of physiologic events and metabolism. Biological processes are thus coordinated for optional functioning of the organism. Under normal nychthermal conditions, rhythms may show a peak just before an expected environmental event such as the rise of body temperature and the peak of plasma cortisol occurring just before awakening. Restorative functions of sleep are maximized by the normal phase of biological rhythms during the night-time hours.

For a shiftworker, however, activity at night will be out of phase with the circadian body temperature and other coupled rhythms. In addition, each time the work schedule rotates, or there is a return to night work after off-work days, for some duration of time after the time shift, the circadian system will be in a desynchronized state.

In humans, circadian rhythms are more easily shifted if all the important zeitgebers, including the light–dark cycle, are synchronously shifted, such as occurs with transmeridian flights. For shiftworkers, zeitgebers shift in a nonsynchronized manner (99). A week's time is necessary after a transmeridian jet flight for the circadian system to adjust to a 6-h time change, a situation where all social time cues, meals, sleep–wake schedule, and light–dark schedule remain in normal phase relationship to each other (100). Laboratory studies of subjects experiencing an inversion of the sleep–wake schedule, with no intervention with a timed light exposure, demonstrated no significant re-entrainment of the temperature rhythm after 10d. Knauth and Rutenfranz (101) failed to find complete inversion of the body temperature rhythm in shiftworkers even after 21 consecutively worked night shifts, and concluded that the circadian system never fully adapts to night work. Other field studies of shiftworkers have also found adaptation to night work to be incomplete (102–105). The slow rate of adaptation by workers to new shift-work schedules is apparently due to competing influences of different zeitgebers (106).

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2.0 Performance and Safety
2.0.1 Characteristics of Performance Rhythms Researchers have been analyzing 24-h variation in human performance for over a century. The circadian nature of human performance rhythms is well documented and was recognized even before the term circadian was coined (107, 108). Initial investigators of time-of-day performance variation were more interested in mental performance and adjusting school schedules to coincide with peak academic ability than they were in industrial safety or productivity. Research efforts therefore focused on learning and memory. The observation that complex cognitive tasks were different from simple ones with respect to diurnal variation was made before the beginning of the twentieth century (108). In the early 1900s, Gates reported differences between the circadian rhythms of different types of cognitive tasks (109).

Despite these early findings, Kleitman (110) concluded there was a general performance rhythm, having a causally related parallelism with the body temperature rhythm. His opinion was based on his observations that performance speed and accuracy for several tasks followed consistent rhythms, with poorest scores in the early AM and late PM and maximum scores at mid-day. However, the six tests Kleitman used (dealing and sorting cards) were immediate-processing, simple repetitive tasks, with low cognitive load.

Colquhoun and associates (111–113) did a series of laboratory shiftwork studies using variations of naval watch schedules. The type of tasks used resembled sonar operations and were low-cognitive-load, maintenance and vigilance, immediate- processing-type tasks. Like Kleitman, this group also reported a positive correlation between the performance rhythm of these simple repetitive tasks and the body temperature rhythm. However, rather than suggest that this was a direct causal relationship, he proposed a unidimensional arousal theory to explain his observations. In this theory, sleepiness is compared to a lack in arousal, and as arousal rises (or the level of sleepiness falls), reaching a maximum in the evening (or minimum for sleepiness), performance also peaks. The theory involves an “inverted U” relationship with increasing levels of arousal allowing improving performance up to a certain arousal level at which time a decline in performance begins. The arousal theory provided an explanation for deviations from parallel relationships with the temperature rhythm demonstrated for

certain tasks, particularly the digit-span memory task, due to there being different levels of optimal arousal for these tasks (114). A detailed discussion of the arousal model, its limitations, and advances in the model are provided in a recent review by Monk (115). Briefly, simple repetitive and vigilance tasks are considered to have a high optimal arousal level and therefore to parallel the arousal rhythm (and also the temperature rhythm) (111–113). Complex, high-memory-load performance has a low optimal arousal and decline over the waking day with a phase inverse to the temperature rhythm (116). In other words, the arousal theory proposes that there is a circadian rhythm for arousal that rises over the waking period, peaking in early evening and generally paralleling the temperature rhythm. The optimum arousal level is low for high-memory-load tasks, and high for low-memory-load tasks.

The arousal theory has been supported by several studies. Research by Folkard (117) and Englund (118) indicates that performance is task dependent and that speed and accuracy may represent different diurnal components of performance with different relationships to arousal. Monk and Folkard (119) tested immediate recall (memory tested within a few minutes after presentation of the material to be learned) and long-term memory of hospital training films in 26 part-time nurses, all having normal day-oriented circadian rhythms.

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3.0 Shiftwork and Health
3.1 General Well-being
3.1.1 Desynchronosis (A Time Shift Is a Time Shift) As has been discussesd in the preceding sections, when individuals experience sudden time shifts, the phase alignment of their previously synchronized biological rhythms is disrupted. Both external and internal desynchronization result. The term *desynchronosis* refers to the presence of rhythm desynchronization with associated signs and/or symptoms of physical and/or mental dysfunction. Probably the most well-recognized examples of desynchronosis are “Monday morning malaise” and “jet lag” (or in proper chronobiological terminology, *transmeridian flight desynchronosis)*. Symptoms of jet lag are universally recognized and include (in order of typical frequency as reported by frequent jet travelers): daytime sleepiness and fatigue, difficulty sleeping at night, poor concentration, slow physical reflexes, irritability, digestive system complaints (e.g., abdominal discomfort, diarrhea, appetite changes), and feelings of depression. Not surprisingly, studies of the general well-being of shiftworkers have demonstrated that shiftworkers experience very similar symptoms (197, 198). That is, symptoms of “shift lag” (199) are essentially the same as those of jet lag. However, the complaints of shiftworkers may not be as readily recognized as being related to time shifts by the non-shift-working community. A side-by-side comparison (Table 107.3) of typical complaints of jet travelers and shiftworkers clearly demonstrates the similarity.

Table 107.3. Symptoms of Jet Lag and Shift Lag

Jet-Lag Symptoms	Shift-Lag Symtoms
Daytime sleepiness/fatigue	Fatigue/falling asleep at work
Inability to sleep at night	Sleep disruption
Poor concentration	Decreased vigilance
Slowed physical reflexes	Impaired performance
Irritability	Irritability

Digestive upset and hunger at unusual times	Gastrointestinal disturbance
Depression	Depression and apathy

Despite the similarity in symptoms of desynchronosis reported by both jet travelers and shiftworkers, there is an important difference between these two groups. For jet travelers, the new time for sleep and activity will be in concert with the 24-h solar day and the social/work schedule of society. These two factors will assist the jet traveler in re-entrainment of biological rhythms. For the night shiftworker experiencing a time shift, the sleep–wake cycle will be opposed to the 24-h solar day and night, and the work schedule will be in conflict with the work/leisure activity of most of the rest of society and often with other family members. Therefore, while jet-lag symptoms are typically limited to a few days, symptoms of shiftwork related desynchronosis are often continually present to some degree when night shift work is a regular part of the work schedule. This is usually true even for those assigned permanently to the night shift, since most of these workers will revert to regular diurnal schedules on their days off. Airline personnel may be subject to the most severe desynchronosis due to combined effects of repeated transmeridian time crossings and shiftwork (200).

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4.0 Shiftwork Scheduling Issues
4.1 Types of Shift Schedules
Shiftwork, broadly defined, refers to work regularly performed outside the normal day shift period from 0700–0800 to 1600–1700. There are many variations of shiftwork schedules (419–422). Work shift systems fall into two general categories, *Continuous* (work coverage is provided continually over the 7-d week) or *discontinuous* (there is a break in work operations at some time during the week, usually during on the weekend period). The general types of shift schedule arrangements include:

1. *Fixed*. Only the day, afternoon/evening, or night shift is worked by an individual employee.
2. *Rotating*. An individual employee rotates between more than one shift. The rotation may be in either a *forward, clockwise* (phase-delay) direction or a *backward, counterclockwise* (phase-advance) direction. A forward rotation progresses from the morning shift to the evening to the night. The backward rotation, of which the "Southern swing" is a common example in the United States, progresses from the day to the night to the evening shift.

   The type of rotation is also classified by how many days on one shift are worked before moving on to another shift (i.e., by the speed of the rotation). The rotation speed may be: (*1*) *slow*—greater than weekly, usually 21d or greater on the same shift; (*2*) *weekly*—5–7d in a row of each shift; or (*3*) *rapid*—1–4d in a row on any one shift. Examples of rapid rotations include:

   1. *Continental*. This is a rapidly rotating system, frequently referred to in European work studies, in which two consecutive, identical shifts are followed by two of another shift, and then three of the third (2–2–3).
   2. *Metropolitan*. This is also a rapidly rotating system of European origin, in which two identical, consecutive shifts follow one another until all three are worked (2–2–2).
3. *Alternativea*.

1. The “compressed” 4-d work week, with either 10- (“4/40”) or 12-h work periods. This may be used in a single, two-shift, or three-shift, continuous or noncontinuous operation.
2. The 8-d week with four, 10-h days followed by 4d off. This is used primarily in firms operating 10h/d, 7d/wk or working 20h/d in two shifts.
3. Flexitime, originated in Europe, gives the employee considerable choice in designing one's own daily work hours to meet weekly requirements.
4. Staggered refers to working hours in which employees are assigned to, or allowed to choose, their starting time, which will determine their quitting time.
5. Split shifts have a hiatus of a few hours separating the work hours performed on the same day. For example, this may be done in service businesses such as restaurants or transportation, where there are major peaks in business.
6. Relief shifts are ones in which the worker may follow any of the above patterns, but the time of work is determined by someone else's absence.

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5.0 Countermeasures
5.1 Employer/Workplace Actions
Chronobiologically sound scheduling strategies and the provision of appropriate occupational health programs for employees are central countermeasures for minimizing deleterious effects of shiftwork. These are discussed in detail in Sections 4.0 and 3.6.3.

Equivalent human resources support including educational programs for workers and their families on shiftwork-related health, safety, and coping topics are also important measures. Monk and Folkard (502) have recommended employers develop a “Shift Work Awareness Programme” for coordinating educational and social support programs. Some proactive companies, having recognized the difficulty night workers with families face in obtaining child care, have established 24-h childcare facilities for their workers (503).

Workplace facilities and environmental conditions can impact tolerance to shiftwork and shiftworker performance. In order to assist employees in dietary countermeasures (see Section 5.1), equivalent canteen/eating facilities should be provided for night workers as for day workers. At a minimum, a microwave, refrigerator, and vending machines with low fat, nutritious foods should be available including dairy products and fruit juices.

Other environmental factors should be assessed, which can be adjusted toward increasing alertness on the job and preventing nodding off when working. For instance, sufficiently intense and uniform lighting will enhance alertness. Nonvariable background noise, which can promote boredom, should be replaced with judiciously used music and, if appropriate, social interactions between workers. Keeping room temperatures below 70°F and maximizing opportunities for physical activity have also been recommended (502, 504).
5.2 Coping Strategies for Shiftworkers and their Families
As the heading of this section implies, in order for individual coping strategies to be effective, families must be involved. In addition, the shiftworker must remember the toll that the shiftwork schedules may take on the family as well. The provision of educational programs for both the worker and family is essential for employees to cope successfully with shiftwork schedules. Educational materials addressing shiftwork issues, including countermeasures published in laymen's terms, are available to assist employers and employees in this endeavor (474, 502, 505, 506). Strategies for

coping with jet lag will not be addressed in this chapter but are reviewed in depth by Comperatore and Krueger (200) and Lamberg (507).

5.2.1 Maximizing Sleep The sleep problems of shiftworkers, both night workers and early morning starters, have been discussed in detail in Section 2.0. A large part of this problem relates to work scheduling issues beyond the control of the worker. However, there are some coping strategies that can be used to maximize sleep within the scheduling constraints.

One often significant interfering factor for night workers in particular is daytime noise, as discussed in Section 2.1.1. Even if the worker is not aware of actually being awakened by noise, sleep quality may be compromised (508). Actions should be taken to soundproof the bedroom as much as possible. In addition to using sound damping items such as ceiling tile and perhaps carpeting, white noise from a fan or air conditioner may be helpful. Family and even neighbor cooperation should be sought to help control noisy activities near the night worker's sleeping quarters. The phone and doorbell should not be audible in the bedroom. Earplugs can also be used to attenuate noise as long as the fit is comfortable.

Light exposure should be minimized to as close to night time conditions as possible. Lined drapery and window blinds or dark room shades may be helpful in this effort. Eye shades are another option for decreasing light exposure.

Applying “sleep hygiene” techniques, initially developed to help patients with insomnia, is also a recommended coping strategy for shiftworkers. Sleep hygiene is a program applying regular procedures and following behavioral rules that enhance the ability to fall asleep and stay asleep. Sleep hygiene recommendations have been recently summarized (509) and include: (*1*) maintaining a regular wake time, (*2*) avoiding excessive time in bed, (*3*) avoiding naps, except if a shiftworker, (*4*) using the bed only for sleeping and conjugal relations, (*5*) avoiding nicotine, caffeine, and alcohol, (*6*) engaging in regular exercise, (*7*) doing a relaxing activity before bedtime, (*8*) not watching the clock, and (*9*) eating a light snack before bed if hungry. Although shiftworkers will not be able to comply with the first recommendation, the others can be followed and may help to promote sleep.

Although the regular use of sleeping pills is not advised, short-acting hypnotics such as triazolam have been shown to improve quality and duration of daytime sleep (510). Occasional use for a day or two, under a physician's care, may be useful when beginning a run of night shifts or following a transmeridian flight. However, caution must be exercised, as impaired cognition has been demonstrated to linger 8h after administration of a 0.5-mg dose (511).

5.2.2 Caffeine and Other Alertness-Enhancing Drugs Caffeine belongs to the xanthene class of drugs. This class of substances has been shown to cause phase shifts of the temperature rhythm in animals (512). The alteration of the circadian pacemaker seen with xanthines may explain the general use of caffeine by many to “get going” in the morning (23). However, its role in shiftwork coping relates to its stimulant effect counteracting sleepiness, and to its ability to delay sleep onset at night (513, 514). Its effect in increasing alertness is most apparent after a time of abstinence, and with repeated doses the effect may diminish (515). Simulated night-shift studies have reported caffeine use to have beneficial effects on alertness and performance, and to decrease sleep tendency as measured by multiple sleep latency tests (516, 517).

It takes about 5h for the effects of caffeine to disappear. Therefore, if caffeine is consumed, it should not be ingested closer than around 5h before bedtime (518). Excessive amounts of caffeine are not recommended for a variety of reasons. Shiftworkers are advised to limit the dose to around 300mg of caffeine per day, and to use during the first half of night or evening shifts. It is important to avoid caffeine during the last half of the evening shift or night shift, since the worker's bedtime will come soon after getting home. Fruit juice is a good alternative drink for the second half of the shift.

Illicit drugs such as amphetamines should never be used for obvious reasons. Due to deleterious side effects, stimulant diet pills should not be used to counteract shiftwork sleepiness. Research is being conducted on some new alertness-enhancing drugs, namely pemoline and modafinil, which may, in the future, have some usefulness for occasional alertness promotion. Findings to date have recently been reviewed by Åkerstedt and Ficca (518). Even if these prove to be effective for counteracting sleepiness, as pointed out by these authors, their use on any regular basis to make work at nonphysiological times tolerable raises ethical questions.

5.2.3 Bright Light and Melatonin Bright light pulses and the administration of melatonin show promise as chronobiotics, that is, for inducing phase shifts of the circadian system allowing for rapid reentrainment to new work–sleep times. The role of light as a zeitgeber is discussed in Section 1.1.2, and the physiological aspects of melatonin and its relationship to light have been reviewed in Section 1.1.4.

In addition to its sleep-inducing property, animal and human laboratory studies suggest that melatonin may effect phase shifts when administered with appropriate timing (519, 520).

Several field studies have demonstrated melatonin to be useful for ameliorating jet-lag symptoms. These have recently been reviewed in detail (200, 521). Five milligrams daily, orally administered, is the pharmacological dose frequently used in research protocols, although lower doses may also be effective (522). Specific instructions (and side-effect warnings) for taking the hormone for east- and westbound flights, as given to subjects participating in jet-lag studies, are included in the review by Arendt and Deacon (521). However, routine use of the product by travelers is not recommended.

There is limited research available on the use of melatonin in shiftwork situations. Beneficial effects on sleep and alertness have been reported associated with bedtime administration, but some performance measures may be adversely affected (523). Although the melatonin may be approved for use by shiftworkers at some time in the future, and it is recognized that there are some shiftworkers reporting benefits from using over-the-counter (OTC) preparations for shift-lag symptoms (524), its use cannot be recommended at this time (474, 521). Because it is a naturally available dietary supplement, melatonin is available OTC; however, licensed controlled preparations are only available as an investigational drug. Purity and strength are not regulated by the FDA in the United States for the OTC preparations (525), which are unfortunately widely available due to the inappropriate marketing of the hormone as a “cure-all” miracle drug. Effects of long-term usage are not known, and inappropriately timed administration may be dangerous due to its sedative effect.

Exposure to bright light has been demonstrated to result in phase shifts of the circadian timing system. The timing of the exposure determines the direction of the shifts, that is, either a phase-advance or phase-delay response (526–528). Figure 107.14 graphically demonstrates the results of a simulated shiftwork study (528) in which enhanced circadian readjustment to night work was achieved using timed, bright light exposure (7,000–12,000 lux, comparable to natural sunlight at dawn). The methodology of this study included provision of sleeping quarters with complete darkness, and strict timing of the sleep period.

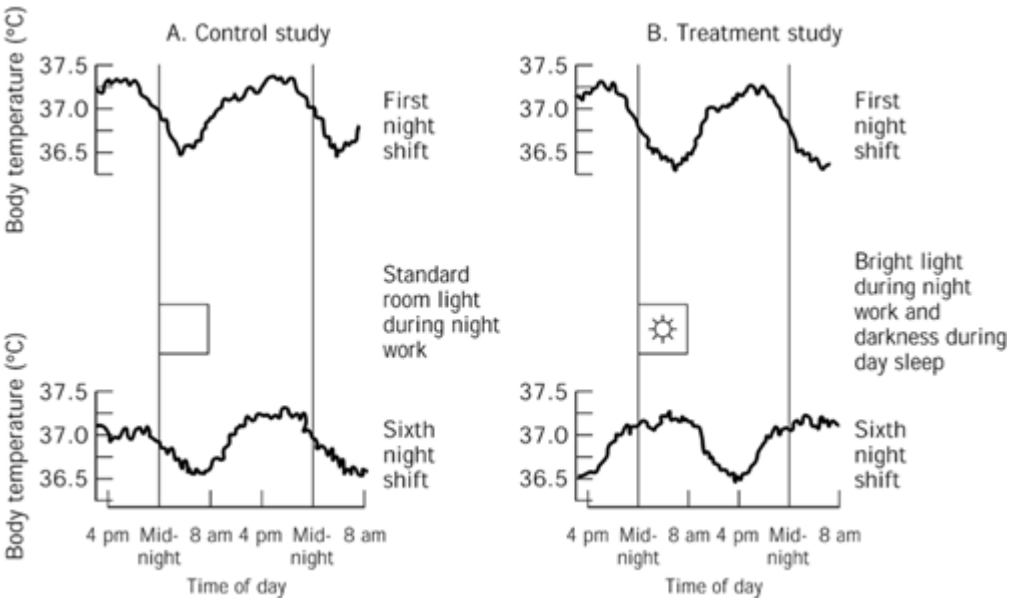

Figure 107.14. Effects of bright light on the adjustment of a worker to shiftwork. Body temperature phase shifts are shown on the first night and on the sixth night of work (A) with normal light levels and (B) with exposure to bright light on the second through fifth night of work. Phase shift of the body temperature rhythm to the night shift is demonstrated with the timed bright light exposure treatments. Adapted with permission from Ref. 528.

Although it is clear that appropriately timed, bright light exposure can enhance adjustment to night shifts, practical application for shiftworkers is a different matter. Not only is the timing of the light exposure critical, prevention of outdoor sunlight exposure at other times is necessary (requiring workers to wear dark goggles for a commute home after dawn), and night time darkness must be maintained in the bedroom/bathroom. In addition, there is considerable individual variation in the degree of phase-shift response.

Recently combined use of melatonin and light have received attention as potentially the most effective way to encourage reentrainment after time shifts (529). Again, practical application for shiftworkers may not be realistic, even when detailed recommendations for exposure/medication timing are available.

5.2.4 Diet and Exercise Good dietary habits and regular exercise are recommended in general for preventive health reasons to prevent/reduce obesity and decrease risks of diseases such as coronary heart disease and diabetes. These recommendations, of course, apply to shiftworkers as well as regular day workers. As pointed out in Section 3.2.2, it may be even more important for shiftworkers to follow preventive health recommendations for reducing the risk of coronary heart disease than for workers in general. However, there is no consistent evidence to date that dietary manipulations, such as the “jet-lag diet” (530), can speed up adjustment to time shifts. Nevertheless, it may be prudent, when trying to stay awake, to avoid foods high in carbohydrates, which may promote sleepiness by stimulating serotonin synthesis and choose protein items instead, which may increase alertness by stimulating release of catecholamines. It is also reasonable to recommend avoidance of heavy, greasy, or otherwise difficult-to-digest meals before bedtime or during the night shift, when the gastrointestinal system is not geared up for the digestion process (200, 531).

Physical fitness training has been demonstrated in shiftworkers to reduce general fatigue and sleepiness at work, increase sleep duration somewhat, and decrease musculoskeletal symptoms. Recommendations for exercise for shiftworkers include: (1) Moderate physical exercise is preferred over intensive training; (2) exercise should be done a few hours before the main sleep period; and (3) for morning or day shifts, the best exercise time is after the shift. After night shifts, the exercise

should be done before an evening nap (386, 532).

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Smoke and Combustion Products

Barbara C. Levin, Ph.D.

1 Introduction

Seventy-six percent of the people that died in structural fires in 1990 died from the inhalation of toxic combustion products, not from burns (1). This percentage has been rising by about one percentage point per year since 1979. Although total deaths in fires are declining, the percentage attributed to smoke inhalation has increased. An area of research called *combustion toxicity* has evolved to study the adverse health effects caused by smoke or fire atmospheres. According to the American Society for Testing and Materials (ASTM), smoke consists of "the airborne solid and liquid particulates and gases evolved when a material undergoes pyrolysis or combustion" (2) and therefore, includes combustion products. In this chapter, a fire atmosphere is defined as all the effluents generated by the thermal decomposition of materials or products regardless of whether that effluent is produced under smoldering, nonflaming, or flaming conditions. The objectives of combustion toxicity research are to identify potentially harmful products from the thermal degradation of materials, to determine the best measurement methods for the identification of the toxicants as well as the degree of toxicity, to determine the effect of different fire exposures on the composition of the toxic combustion products, to predict the toxicity of the combustion atmospheres based on the concentrations and the interaction of the toxic products, and to establish the physiological effects of such products on living organisms. The ultimate goals of this field of research are to reduce human fire fatalities due to smoke inhalation, to determine effective treatments for survivors, and to prevent unnecessary suffering of fire casualties caused by smoke inhalation. Other reviews of various aspects of this subject can be found in Refs. 3–8.

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2 Fire Death Statistics In the United States

According to the U.S. Fire Administration, fire kills more people in the United States than the combination of floods, hurricanes, tornadoes, and earthquakes. Although the reasons are not clear, the number of fire deaths per capita in the United States and Canada is about double the international average of the other countries in the industrialized world (9). Fire statistics collected by the National Fire Protection Association (NFPA) indicated that approximately 1,795,000 fires occurred in the United States in 1997, the latest year for which complete statistics are available (10). Calculated another way, these statistics translate into a fire occurring in the United States every 18 sec, in property located outside every 37 sec, in a structure every 57 sec, in a residence every 78 sec, and in a motor vehicle every 79 sec. These fires caused 4,050 deaths and 23,750 reported injuries in 1997. This number for injuries is believed to be less than the actual number, since many injuries are not reported. The property loss for 1997 is estimated at 8.525 billion dollars.

In 1997, residential fires accounted for only 22.6% of the total fires, but were responsible for 83% of all fire deaths and 75% of the reported injuries. Of 552,000 fires reported in structures, 17,000 or 3% were in a category designated as Industry, Utility, and Defense by the NFPA. These numbers only include those fires handled by public fire departments and reported to the NFPA and do not include fires handled by private companies or fire suppression systems. Although in the years 1977–1997 the number of civilian fire fatalities in homes dropped from 6000 to 3390, fires in homes still cause the greatest concern to the fire community. In 1997, only 120 deaths occurred in the category of nonresidential structures, which includes public assembly, educational, institutional, store and office, industry, utility, storage, and special structures (10). Statistics show that children under five and adults over 65 years of age are the most frequent casualties of residential fires (9). This is attributed to their inherent difficulties in trying to escape. Statistics also show that males are more likely to die in fires than females, especially males between the ages of 25 to 34 (9, 11, 12). In 1997 as in past years, the South had the highest fire incident rate (7.8 per thousand inhabitants) when compared with other geographical areas of the U.S. However, for the first time, the Northeast tied with the South to claim the highest death rates (17.5 per million people) (10).

One must distinguish between the causes of fires and the causes of fire deaths. The primary causes of residential fires have been shown to be heating and cooking (9, 11). Lack of central heat and the incorrect use of portable space heaters are two of the reasons given for the high fire and death rate in the South. Heating fires result in the highest property losses, primarily because cooking fires are usually noticed and extinguished before getting out of control. Fire deaths, however, usually result from fires ignited by cigarettes (11). The most common fire scenario leading to fire deaths is one in which a person (usually intoxicated) falls asleep in an upholstered chair while smoking (9). The cigarette falls into a crevice and starts the upholstered chair smoldering. The individual awakes and goes to bed unaware of the danger. The chair can smolder for an extended period of time [an hour was not unusual in laboratory tests at the National Institute of Standards and Technology (NIST)] before bursting into flames. Once the flaming starts, the smoke will fill the room and escape to the other rooms. It is common to find people who have died from smoke inhalation (not burns) in or near their beds, indicating that their little or no effort to escape was probably due to no warning and incapacitation from the asphyxiants in the smoke. Smoke detectors in this scenario would save many lives. Statistics have shown that working smoke detectors double one's probability of escaping alive. Recently, the problem has arisen that many homes have smoke detectors that are nonfunctioning because the batteries were removed following a false alarm (usually from smoke produced by a kitchen or wood stove) or because old batteries were never replaced.

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3 Generation of Toxic Gases in Fires; Adverse Effects of Particulates
The adverse effects from smoke inhalation are believed due mainly to toxic gas exposures, although the role of the particulates alone and in combination with fire gases needs further investigation. The importance, therefore, of determining the identities and concentrations of toxic gases produced from materials thermally decomposed under various fire conditions is evident. In addition, the increased variety of plastics in buildings and homes has raised the issue of whether synthetic materials may produce unusually or extremely toxic combustion products. In this chapter, the phrase "extremely toxic" is a relative term indicating that the effluent from the thermal decomposition of very small quantities of a material has been noted to cause death of experimental animals (usually rats or mice) under controlled laboratory conditions. "Unusually toxic" indicates that the toxic effect cannot be totally attributable to the combustion gases (either singly or in combination) that are normally considered the main toxicants. In 1975, the journal *Science* documented a case in which an experimental rigid polyurethane foam containing a fire retardant produced a very unusual toxic combustion product identified as 4-ethyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane-1-oxide (commonly referred to as a bicyclic phosphate ester) (13). Bicyclic phosphate compounds have been shown to cause seizures at very low concentrations. Based on these test results, this fire-retarded rigid polyurethane foam never became commercially available. To a large extent, however, it was this case that generated the burgeoning interest in the field of combustion toxicology and the widespread concern about the potential formation of "supertoxicants." Although research since the 1970s has shown that this concern is largely unfounded, the bicyclophosphate ester case and at least one other product that generated extremely toxic combustion products have indicated the need to test new formulations or materials containing new combinations of compounds to ensure that extremely or unusually toxic products are not generated.

The gas composition of smoke depends on the chemical composition, the molecular structure and polymer formulation of the burning material, which may include a variety of additives, plasticizers, stabilizers, flame retardants, cross-linking agents, fillers, and blowing agents. In addition, the conditions of thermal degradation, such as temperature, oxygen availability, and ventilation, will affect the nature of the combustion atmosphere. In a series of literature reviews by NIST on the generation of combustion products and the combustion product toxicity from seven plastics [acrylonitrile-butadiene-styrenes (ABS), nylons, polyesters, polyethylenes, polystyrenes, poly(vinyl chlorides) (PVC), and rigid polyurethane foams] commonly found in materials and products, and decomposed under various thermal and atmospheric conditions, over 400 different decomposition products were noted (14–21). At about the same time, the Consumer Product Safety Commission reviewed the combustion products and the toxicity of those combustion products generated from acrylics, phenolics, polypropylene, and flexible polyurethane foam (22–25), and the National Academy of Sciences did the same type of literature review on an additional 10 plastics, namely, acetal, aramid, cellulose acetate butyrate, epoxy resins, melamine–formaldehyde, polybutylene, polycarbonate, polyphenylene oxide, polytetrafluoroethylene, and urea–formaldehyde (26). Many of the combustion products were common to more than one plastic. In addition, there are probably many other combustion products that were not detected. At this time, the toxicity of most of these individual compounds is not known, and little has been done to tackle the enormous problem of determining the toxicity of combinations of these compounds. It is important to note that lack of detection of a specific combustion product from a material may only mean that the particular analytical techniques used were not suitable to detect that compound or that the investigator did not specifically analyze for that combustion product. Animal testing becomes important to ensure that an unsuspected and, therefore, undetected toxic byproduct has not formed.

Since the number of compounds one can reasonably analyze in any one test is limited, knowledge of

the chemical composition, molecular structure, and formulation of the polymer can be used to provide some indication of the main gaseous products, which may or may not be generated under specified experimental conditions. However, one needs to be cautious when predicting the combustion products from generic materials of unknown formulations. For example, one would expect nitrogen-containing materials (e.g., ABS, nylons, rigid and flexible polyurethanes) to produce hydrogen cyanide (HCN) and not expect HCN from a material like PVC. However, PVC containing zinc ferrocyanide, an additive being tested as a smoke suppressant, [this material was never made commercially available after toxicity testing indicated that its combustion products produced very rapid deaths of experimental animals (rats)] and a vinyl chloride–vinylidene chloride copolymer were found to generate HCN. In a similar fashion, based on the chemical composition, PVC is the only one of the seven plastics reviewed by NIST that would be expected to generate chlorinated combustion products. However, widespread usage of halogenated fire retardants in plastic formulations makes predicting which materials will produce halogenated products extremely difficult. In addition, many of the fire extinguishing agents contain halogens and can interact with the other combustion products in unpredictable ways when they are used to extinguish fires, making the problem of assessing health risks of workplace exposure during and after suppression difficult.

Temperature also plays an important role in influencing the production of decomposition products. In general, as the temperature and thus the rate of decomposition increases, the quantity of the more complex compounds and heavier hydrocarbons decreases and the concentrations of carbon monoxide (CO), carbon dioxide (CO_2), and nitrogen dioxide (NO_2) increase. The generation of HCN has also been shown to increase as a function of temperature. Another example is hydrogen chloride (HCl), the detection of which begins when stabilized PVC is heated to approximately 200°C; rapid dehydrochlorination then occurs at about 300°C (16). On the other hand, more acrolein was generated from polyethylene under lower temperature, nonflaming conditions than under higher-temperature flaming conditions (18).

As mentioned earlier, more work is needed to examine the adverse effects of the particulate matter that is also produced when materials are thermally decomposed. Examination of the smoke particulate and condensible matter are important for a number of reasons. First, many of the thermal degradation products may condense or be adsorbed by the soot particles and be transported along with the smoke into the body. Hydrogen chloride is one example of a compound that may be transported in such a fashion or can form a corrosive acid mist in moist air, such as that found in a person's lung. One study of the particulate matter that formed during the smoldering decomposition of rigid polyurethane foam showed that many of the compounds detected in the soot fraction were not found in the volatile fraction (19, 27). Free radicals, which form in fires and are of toxicological concern due to their high reactivity (28–30), are usually considered to have very short life spans; however, if adsorbed onto soot particles, their lifetimes can be considerably longer, and if the soot particle is the correct size, they can be inhaled deep into the individual's respiratory system. In addition, the particulate matter may interfere with the escape and rescue of individuals by causing the obscuration of vision, eye irritation (the eyes clamp shut and the victim is unable to see), and upper respiratory distress. An extreme case indicating the adverse effect of particulates was noted in experiments conducted at NIST. Rats exposed for 30 min to the smoke from flaming polystyrene died during the exposures and the concentration of CO in the blood, even in combination with CO_2, was too low to account for the deaths (31). Pathological examination of these rats showed that their respiratory passages were completely blocked by soot and that suffocation was the likely cause of death (B. C. Levin, NIST, unpublished data).

Particulates have also been implicated in the toxicity of polytetrafluoroethylene (PTFE). Using the National Bureau of Standards (NBS) cup furnace test method, the combustion products of PTFE were found to be 300 times more toxic than other materials decomposed in a similar fashion (32, 33). Further studies showed that inhalation of the combustion products of PTFE decomposed in the NBS cup furnace caused focal hemorrhages, edema, and fibrin deposition in the lungs of rats (34). These same studies showed that with time, focal interstitial thickenings developed due to hypertrophy and

hyperplasia of alveolar cells and macrophages accumulated in the alveoli. Thrombosis of pulmonary capillaries and disseminated intravascular coagulation also occurred. Renal infarcts were common. The exact reason of the unusual toxicity of PTFE's combustion products is unknown and has generated a great deal of interest (35–37). The specific heating conditions of the NBS cup furnace (38, 39) and the particulate fraction from PTFE have been cited (40–42). However, thermal decomposition in the U. Pitt I test method also produced a toxicity classification of "much more toxic than wood" (35, 43) and decomposition in the German Din System produced a toxicity at least 10 times more toxic than wood (44). Full-scale fire tests seem to implicate hydrogen fluoride or carbonyl fluoride as the toxic agent (45).

An extensive review on the toxicology of soot which concentrated on the induction of respiratory diseases and the potential long term carcinogenic effects was published in 1983 (46).

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4 Toxic Potency versus Fire Hazard Versus Fire Risk
Death in a fire may be caused by:

1. Carbon monoxide (CO)
2. Toxic gases in addition to CO
3. Oxygen (O_2) at levels too low to sustain life
4. Incapacitation—either physical (inability to escape) or mental (incorrect decision making)
5. Bodily burns from flame contact
6. Very high air temperatures
7. Smoke density or irritants in smoke that affect vision and interfere with ability to escape
8. Psychological effects (e.g., fear, shock, and panic)
9. Physical insults (e.g., building or ceiling collapses, broken bones from jumping from upper floors).

Research in the field of combustion toxicology is primarily concerned with items 1–4, all of which are related to the toxic potency of the fire gas effluent. Toxic potency is defined by ASTM as "A quantitative expression relating concentration (of smoke or combustion gases) and exposure time to a particular degree of adverse physiological response, for example, death on exposure of humans or animals" (2). This definition is followed by a discussion, which states, "The toxic potency of smoke from any material or product or assembly is related to the composition of that smoke which, in turn, is dependent upon the conditions under which the smoke is generated." One should add that the LC_{50} is a common endpoint used in laboratories to assess toxic potency. (The LC_{50} value is the result of a statistical calculation based on multiple experiments, each with multiple animals, and indicates the concentration at which 50% of the experimental animals exposed for a specific length of time would be expected to die either during the exposure time or the post-exposure observation period.) In the comparison of the toxic potencies of different compounds or materials, the lower the LC_{50} (i.e., the smaller the amount of material necessary to reach the toxic endpoint), the more toxic the material is.

It is important to note that a toxicity assessment based on lethality due to toxic gases is only part of the total fire hazard that needs to be evaluated especially when one is making choices as to the best material for a specific end use. ASTM defines "fire hazard" as the potential for harm associated with fire (2). The discussion that follows this definition states, "A fire may pose one or more types of

hazard to people, animals or property. These hazards are associated with the environment and with a number of fire-test-response characteristics of materials, products or assemblies including but not limited to ease of ignition, flame spread, rate of heat release, smoke generation and obscuration, toxicity of combustion products and ease of extinguishment." Other factors that need to be evaluated when considering a material for use in a given situation include the quantity of material needed, its configuration, the proximity of other combustibles, the volume of the compartments to which the combustion products may spread, the ventilation conditions, the ignition and combustion properties of the material and other materials present, the presence of ignition sources, the presence of fire protection systems, the number and type of occupants, and the time necessary to escape.

"Fire risk" is defined as "An estimation of expected fire loss that combines the potential for harm in various fire scenarios that can occur with the probabilities of occurrence of those scenarios" (2). The discussion following the definition of fire risk states, "Risk may be defined as the probability of having a certain type of fire, where the type of fire may be defined in whole or in part by the degree of potential harm associated with it, or as potential for harm weighted by associated probabilities. Risk scales do not imply a single value of acceptable risk. Different individuals presented with the same risk situation may have different opinions on its acceptability." A simple way to explain the difference between fire hazard and fire risk is to compare the fire to sky diving, a very hazardous sport; however, if one never goes sky diving, no risk is incurred.

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5 Toxicity Assessment: Animal Exposures
In most combustion toxicology experiments, the biological endpoint has been lethality or incapacitation of experimental animals, usually rats or mice. Incapacitation (sublethal effects) in a fire can be as perilous as lethality if an individual becomes incapable of correct decision making or physically unable to move. Under these circumstances, the ability to escape will be lost, and death will occur unless the individual is rescued. Therefore, many fire scientists are concerned with the levels of combustion products or amounts of materials that when combusted will cause incapacitation. However, an incapacitation model for use in laboratory testing has been especially difficult to develop. Most of the tests for incapacitation that have been designed are based on the physical-motor capability of an experimental animal to perform some task (e.g., running in a motorized wheel, jumping onto a pole or lifting a paw to escape a shock, running in a maze, or pushing the correct lever to open a door to escape an irritating atmosphere) (47–49). The concentration of toxic combustion products that cause the loss of these types of physical-motor capabilities is usually close to the concentration that is lethal and does not usually add much additional information. More recently, however, there have been attempts at examining neurological endpoints such as measuring the increased number of errors by humans doing mathematical problems while exposed to low levels of CO (Arthur Callahan, Naval Submarine Medical Research Laboratory, Groton, CT, private communication) or exposing rats and pigeons to a complete neurobehavioral battery of 25 tests (50).

Whether one needs to examine incapacitation or lethality depends upon the problem one is trying to solve. To determine the best material for a particular end-use application, the lethality endpoint has proven to be more definitive and will flag the materials that produce extremely toxic combustion products better than an incapacitation endpoint. There are at least two reasons for this: (*1*) Incapacitation is only measured during the exposure, which is usually 30 min or less, but lethality can also occur during the post-exposure observation period, which can be two weeks or longer. A material that only causes delayed effects during the post-exposure period (e.g., a material that generates HCl) can thus have an LC_{50} value that is lower (more toxic) than the incapacitation EC_{50}

value (i.e., the amount of thermally decomposed material necessary to cause post-exposure deaths is less than the amount needed to cause incapacitation during the exposure). (The definition of the EC_{50} is essentially the same as that of the LC_{50}, except incapacitation rather than lethality is the endpoint, and incapacitation is monitored only during the exposure and not during the post-exposure period.) (*2*) In many cases in which the combustion products contain high concentrations of irritant gases, the animals would only appear to be incapacitated (i.e., they would stop responding to the incapacitation test indicator due to the high irritant quality of the smoke), but when removed from the combustion atmosphere, would immediately start responding normally.

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6 Toxicity Assessment: Predictive Models
In the 1970s, there were essentially two experimental strategies to examine the issues raised by the field of combustion toxicology: (*1*) the analytical chemical method and (*2*) the animal exposure approach. In the analytical chemical method, investigators thermally decomposed materials under different experimental conditions and tried to determine every combustion product that was generated (14, 51). This approach generated long lists of compounds. The toxicity of most of these individual compounds was unknown, and the concept of examining the toxicity of all the various combinations of compounds was and still is considered an impossible task. An additional problem with the analytical method was that, as mentioned earlier, one could not be certain that every toxic product was detected and identified. This approach enabled one to identify many of the multiple products that were generated, but not know the toxic potency of all the identified compounds, especially when combined.

In the animal exposure approach, the animals (usually rats or mice) serve as indicators of the degree of toxicity of the combustion atmospheres (32, 52–54). The materials of concern are thermally decomposed under different combustion conditions, and the animals are exposed to the combined particulate and gaseous effluent. Multiple animal experiments (each with multiple animals) with different concentrations of material are conducted to determine an EC_{50} (incapacitation) or an LC_{50} (lethality) for a specific set of combustion conditions. Each material would then have a particular EC_{50} or an LC_{50} value that can be used to compare the toxicities of different materials decomposed under the same conditions. The lower the EC_{50} or LC_{50}, the more toxic the combustion products from that material. In this approach, one knows the relative toxicity of a material as compared to another material, but does not know which of the toxic gases is responsible for the adverse effects.

In the 1980s, investigators began examining the possibility of combining the analytical chemical method with the animal exposure approach to develop empirical mathematical models to predict the toxicity (8, 31, 55, 56). These predictions were based on actual experiments with animals and their response to each of the main toxic combustion gases, CO, CO_2, low O_2, HCN, NO_2, HCl, and hydrogen bromide (HBr) and various combinations of these gases. The advantages of these predictive approaches are (*1*) The number of test animals is minimized by predicting the toxic potency from a limited chemical analysis of the smoke; (*2*) smoke may be produced under conditions that simulate any fire scenario of concern; (*3*) fewer tests are needed, thereby reducing the overall cost of the testing; and (*4*) information is obtained on both the toxic potency of the smoke (based on the mass of material burned) and the responsible gases (based on the primary toxic gases in the mixture). The prediction is checked with one or two animal tests to assure that an unexpected gas or toxic combination has not formed. The results of using these empirical mathematical models indicated that, in most cases, one could predict the toxic potency of a combustion atmosphere based on the main toxic gases and did not need to worry about the effects of minor or more obscure gases.

A. Primary Toxic Combustion Gases

Complete combustion of a polymer containing carbon, hydrogen, and oxygen in an atmosphere with sufficient O_2 yields CO_2 and H_2O. It is during incomplete combustion under various atmospheric conditions in either flaming or nonflaming modes that compounds of greater toxicological concern are generated. When O_2 is limited, as in nonflaming or ventilation-limited fires, the primary gases formed during the combustion of most materials are CO, CO_2, and H_2O. If the materials contain nitrogen, HCN and NO_2, two principal thermo-oxidative products of toxicological concern, are also likely to be generated. Halogenated or flame-retarded materials generally produce HCl or HBr. Other commonly found fire gases include nitrogen oxides (NO_x), ammonia (NH_3), hydrogen sulfide (H_2S), sulfur dioxide (SO_2), and fluorine compounds. One also needs to consider that in fire situations, O_2 levels drop and exposure to low O_2 atmospheres will have additional adverse physiological effects. Some of these toxic combustion gases (e.g., CO, HCN, low O_2) produce immediate asphyxiant symptoms, while others (e.g., HCl, HBr, NO_2) fall into an irritant category and produce symptoms following the exposures.

B. The **N**-Gas Models

The *N*-gas models for predicting smoke toxicity were founded on the hypothesis that a small number (*N*) of gases in the smoke account for a large percentage of the observed toxic potency. These predictive models were based on an extensive series of experiments conducted at NIST on the toxicological interactions of the primary gases found in fires (8, 31, 55–60). Both the individual gases and complex mixtures of these gases were examined. To use these models, materials are thermally decomposed using a bench-scale method that simulates realistic fire conditions, the concentrations of the primary fire gases—CO, CO_2, low O_2, HCN, HCl, HBr, and NO_2—are measured, and the toxicity of the smoke using the appropriate *N*-gas model is predicted. The predicted toxic potency is checked with a small number of animal (Fischer 344 male rats) tests to assure that an unanticipated toxic gas was not generated or an unexpected toxicological effect (e.g., synergism or antagonism) did not occur. The results indicate whether the smoke from a material or product is extremely toxic (based on mass consumed at the predicted toxic level) or unusually toxic (the toxicity cannot be explained by the combined measured gases). These models have been shown to predict correctly the toxicity in both bench-scale laboratory tests and full-scale room burns of a variety of materials of widely differing characteristics chosen to challenge the system (31, 61). The six-gas model (without NO_2) is now included in two national toxicity test method standards—ASTM E1678, approved by the American Society for Testing and Materials (ASTM) (62), and NFPA 269, approved by the National Fire Protection Association (63). It is also included in an international standard (ISO 13344:1996) that was approved by 16 member countries of the International Standards Organization (ISO), Technical Committee 92 (TC92) (64).

The objectives of developing the *N*-gas models were:

- To establish the extent to which the toxicity of a material's combustion products could be explained and predicted by the interaction of the major toxic gases generated from that material in the laboratory or whether minor and more obscure combustion gases needed to be considered
- To develop a bioanalytical screening test and a mathematical model that would predict whether a material would produce extremely toxic or unusually toxic combustion products
- To predict the occupant response from the concentrations of primary toxic gases present in the environment and the time of exposure
- To provide data for use in computer models designed to predict the hazard that people will experience under various fire scenarios

1 The Six-Gas Model The six-gas model (see Eq. 1) was based on studies at NIST on the toxicological interactions of six gases, CO, CO_2, HCN, low O_2 concentrations, HCl, and HBr. First,

individual gases in air were tested to determine the concentrations necessary to cause 50% of the laboratory test animals (Fischer 344 male rats) to die either during the exposure (within exposure LC_{50}) or during the exposure plus a 14-d post-exposure observation period (within plus post-exposure LC_{50}). The studies on HCl and HBr were conducted at Southwest Research Institute (SwRI) under a grant from NIST (65). Similar measurements for various combinations of these gases indicated whether the toxicity of the mixtures of gases was additive, synergistic, or antagonistic.

Based on these empirical results, the following six-gas model was developed, where the numbers in brackets indicate the time-integrated average atmospheric concentrations:

$$\frac{m[\mathrm{CO}]}{[\mathrm{CO_2}]-b}+\frac{[\mathrm{HCN}]}{\mathrm{LC_{50}\,HCN}}+\frac{21-[\mathrm{O_2}]}{21-\mathrm{LC_{50}\,O_2}}+\frac{[\mathrm{HCl}]}{\mathrm{LC_{50}\,HCl}}+\frac{[\mathrm{HBr}]}{\mathrm{LC_{50}\,HBr}}=N\text{-gas value} \qquad (1)$$

during a 30-min exposure period [(ppm × min)/min or for O_2 (% × min)/min] (3, 8, 53, 60, 62–64). The other terms are defined in the following paragraphs.

Under the experimental conditions used at NIST and with Fischer 344 male rats, the 30-min LC_{50} value of CO_2 is 47% (470,000 ppm) with 95% confidence limits of 43–51% (56, 57, 59). (*Caution:* The values given for use in Eqs. 1 and 3 are dependent on the test protocol, on the source of test animals, and on the rat strain. It is important to verify the above values whenever different conditions prevail and if necessary, to determine the values that would be applicable under the new conditions.) No deaths occurred in rats exposed to 26% CO_2 for 30 min. In a real fire, the highest theoretically possible concentration of CO_2 is 21%, a concentration that could only occur if all the atmospheric O_2 were converted to CO_2, an event highly improbable. Therefore, CO_2 concentrations generated in fires are not lethal. However, CO_2 is a respiratory stimulant causing an increase in both respiratory rate and tidal volume. It also increases the acidosis of the blood. When combined with any of the other tested gases, CO_2 has a synergistic toxicological effect; that is, the toxicities of the other gases are increased in the presence of CO_2 (Table 108.1). Empirically, however, we found that the effect of the CO_2 can only be added into the *N*-gas equations once. Therefore, we included the CO_2 effect with the CO factor since we had more data on the effect of different concentrations of CO_2 on the toxicity of CO and CO is the toxicant most likely to be present in all fires. The results on the synergistic effect of CO_2 on CO indicated that as the concentration of CO_2 increases (up to 5%), the toxicity of CO increases. Above 5% CO_2, the toxicity of CO starts to revert back towards the toxicity of the CO by itself. The terms *m* and *b* in Eq. 1 define this synergistic interaction and equal –18 and 122,000, respectively, if the CO_2 concentrations are 5% or less. For studies in which the CO_2 concentrations are above 5%, *m* and *b* equal 23 and –38,600, respectively.

Table 108.1. Synergistic Effects of CO_2

	LC_{50} Values[b]	
Gas[a]	Single Gas	With 5% CO_2
CO_2	470,000 ppm	—

CO	6,600 ppm	3,900 ppm
NO_2	200 ppm	90 ppm
O_2	5.4%	6.4%

[a] All gases were mixed in air.

[b] 30-min exposures of Fischer 344 rats; deaths occurred during and following the exposures.

In rats, the 30-min LC_{50} for CO is 6,600 ppm, and with 5% CO_2, this value drops to 3,900 ppm. Exposure to CO in air only produced deaths during the actual exposures and not in the post-exposure observation period; however, exposures to CO plus CO_2 also caused deaths in the post-exposure period. Carbon monoxide is a colorless, odorless, tasteless, and nonirritating poisonous gas. The toxicity of CO comes from its binding to the hemoglobin in red blood cells and the formation of carboxyhemoglobin (COHb). The presence of CO on the hemoglobin molecule prevents the binding of O_2 to hemoglobin (O_2Hb) and results in hypoxia in the exposed individual. Since the binding affinity of hemoglobin for CO is 210 times greater than its affinity for O_2, only 0.1% CO (1000 ppm) is needed to compete equally with O_2, which is normally present at 20.9% in air (20.9%/210 ≈ 0.1%). Thus only 1000 ppm of CO in the atmosphere is enough to generate 50% COHb, a value commonly quoted (but not necessarily proven) as the concentration that is lethal to humans. The time to get to 50% COHb at 1000 ppm CO would be longer than 30 min.

The LC_{50} value of HCN is 200 ppm for 30-min exposures or 150 ppm for 30-min exposures plus the post-exposure observation period. HCN caused deaths both during and following the exposures.

The 30-min LC_{50} of O_2 is 5.4%, which is included in the model by subtracting the combustion atmospheric O_2 concentration from the normal concentration of O_2 in air, that is, 21%. The LC_{50} values of HCl or HBr for 30-min exposures plus post-exposure times are 3,700 and 3,000 ppm, respectively. HCl and HBr at levels found in fires only cause post-exposure effects.

The pure- and mixed-gas studies showed that if the value of Eq. 1 is 1.1 ± 0.2, then some fraction of the test animals would die. Below 0.9, no deaths would be expected, and above 1.3, all the animals would be expected to die. Since the concentration–response curves for animal lethalities from smoke are very steep, it is assumed that if some percentage (not 0 or 100%) of the animals die, the experimental loading is close to the predicted LC_{50} value. Results using this method show good agreement (deaths of some of the animals when the *N*-gas values were above 0.9) and the good predictability of this approach.

This model can be used to predict deaths that will occur only during the fire exposure or deaths during and following the fire. To predict the deaths that would occur both during and following the exposures, Eq. 1 is used as presented. To predict deaths only during the exposures, HCl and HBr, which only have post-exposure effects, should not be included in Eq. 1. In small-scale laboratory tests and full-scale room burns, Eq. 1 was used successfully to predict the deaths during and following exposures to numerous materials (61, 66). In the case of PVC, the model correctly predicted the results as long as the HCl was greater than 1000 ppm; therefore, it is possible that HCl concentrations under 1000 ppm may not have any observable effect on the model even in the post-exposure period. More experiments are necessary to show whether a true toxic threshold for HCl does exist.

Although most of the work at NIST concentrated on deaths during or following 30-min exposures, the LC_{50}s of many of these gases both singly and mixed were determined at times ranging from 1 to 60 min and in all the cases examined, the predictive capability of Eq. 1 holds if the LC_{50}s for the

other times are substituted into the equation.

2 The Seven-Gas Model; Addition of NO_2 to the **N**-Gas Model Nitrogen dioxide is an irritant gas that will cause lachrymation, coughing, respiratory distress, increases in methemoglobin levels, and lung edema (67). Single brief exposures to less than lethal concentrations can cause lung damage, emphysema, or interstitial fibrosis. Low levels have been alleged to increase one's susceptibility to respiratory infections, and aggravate one's reactions to allergens. Impairment of dark adaptation has also been noted. Delayed serious effects can be observed as late as two to three weeks following exposures. In the lungs, NO_2 forms both nitric (HNO_3) and nitrous (HNO_2) acids, which are probably responsible for the damage to the lung cells and connective tissue.

In fires, NO_2 may arise from atmospheric nitrogen fixation, a reaction that is material independent, or from the oxidation of nitrogen from nitrogen-containing materials. To examine the generation of NO_2 from nitrogen fixation, a small study was undertaken at NIST. In two full-scale fires of rooms in which the main source of fuel was polystyrene- covered walls, only low levels of NO_x (10 and 25 ppm, respectively) were found, indicating little nitrogen fixation under these conditions (59). A real example of burning nitrogen-containing materials was the 1929 Cleveland Clinic fire, in which 50,000 nitrocellulose x-ray films were consumed (68). The deaths of 97 people in this fire were attributed mainly to NO_x. An additional 26 people died between 2 h and 1 mo following the fire, and 92 people were treated for nonfatal injuries. In laboratory tests of nitrogen-containing materials under controlled conditions, 1–1000 ppm of NO_x was measured (61, 69–71). In military tests of armored vehicles penetrated by high-temperature ammunition, NO_2 levels above 2000 ppm were found (72).

a Individual and Binary Mixtures In small-scale laboratory tests of NO_2 in air, deaths of Fischer 344 male rats occur only in the post-exposure period, and the LC_{50} value following a 30-min exposure is 200 ppm (59). Carbon dioxide plus NO_2 show synergistic toxicological effects (59). The LC_{50} for NO_2 following a 30-min exposure to NO_2 plus 5% CO_2 is 90 ppm (post-exposure deaths) i.e., the toxicity of NO_2 doubled.

The details of the following research are provided in Ref. 60. As mentioned, CO produces only within-exposure deaths, and its 30-min LC_{50} is 6600 ppm. In the presence of 200 ppm of NO_2, the within-exposure toxicity of CO doubled (i.e., its 30-min LC_{50} became 3300 ppm). An exposure of approximately 3400 ppm CO plus various concentrations of NO_2 showed that the presence of CO would also increase the post-exposure toxicity of NO_2. The 30-min LC_{50} value of NO_2 went from 200 to 150 ppm in the presence of 3400 ppm of CO. A concentration of 3400 ppm of CO was used as that concentration would not be lethal during the exposure, and any post-exposure effects of CO on NO_2 would become evident; the LC_{50} of CO (6600 ppm) would have caused deaths of the animals during the 30-min exposure.

The 30-min LC_{50} of O_2 is 5.4% and the deaths occur primarily during the exposures. In the presence of 200 ppm of NO_2, the within-exposure LC_{50} of O_2 and its toxicity increased to 6.7%. In the case of O_2, increased toxicity is indicated by an increase in the value of the LC_{50}, since it is more toxic to be adversely affected by a concentration of O_2 ordinarily capable of sustaining life. Exposure of the animals to 6.7% O_2 plus various concentrations of NO_2 showed that the NO_2 toxicity doubled (i.e., its LC_{50} value decreased from 200 to 90 ppm).

One of the most interesting findings was the antagonistic toxicological effect noted during the experiments on combinations of HCN and NO_2. As mentioned, the 30-min LC_{50} for NO_2 alone is 200 ppm (post-exposure) and the 30-min within-exposure LC_{50} for HCN alone is also 200 ppm. These concentrations of either gas alone are sufficient to cause death of the animals (i.e., 200 ppm HCN or 200 ppm NO_2 would cause 50% of the animals to die either during the 30-min exposure or following the 30-min exposure, respectively). However, in the presence of 200 ppm of NO_2, the within-exposure HCN LC_{50} concentration increases to 480 ppm, or, stated in other words, the toxicity of HCN decreases by 2.4 times.

The mechanism for this antagonistic effect is believed to be as follows: In the presence of H_2O, NO_2 forms nitric acid (HNO_3) and nitrous acid (HNO_2) (73). These two acids are the most likely suspects responsible for the lung damage leading to the massive pulmonary edema and subsequent deaths noted following exposure to high concentrations of NO_2. Nitrite ion (NO_2^-) formation occurs in the blood when the nitrous acid dissociates. The nitrite ion oxidizes the ferrous ion in oxyhemoglobin to ferric ion to produce methemoglobin (MetHb) (Eq. 2) (74). MetHb is a well-known antidote for CN^- poisoning (75). MetHb binds cyanide-forming cyanmethemoglobin, which keeps the cyanide in the blood and prevents it from entering the cells. In the absence of MetHb, free cyanide will enter the cells, react with cytochrome oxidase, prevent the utilization of O_2, and cause cytotoxic hypoxia. If, on the other hand, cyanide is bound to MetHb in the blood, it will not be exerting its cytotoxic effect. Therefore, the mechanism of the antagonistic effect of NO_2 on the toxicity of cyanide is believed to be due to the conversion of oxyhemoglobin [$O_2Hb(Fe^{2+})$] to methemoglobin [$MetHb(Fe^{3+})$] in the presence of nitrite:

$$2\,H^+ + 3\,NO_2^- + 2\,O_2\,Hb(Fe^{2+}) \Rightarrow 2\,MetHb\,(Fe^{3+}) + 3\,NO_3^- + H_2O \qquad (2)$$

b Tertiary Mixtures of NO_2, CO_2, and HCN Earlier work indicated that the presence of 5% CO_2 with either HCN or NO_2 produced a more toxic environment than would occur with either gas alone (31, 59). The antagonistic effects of NO_2 on HCN indicate that the presence of one LC_{50} concentration of NO_2 (~ 200 ppm) will protect the animals from the toxic effects of HCN during the 30-min exposures, but not from the post-exposure effects of the combined HCN and NO_2. Thus it was of interest to examine combinations of NO_2, CO_2, and HCN (60). In this series of experiments, the concentrations of HCN were varied from almost 2 to 2.7 times its LC_{50} value (200 ppm). The concentrations of NO_2 were approximately equal to one LC_{50} value (200 ppm) if the animals were exposed to NO_2 alone and approximately ½ the LC_{50} (90 ppm) if the animals were exposed to NO_2 plus CO_2; the concentrations of CO_2 were maintained at approximately 5%; and the O_2 levels were kept above 18.9%. The results indicated that CO_2 does not make the situation worse, but rather provided additional protection even during the post-exposure period. In each of six experiments, some or all of the animals lived through the test even though they were exposed to greater than lethal levels of HCN plus lethal levels of NO_2, and in four tests, some of the animals lived through the post-exposure period even though the animals were exposed to combined levels of HCN, NO_2 and CO_2 that would be equivalent to 4.7–5.5 times the lethal concentrations of these gases. One possible reason that CO_2 seems to provide an additional degree of protection is that NO_2 in the presence of 5% CO_2 produces 4 times more MetHb than does NO_2 alone (59).

c Mixtures of CO, CO_2, NO_2, O_2, and HCN The initial design of these experiments was to look for

additivity of the CO/CO_2, HCN, and NO_2 factors keeping each at about $\frac{1}{3}$ of its toxic level, while keeping the O_2 concentration above 19% (60). When these initial experiments produced no deaths, we started to increase the concentrations of CO up to $\frac{1}{3}$ of the LC_{50} of CO alone (6600 ppm), HCN was increased to 1.3 or 1.75 times its LC_{50} depending on whether the within-exposure LC_{50} (200 ppm) or the within- and post-exposure LC_{50} (150 ppm) is being considered, and NO_2 was increased up to a full LC_{50} value (200 ppm). The results indicated that just adding an NO_2 factor (e.g., $[NO_2]/LC_{50}\ NO_2$) to Eq. 1 would not predict the effect on the animals. A new mathematical model was developed and is shown as Eq. 3. In this model, the differences between the within-exposure predictability and the within-exposure and post-exposure predictability is: (1) the LC_{50} value used for HCN is 200 ppm for within-exposure or 150 ppm for within-exposure and post-exposure and (2) the HCl and HBr factors are not used to predict the within-exposure lethality, only the within-exposure and post-exposure lethality. According to Eq. 3, animal deaths will start to occur when the *N*-gas value is above 0.8 and 100% of the animals will die when the value is above 1.3. Results indicated that in those few cases where the values were above 0.8 and no deaths occurred, the animals were severely incapacitated (close to death), as demonstrated by no righting reflex or eye reflex.

The *N*-Gas Model Including NO_2

$$N\text{-gas value} = \frac{m[CO]}{[CO_2]-b} + \frac{21-[O_2]}{21-LC_{50}O_2} + \left(\frac{[HCN]}{LC_{50}\ HCN}\ \frac{0.4[NO_2]}{LC_{50}NO_2}\right) + 0.4\left(\frac{[NO_2]}{LC_{50}NO_2}\right) + \frac{[HCl]}{LC_{50}HCl} + \frac{[HBr}{LC_{50}H} \quad (1)$$

For an explanation of these terms, see the paragraphs following Eq. 1. Eq. 3 should be used to predict the within-exposure plus post-exposure lethal toxicity of mixtures of CO, CO_2, HCN, reduced O_2, NO_2, HCl, and HBr. The LC_{50} values will be the same as those given for Eq. 1 using 150 ppm for HCN and 200 ppm for NO_2. If one wishes to predict the deaths that will occur only during the exposure, the LC_{50} value used for HCN should be 200 ppm, and the HCl and HBr factors should not be included. To predict the lethal toxicity of atmospheres that do not include NO_2, Eq. 1 should be used.

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7 Combustion Toxicity Test Methods
The toxicity of the combustion products from any new material formulation or product containing additives or new combinations of additives needs to be examined. Material and polymer chemists are currently trying to develop new “fire-safe” materials (5). The terms “fire-safe” or “fire resistant” are not the same as noncombustible. Unless these new materials are truly noncombustible, some thermal decomposition will occur when the materials are exposed to fire conditions. Both the toxic gases and the irritants that are present in all smoke need to be considered potential dangers. The toxic products can cause both acute and delayed toxicological effects. It is the acute and extremely short-term effects that prevent escape from burning buildings by causing faulty judgement, incapacitation, and death. The irritants in the smoke can also interfere with one's ability to escape by causing severe coughing and choking and by preventing one from keeping one's eyes open long enough to find the exits. In addition, the delayed effects, such as tissue or organ injury, mutagenicity, carcinogenicity, and teratogenicity need to be studied, since they may ultimately lead to permanent disability and

post-exposure deaths. Some of the issues involved in delayed effects are addressed in a paper by Lewtas (76) and a review by Barfknecht (46). The current advances in the field of genetics provide investigators with new opportunities to examine the effects of combustion products at the molecular level. One objective could be to determine whether these toxic products cause DNA damage and/or mutations. Specific problems of interest include: does the damage occur in nuclear DNA and/or mitochondrial DNA; are certain areas of the DNA more prone to these mutations (i.e., are there hot spots?); can we categorize the types of mutations (e.g., transitions, transversions, deletions, insertions); and how efficient are the repair mechanisms? Are these mutagens also known to be carcinogens?

Toxicity screening tests for both the acute and delayed effects are, therefore, needed to evaluate the combustion products, including any irritants that may be present in newly proposed materials and products. It is imperative that the materials and products be tested under experimental conditions that simulate realistic fire scenarios of concern (e.g., flash-over conditions emanating from, first, smoldering and then, flaming of upholstered furniture in homes or smoldering fires in concealed spaces in aircraft). The ideal tests should be simple, rapid, inexpensive, use the least amount of sample possible (since, in many cases, only small amounts of a new experimental material may be available), use a minimum number of test animals, and have a definitive toxicological endpoint for comparison of the multiple candidates.

While faulty judgement and incapacitation are significant causes of worry since they can prevent escape and cause death, they are extremely difficult and complex endpoints to define and measure in nonhuman test subjects. Death of experimental animals (e.g., rats), on the other hand, is a more definitive and easily determined endpoint and can be used to compare the relative toxicities of alternate materials deemed suitable for the same purpose. The assumption made here is that if the combustion products of material *X* are significantly more lethal than those of material *Y*, the combustion products of *X* would probably cause more incapacitation and more impairment of judgment than *Y* as well. The number of experimental animals can be significantly reduced by utilizing one of the predictive mathematical models developed for combustion toxicology such as the *N*-gas models previously discussed in this chapter.

Many test methods for the determination of the acute toxicity of combustion products from materials and products have been developed over the past two decades and continue to be developed and/or improved (52). In 1983, thirteen of the methods published up to that time were evaluated by Arthur D. Little, Inc., to assess the feasibility of incorporating combustion toxicity requirements for building materials and finishes into the building codes of New York State (77). On the basis of seven different criteria, only two methods were found acceptable. These two methods were the flowthrough smoke toxicity method developed at the University of Pittsburgh (43, 54, 78) and the closed-system cup furnace smoke toxicity method developed at NIST [known at that time as the National Bureau of Standards (NBS)] (32, 53). In 1991 and 1992, Standard Reference Materials were developed at NIST and made available to the users of these methods to provide assurance that they are performing the methods correctly (53, 54). Based on the results of the Arthur D. Little report, the state of New York under Article 15, Part 1120 of the New York State Fire Prevention and Building Code decided to require that building materials and finishes be examined by the method developed at the University of Pittsburgh and that the results be filed with the state (79). It is important to note, however, that although the results are filed, the state of New York does not regulate any materials or products based on the results of this or any other toxicity test at this time.

Since 1983, a number of new approaches to assess acute combustion toxicity have been examined. These approaches include a radiant furnace smoke toxicity protocol developed by NIST and SwRI (61, 80–82), the University of Pittsburgh II radiant furnace method (83–85), and the National Institute of Building Sciences (NIBS) toxic hazard test method (86, 87). All three use radiant heat to decompose materials.

The NIST radiant test and the NIBS toxic hazard test use the same apparatus, consisting of three

components: a radiant furnace, a chemical analysis system, and an animal exposure chamber. The chemical analysis system, and animal exposure system are identical to that developed for the NBS cup furnace smoke toxicity method. Although the apparatus of both methods are essentially the same, they have different toxicological endpoints. In the NIST method, an approximate LC_{50}, based on the *mass* of material needed to cause lethality in 50% of the test animals during a 30-min exposure and/or a 14-day post-exposure period, is the determinant of toxicity. The number of animals needed to run the test is substantially reduced by first estimating the LC_{50} by the *N*-gas model and analytical tests without animals. This estimate is then verified with one or two animal tests to assure that no unforeseen gas was generated. The toxicological endpoint of the NIBS toxic hazard test is the IT_{50}, the irradiation *time* (the time that the material is exposed to the radiant heat) that is required to kill 50% of the animals during a 30-min exposure or 14-d post-exposure time. The actual results of the NIBS test with 20 materials indicated that the test animals died in very short periods of time (personal communication) and the test was unable to discriminate very well between materials. These results substantiate the thesis that mass (the smaller the mass necessary for an LC_{50}, the more toxic the material) is a better indicator of acute toxicity than time.

Both the NIST and NIBS test procedures are designed to simulate a post-flashover scenario. The premise for simulating a post-flashover fire is that most people that die from inhalation of toxic gases in *residential* fires are affected in areas away from the room of fire origin. Smoke and toxic gases are more likely to reach these distant areas following flashover. This scenario may not be relevant in certain circumstances (e.g., aircraft interior fires, where a smoldering fire in a concealed space may cause significant problems if the plane is over a large body of water and unable to land for a considerable period of time).

The NIST radiant test has been accepted by the American Society for Testing and Materials (ASTM) as a national standard designated ASTM E1678 and entitled “Standard Test Method for Measuring Smoke Toxicity for Use in Fire Hazard Analysis” (62). The National Fire Protection Association (NFPA) has also adopted the NIST Radiant Test Method as a national standard called “Standard Test Method for Developing Toxic Potency Data for Use in Fire Hazard Modeling,” NFPA 269 (63). In 1995, the International Standards Organization, Technical Committee 92, Subcommittee 3 (ISO/TC92/SC3) on Toxic Hazards in Fire published an international standard for combustion toxicity after approval by 16 countries (64). This standard—ISO/IS 13344, entitled “Determination of the Lethal Toxic Potency of Fire Effluents”—describes the mathematical models (including the *N*-gas model) available for predicting the toxic potency of fire atmospheres based on the toxicological interactions of the main combustion gases present. In the international standard, investigators have the flexibility of designing or choosing a system that will simulate conditions relevant to their fire scenario, rather than having to accept a designated combustion system.

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8 Toxicant Suppressants

Fire scientists are very familiar with fire-retardant chemicals, which are defined by ASTM as “Chemicals, which when added to a combustible material, delay ignition and combustion of the resulting material when exposed to fire” (2). The discussion adds “A fire-retardant chemical can be a part of the molecular structure, an admixture or an impregnant.” The term *toxicant suppressant*, however, is a new expression arising from research at NIST that demonstrated that the addition of copper compounds to flexible polyurethane foam (FPU) significantly reduced the generation of hydrogen cyanide (HCN) as well as the toxicity of the combustion products when the foam was thermally decomposed (88–92). These experiments were designed to simulate the nonflaming and

then flaming stages of a chair ignited by a cigarette (a two-phase heating system which simulates the fire scenario that results in the most fire deaths in the U.S.) (93). The term toxicant suppressant may be defined as a chemical that when added to a combustible material significantly reduces or prevents one or more toxic gases from being generated when that material undergoes thermal decomposition. The resultant gas effluent should be less toxic than that from the untreated material; that is, the toxic gas whose concentration is being reduced should not be converted to an equally or more toxic product.

The results of these studies at NIST indicated that:

1. Hydrogen cyanide concentrations in the thermal decomposition products from a flexible polyurethane foam were reduced approximately 85% when the foam was treated with 0.1% or 1.0% Cu_2O and thermally decomposed via a two-phase heating system in the cup furnace smoke toxicity apparatus.
2. The copper or copper compounds could be added to the foams during or after the foams were formulated and still be operative in reducing the toxicity and HCN yield. (The BASF Corporation prepared the foams that had the Cu powder and Cu_2O added during formulation.) The addition of the copper or copper compounds during formulation did not affect the foaming process or the physical appearance on the foams except for a slight change of color.
3. Low levels of the copper compounds were effective. In particular, when cupric oxide (CuO) was used, the concentration of copper needed was only 0.08% by weight and when cuprous oxide (Cu_2O) was used, only 0.07% by weight was needed to significantly reduce the generation of HCN.
4. Full-scale room burns indicated that the presence of Cu_2O in the FPU reduced the HCN generation by approximately 50–70% when the experimental plan was designed to simulate a realistic scenario (the foams contained 1.0% Cu_2O, were covered with a cotton upholstery fabric and arranged to simulate a chair; smoldering was initiated with cigarettes, and flaming occurred spontaneously).
5. Under small-scale conditions, less than 3 ppm of NO_x was generated from the un-treated foams, whereas a range of 3–33 ppm of NO_x was measured from the 0.1–1.0% Cu_2O-treated foams. About 6% of the HCN appeared to be converted to NO_x. In the full-scale room tests, approximately 23% of the HCN appeared to be converted to NO_x. Since we have shown in our laboratory that NO_2 acts as an antagonist to HCN, this amount of NO_x may also act to counteract the immediate toxic effects of any residual HCN.
6. Since the atmospheric oxygen (O_2) concentrations can reach very low levels in real fires, it was important to know if the reduction of HCN by copper would occur under low O_2 conditions. Small-scale tests with the ambient O_2 concentrations as low as 6% indicated that the HCN levels were reduced by as much as 82% when the FPU was treated with 0.1% Cu_2O.
7. The toxicity of the gas effluent was also reduced (an indication that the HCN was not being converted into some compound that was even more toxic). Fewer animal (Fischer 344 rats) deaths occurred during the 30-min exposures to the FPU treated with the copper and copper compounds compared to the untreated FPU. Toxicity based on LC_{50} values was reduced 40–70% in the small-scale tests with 0.1% Cu_2O-treated foams. The blood cyanide levels in the animals exposed to combustion products from the CuO-treated foams for 30 min were ½ to ¼ those measured in the animals exposed to the smoke from the same amount of untreated foam.
8. Post-exposure deaths were also reduced in the animals exposed to the combustion products from the Cu and Cu_2O-treated FPU foams in the small-scale tests. These delayed post-exposure deaths have not been observed in animals exposed to combustion products from flexible

polyurethane foams decomposed in large-scale room fire tests. The specific cause of these post-exposure deaths is not known.

9. No differences in flammability characteristics between the 0.1% Cu_2O-treated and untreated FPU foam were observed. These characteristics were examined to assure that the positive effect on toxicity was not contradicted by negative effects on the flammability properties. The flammability characteristics examined were: (a) ignitability in three systems [the cup furnace smoke toxicity method, the cone calorimeter, and lateral ignition and flame spread test (LIFT)], (b) heat release rates under small-scale (cone calorimeter) and medium-scale (furniture calorimeter) conditions, (c) heats of combustion under small-scale (cone calorimeter) and medium-scale (furniture calorimeter) conditions, (d) CO/CO_2 ratios under small-scale (cone calorimeter) and medium-scale (furniture calorimeter) conditions, (e) smoke obscuration (cone calorimeter), and (f) rate of flame spread (LIFT).
10. Research conducted at the BASF Corporation indicated that the physical properties of the 1.0% Cu_2O-treated FPU were not significantly different from the comparable untreated FPU. The physical properties examined were tensile strength, elongation, tear strength, resilience, indentation force deflection, support factor, compression sets, and air flow.
11. The use of melamine-treated FPU is becoming more common (94, 95); it is one of two FPU foams currently allowed in Great Britain. Small-scale tests indicated that a melamine-treated FPU generated 6 times more HCN than an equal amount of a non-melamine-treated foam. The presence of Cu_2O reduced the HCN from the melamine foam by 90%.

Jellinek and co-workers in the late 1970s also showed that the concentrations of HCN generated from the thermal decomposition of a polyurethane at 300 and 400°C decreased when flowed through copper compounds (96, 97). In their studies, the polyurethane films were very thin (15 mm thick and 50 mg in weight). In some experiments, the metal powder was mixed with the polymer and, in others, copper metal films of 400 to 1000 Å were deposited on top of the polymer films. In most cases, the percent of copper was 10% or greater. The lowest concentration that they tested was a 2.6% copper film, which inhibited the evolution of HCN by 66%. Their experiments indicated that the copper is probably acting as an oxidative catalyst, which would decompose gaseous HCN into N_2, CO_2, H_2O, and small amounts of nitrogen oxides. Further research is needed to determine if this is the actual molecular mechanism that allows copper to act as an HCN toxicant suppressant.

Levin and her co-workers' research differed from that of Jellinek in that much larger samples of FPU (including full-scale room burns of cushions and simulated chairs), much smaller concentrations of copper were used, and the toxicity of the combustion products from the copper-treated FPU was also examined.

Unpublished data of Levin also indicated that a wool fabric treated with copper would generate 50% less HCN than the untreated fabric. These results demonstrate a potentially more universal effect, namely, that treating nitrogen-containing materials with copper compounds will probably reduce the HCN generated when that material is exposed to fire conditions. Taking these results one step further, one could develop other toxicant suppressants that when added to materials and products would now prevent or significantly reduce the toxic effluents that are generated when they are thermally decomposed.

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9 Conclusions

The field of toxicology of combustion products has come a long way since the early 1970s, when the National Commission on Fire Prevention and Control submitted their report entitled "America Burning" to President Nixon (98). That report, which included the statement that "Appallingly, the richest and most technologically advanced nation in the world leads all the major industrialized countries in per capita deaths and property loss from fire," provided the impetus to determine the cause of and to try to solve this major problem being experienced by the United States. It was shortly thereafter that Petajan et al. published their paper in *Science* entitled "Extreme Toxicity from Combustion Products of a Fire-Retarded Polyurethane Foam" (13) and raised the specter of "supertoxicants" emanating from combustion atmospheres. In the following years, the field of combustion toxicology expanded greatly, and many materials and products were tested by various test methods. With the exception of the material described in the Petajan et al. paper and one other product described in Section 3, the concern about "Supertoxicants" has proven to be largely unfounded. However, the potential that the combustion products from new formulations or combinations of compounds may prove to be extremely or unusually toxic has encouraged manufacturers to test their new products. The state requirements of New York has also been a motivating force for manufacturers to test the building products they wish to sell in New York (79). This testing may have prevented dangerous products from reaching the marketplace.

After reaching a peak in the 1980s, the amount of research in the area of combustion toxicology has declined significantly. With the exception of some military laboratories, very few laboratories are still doing this type of research. The Building and Fire Research Laboratory at the National Institute of Standards and Technology, where much of the research quoted in this chapter was conducted, abolished its combustion toxicology research program in 1992. Some of the areas that remain to be examined include: the effects of the addition of more gases and heat to the *N*-gas model; the effects of particulates alone and in combination with the *N*-gases; the effects of chronic exposures to fire atmospheres (e.g., those experienced by fire fighters); sublethal effects on the neurological and other organ systems; mutagenic, teratogenic, and carcinogenic effects of acute and chronic exposures; the development of improved therapeutic methods for the treatment of smoke (including particulates) inhalation victims; and additional research on toxicant suppressants with the ultimate aim of developing fire-safe materials (i.e., materials that do not produce toxic gases even when they are thermally decomposed). Since 80% of fire deaths are the result of smoke inhalation, a less toxic smoke could significantly increase the time available for escape and reduce the number of injuries and deaths from fire.

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Notes
Certain commercial equipment, instruments, materials, or companies are identified in this chapter to specify adequately the experimental procedure. Such identification does not imply recommendation or endorsement by the author, nor does it imply that the materials or equipment identified are the best available for the purpose.

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Chemical and Physical Agent Interaction

Per Nylén, Ph.D., Ann-Christin Johnson, Anders Englund, MD

1 Introduction

This chapter, concerning interactions at simultaneous or successive exposure to both physical and chemical factors, focuses on the industrial environment. Examples of this kind of interaction can probably be found in a large variety of totally different and unrelated areas, and the present text is not intended to be a complete review but to present illustrative examples of studies and occupational areas in which such interactions are included. Reported findings are of both physicochemical and biological nature, most often descriptive observations, and referred papers rarely include mechanistic information or hypotheses. Exposure levels are often higher than those found at today's work sites, and the possibility of using data for making reasonable, adequate extrapolations often remains unknown. Despite these limitations, it is the main intentions of the present text to inform and alert occupational health practitioners and other interested readers about what attempts have been made so far to gain knowledge about the situation in the vast majority of work sites, specifically, combined exposure to both at least one physical agent and one chemical agent.

The presentation is ordered using the respective physical factors as subtitles under which published data concerning the particular factor's interaction with different chemicals are presented. Physical factors presented are mechanical factors such as sound waves (most often referred to as “noise”) and vibrations; the thermal factors heat and cold, electrostatic fields; and electromagnetic radiation from low frequency fields, radio frequencies, visible light, ultraviolet light, to ionizing radiation. Since many of these physical factors most naturally interacts with sensory functions, the text often focuses on interactions seen as sensory and nervous system alterations in both animals and humans.

Exposures to physical factors and chemicals that are not primarily related to occupational exposure, for example, the multitude of drugs that can interact with sunlight, are considered as being a general toxicological problem rather than a specific occupational toxicological issue. Readers interested in such interactions are therefore referred to the pharmacological literature.

1.1 Frequency of Mixed Exposure to Physical and Chemical Factors

It has been estimated that the number of chemical agents frequently used occupationally is of the magnitude of 10^4 (1). If the number of physical factors of significant occupational importance is ~10, the number of possible combined exposures to both a physical and a chemical agent is approximately 10^5. Furthermore, occupational exposure to industrial chemicals is in itself most often multiple (2–4); that is, workers are exposed to two or more chemicals simultaneously, or with a short delay between the individual exposures. In one study (5) it was found that many car and industrial painters were exposed daily to 10 different solvents, and weekly to about 20 solvents. Adding known exposure to physical factors in this occupation such as light, noise, vibrations, and heat makes the

number of possible interactions between chemical and physical agents huge in this group, and most certainly in many other groups of workers.

Almost by definition, all occupational exposures to chemicals also include exposure to at least one physical agent, such as visible light, noise, vibration, and heat. It may be argued that studying specific combinations is of limited use for risk assessment since the number of physical and chemical agents present and used occupationally is so large. Some combinations of physical and chemical agents occur more frequently than others, because of the use of commercial products containing fixed chemical mixtures. The number of agents is nevertheless so large that toxicological testing of all combinations individually seems unrealistic. This fact has contributed to an interest in models for general risk approximation at combined exposure.

1.2 Frequency of Nonadditive Interactions

Within the area of developmental toxicology, interactive effects have been studied after concurrent exposures to a variety of chemical and physical agents, including therapeutic drugs, industrial agents, and some biological organisms or their toxins. Of approximately 160 reports of concurrent exposures reviewed (6), about one-third report no interactive effects (including additive effects, usually referring to response as opposed to dose additivity); another third report antagonistic effects, and the final third report potentiating or synergistic effects. It was, however, pointed out that the quality of the studies and the used terminology were highly variable.

In a review of approximately 600 studies concerning combined exposure to different chemicals, synergistic interactions were also reported in about 30% of the studies (7). Antagonistic effects were also reported in about 30%, which made nonadditive interactions in total more common than additive ones.

The terminology used to describe additive or nonadditive outcomes in the information presented is not consistent. The lack of unified terminology is general within the research area, but promising initiatives have been taken (8). In referred papers, the statistical procedures are sometimes undefined as well as the use of interaction descriptors such as *synergistic, hyperadditivity*, and *enhancement of risk*. These missing pieces of information do not, however, motivate a total rejection of the reported findings. Even if the degree of synergism, for instance, were not exactly and reliably quantified, the fact that a more-or-less pronounced synergistic interaction probably was observed would be of great interest to both practitioners and researchers who deal with combined exposure interactions.

1.3 Methods for Risk Assessment of Combined Exposures in Risk Management

1.3.1 Mixtures Including Chemical Agents Only In the United Kingdom (9), the United States (10), and Sweden, for instance, proposed procedures for occupational risk assessment of exposure to mixtures of chemicals include calculation of a hazard index (HI).

$$HI = \frac{E_1}{L_1} + \frac{E_2}{L_2} + \cdots + \frac{E_i}{L_i} \qquad (1)$$

where E_i = exposure level to the toxicant L_i = occupational exposure limit value level for the toxicant.

If HI is below 1.0, the combined exposure is considered acceptable, thus a person exposed to the contaminants is regarded as protected against ill health. Use of this model includes an assumption that the chemicals act on the same organ system. If the included chemicals have different toxic endpoints, and there is no evidence of toxic interaction, it has been suggested that the guidelines for a single exposure may provide acceptable protection also at mixed exposure (2, 11). If it is not known whether the substances in the combination have different modes of action, it has been suggested that the combined effect should be assumed to be additive, since the allowed level of the combined exposure will then be lower than if independence is assumed (1).

Equation (1) should be used with some limitations kept in mind. It does not predict nonadditive

interactions, even if the possibility of such interactions is sometimes commented upon in regulatory texts. Further, the dose–response functions of the individual agents or the mixtures may not be linear.

Mixed exposure is, in addition, also more difficult to define qualitatively and quantitatively than individual exposures, which increases the uncertaninty of its effects. Finally, only substances given an occupational exposure limit value can be included in the HI calculation. The applicability of the HI equation is thus limited, which leaves a number of common combined exposures without guidelines.

1.3.2 Mixtures Containing both Physical and Chemical Agents No consensus exists concerning risk assessment of occupational exposures that include both chemicals and physical agents, such as noise or light. An attempt including similarities with equation (1) concerning exposure to toluene and noise has been presented by the Danish Institute of Occupational Health. To calculate the contribution of noise using equation (2), using the logarithmic unit dB, the measured sound pressure should be normalized, that is, a doubled sound pressure should have the same impact as a doubled concentration:

$$L_h = C_0/C_{lv} + \frac{10^{n_0/10}}{10^{n_{lv}/10}} \qquad (2)$$

where C_0 = actual concentration of solvent C_{lv} = occupational exposure limit value of solvent n_0 = actual level (dB) of noise n_{lv} = occupational exposure limit value of noise (often 85 dB)

A consideration of the complexity of the different variables that can influence possible interactions at combined exposure has led the “commission for the investigation of health hazards of chemical compounds in the work area” in Germany to conclude that occupational exposure limit values for mixtures cannot be satisfactorily ascertained by simple calculations, but can be assigned only as an estimate after specific toxicological considerations or examination of the mixture in question (12).
1.4 A Gap in Knowledge
The number of physical–chemical agent combinations on which interaction data are available is minute, compared to the total number of occupationally relevant combined exposures. No method with reliable precision for general risk assessment is available, despite the fact that such combined exposures probably represent the large majority of occupational exposures. Mechanistic models are rare. In a review on interaction between low level radiation and other environmental agents (13), several proposed mechanisms are presented. Multistep mechanisms are pointed out as theoretically the most critical interactions. Here, two or more agents can promote different necessary steps, needed for the toxic effect(s), that at single exposure have low probability of simultaneous occurrence.

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2 Noise
2.1 Interactions between Noise and Chemical Agents: Effects on Hearing
2.1.1 Noise-Induced Hearing Loss The most prominent effect of noise exposure is hearing loss in humans and experimental animals, but several factors such as age, heredity, and exposure to ototoxic substances may influence the degree of hearing loss. The hearing loss caused by noise can thus be potentiated or summated to the effects caused by exposure to chemical agents. Much interest has focused on the combined exposure to noise and various ototoxic agents.

The degree of damage from noise exposure depends on the characteristics of the noise, such as the intensity, duration, and frequency of the exposure. In experimental animals, species differences are found. Several different temporary or permanent impairments to the auditory system have been demonstrated after excessive exposure to noise. Direct mechanical destruction, metabolic exhaustion followed by oxidative stress in the cochlear hair cells, and changes in the cochlear vascular system have been postulated as important etiological factors for noise-induced damage (14, 15). Permanent hearing loss after noise exposure is associated with damage to the hair-cell stereocilia, as shown on fusion and fracture of inner hair cell (IHC) stereocilia in rabbits (16). The outer hair cells (OHCs) may also be damaged or lost (16, 17). The degree of damage after noise exposure is often correlated to noise level and exposure time. However, influence of internal as well as external factors can modulate the degree of damage caused by a certain noise exposure. New knowledge has shown that the efferent system in the brainstem modulates the mechanical response of the organ of Corti in the inner ear. The inner ear can by this mechanism be protected from noise induced hearing loss (18, 19). Thus also blocking of efferent control may cause an indirect potentiation of noise-induced hearing loss since the modulation can be disturbed, as has been shown in guinea pigs given strychnine, which inhibits the efferent control (20).

2.1.2 Combined Exposure to Noise and Ototoxic Drugs Many commonly used drugs are known to be ototoxic, some causing reversible, but most causing irreversible, hearing loss. The ototoxic drugs are found among many different categories of drugs. The interaction between noise and drugs might be of interest for the mechanistic understanding of effects after occupational exposure to noise and chemicals even if some, but not all, drugs are mainly used in hospitals.

2.1.2.1 Acetyl Salicylic Acid and Other Nonsteroidal Anti-inflammatory Drugs Acetyl salicylic acid (ASA) is one of the most commonly used nonprescription drugs; therefore, this is the drug that should have the highest interest concerning interaction with occupational noise exposure since it is often used by the working population at work. ASA and other salicylates cause a reversible hearing loss of 20–40 dB often associated with tinnitus after acute intoxication and long-term administration. The hearing returns to normal within 24–72 h after cessation of the drug intake. The mechanism for the ototoxicity may be related to biochemical and subsequent electrophysiological changes in the inner ear. Localized drug accumulation and vasoconstriction in the inner ear have been suggested to be mediated by the antiprostaglandin activity of these drugs (21).

The issue as to whether combined exposure to ASA and noise can cause a more severe hearing loss than the single exposures is, however, a subject of discussion. The results from several investigations are not consistent. In humans, increased temporary threshold shifts (TTSs) were shown after combined exposure (22, 23), whereas another study failed to produce a higher TTS (24). Different doses were used in these studies, and the temporary interaction possibly occurs only after high doses of ASA (> 1–2 g/day). An additive effect of noise and ASA on the TTS is supported by the results of a study in chinchillas (25). Permanent threshold shift was not found in other similar experiments (26, 27). In guinea pigs an existing noise-induced damage attenuated the additional ototoxicity of salicylate, whereas attenuation did not occur when salicylate administration preceded noise exposure (28). In rats, a more extensive hair-cell loss was found after combined exposure to high doses of both agents than after the noise exposure alone (29). When taking all these studies into account, it is not possible to conclude whether a permanent synergistic interaction between noise and ASA exists. If it does, it is probably not pronounced.

2.1.2.2 Aminoglycoside Antibiotics These antibiotics are among the most well known and thoroughly investigated ototoxic substances. They should be used only in case of life-threatening infections mainly because of their toxicity. Aminoglycosides cause a high frequency hearing loss followed by loss of outer hair cells starting with the inner row in the basal turn of the cochlea, continuing with the second and third rows and spreading up through the cochlea, also involving lower frequencies. The hair-cell loss causes a loss of auditory sensitivity of ~40 dB (30). The hair cells of the cochlea accumulate aminoglycosides, and noise exposure has been shown to increase the uptake of the drug into the cells (31).

Interactions between noise and aminoglycoside antibiotics, resulting in enhanced auditory thresholds as well as increased hair-cell loss, have been demonstrated in several animal experiments as well as in humans (27, 32–34).

2.1.2.3 Anti cancer Drugs Another drug that causes irreversible hearing loss in humans and experimental animals is the cytostatic agent *cis*-platinum. This drug is used as a chemotherapuetic agent in treatment of cancer, in the lungs, testis, and ovaries. A loss of outer hair cells starting at the basal turn of the cochlea has been shown. Both additive and synergistic effect on the threshold shift have been reported in chinchillas simultaneously exposed to cisplatin and noise (27, 34, 35). Other chemotherapeutic agents, such as carboplatinum, have also been shown to be ototoxic, and suggestions of interactions with noise have been proposed (27, 34, 36, 37). The mechanism for *cis*-platinum ototoxicity has been suggested to result from oxidative stress in the inner ear (12).

Interactive effects on hearing have also been shown between *cis*-platinum and another physical factor—irradiation treatment in cancer patients (38, 39).

2.1.2.4 Other Drugs Interactions after combined exposure to loop diuretics and noise have not demonstrated a clear difference between the effect caused by noise alone and that induced by the combined exposure (33, 34). The mechanism for the ototoxic effect of diuretics is mainly through alterations in the stria vascularis in the cochlea. Also, antimalarial drugs and other antibiotics than the aminoglycosides have shown some ototoxicity (27, 34, 36) that might interact with noise exposure.

2.1.3 Combined Exposure to Noise and Other Chemicals 2.1.3.1 Solvents and Noise 2.1.3.1.1 Ototoxicity of Solvents The ototoxicity of solvents was first discovered by Pryor et al. (40–42), who conducted neurobehavioural studies in rats and found a frequency-specific hearing loss after exposure to toluene. Several other animal studies have further investigated the otoxicity of solvents. Currently certain solvents such as toluene, xylene, styrene, trichloroethylene, ethylbenzene, and *n*-heptane have been shown to be ototoxic in rats. The ototoxicity consists of a midfrequency loss of OHCs. The loss starts in the mid to basal cochlea at the third row of OHCs and progresses along the frequencies subsequently affecting all rows of outer hair cells (43–48). The mechanism of toluene ototoxicity has been investigated by using isolated outer hair cells *in vitro*. A dose-response relationship was observed in the extent of OHC shortening induced by toluene, and toluene also enhanced free intracellular calcium levels of both OHCs and spiral ganglion cells within 5 min of exposure (49, 50).

After the initial animal studies, reports from occupational exposure of solvents causing hearing loss began to appear in the literature. Studies of occupational exposure to solvent mixtures have reported different kinds of alterations in the auditory system. In some studies on workers exposed to aliphatic and aromatic solvents, abnormalities in interrupted speech discrimination and cortical response audiometry tests that assess more central portions of the auditory pathways, were observed. Indications of a dose response relationship were also found, as well as affected vestibular function (51–53).

Trichloroethylene exposure can cause hearing deficiency in humans as shown by audiometric measurements in workers exposed 1–23 years (54). In these workers the vestibular system was also affected as shown by nystagmography.

Rotogravure printers chronically exposed to toluene, without any hearing loss as shown by audiometry, have shown alterations in the latencies in auditory brainstem recordings measured as effects of repetition rate (55).

Styrene exposure often occurs as a single solvent exposure in the plastics industry, and these workers have been investigated in several studies. Effects on cortical responses from the auditory system

were found together with vestibular disturbances in workers exposed to styrene in a boat-building shop in Sweden (56). Muijser et al. (57), used high frequency tone audiometry (≤ 20 kHz) to determine the frequency-specific effect of styrene-exposed workers, and a difference in hearing threshold was demonstrated between directly and indirectly exposed workers at 8 kHz, but not at higher frequencies. This finding is interesting in view of the above mentioned reports of midfrequency loss in animal experiments (43, 44, 46, 47).

2.1.3.1.2 Combined Exposure to Solvents and Noise 2.1.3.1.2.1 Animal Experiments In animal experiments, the interaction between solvents and noise was first reported by Johnson et al. (58, 59) who exposed rats sequentially to toluene and noise. This combination caused a more severe loss of auditory sensitivity than did toluene alone or noise alone. At some frequencies, a potentiation was found when the toluene exposure preceded the noise exposure, while the reversed exposure order resulted in only an additive effect. In more recent experiments, Lataye and Campo (44, 45) exposed adult rats to toluene and noise and to styrene and noise simultaneously. These studies confirm the interaction between toluene and noise on auditory brainstem response thresholds as well as showing a similar or worse synergistic interaction between styrene and noise. The studies also add new morphological data. The rats mono-exposed to toluene or styrene showed loss of OHCs (predominantly in the third row). In contrast, the noise-exposed rats showed damaged stereocilia of OHCs but no cell loss. The combined exposure group the OHC loss was further enhanced, implicating an interacting effect. No interaction between styrene and noise was found in guinea pigs after acute exposure to styrene (7 h) and noise (60), a negative finding that could be due to the short solvent exposure or a species difference.

2.1.3.1.2.2 Human Studies In work environments where solvent exposure occurs, a high level of noise exposure is also common. A critical aspect of solvent ototoxicity, therefore, is the possible interaction with noise. The combined effects of solvents and noise have thus been investigated also in work environments. In shipyard painters a higher degree of hearing loss than could be expected from the noise exposure alone was found (61). In a paper mill factory the most severe cases of hearing loss were seen among solvent-exposed workers from the chemical department, in which the noise exposure was lower than in other studied parts of the factory (62).

In 1990, Bielski (63) found an increased prevalence of hearing disorders in workers exposed to noise and a mixture of solvents that included toluene, benzene, styrene, xylene, and butyl acetate.

Audiometric measurements were conducted on workers exposed to carbon disulfide and noise in a viscose rayon factory (64). A high proportion of hearing losses that could be related to the work environment was determined in all age groups (60% of the workers). There was also a correlation between exposure time and degree of hearing loss.

In a cross-sectional occupational study of exposure to solvents and noise, four groups of workers in a printing plant were tested audiometrically. Workers exposed to noise [88–98 dB(A)] and toluene (100–365 ppm) were compared to groups of workers exposed solely to noise 88–97 dB(A), or workers exposed to a mixture of solvents in which toluene was the major component. A fourth group served as controls. The adjusted relative risk estimates for hearing loss were 4 times higher [95% confidence interval (95% CI) 1.4–12.2] for the noise group, 5 times higher (95% CI 1.4–17.5) for the solvent-mixture group, and 11 times higher (95% CI 4.1–28.9) for the noise and toluene group. These findings strongly suggest that an interaction between noise and toluene took place. The results from the acoustic reflex findings suggest a non-cochlear site of the lesion. A peripheral component of the observed hearing loss was, however, not excluded (65).

In a later study, Morata et al. investigated the hearing in petroleum workers exposed to noise and solvent mixtures. The exposures for both noise and solvents where within the exposure limits. The prevalence of hearing loss in exposed workers exceeded the prevalence in unexposed controls. The adjusted odds ratios (ORs) varied between 1.8 and 3.0 in the different departments compared to unexposed controls (66). In another study among rotogravure printing workers, a significant

association was found between the biological marker of toluene in urine and the degree of hearing loss (67). In this study no interaction with noise was found; only toluene exposure showed the association with hearing loss.

Jacobsen et al. (68) studied the relationship between occupational exposure to solvents and self-assessed hearing problems in a cross-sectional study of 3284 Danish men aged 53–74 years. The adjusted relative risk for hearing impairment after exposure to mixed solvents for ≥ 5 years was 1.4 (95% CI 1.1–1.9) in men without occupational exposure to noise. In men exposed to both solvents and noise, the effect of the noise effect dominated and no synergistic or additive effect could be demonstrated.

Combined exposure to styrene and noise was investigated in workers exposed to a mixture of polystyrene resin, methanol, and methyl acetate at levels below threshold limit values (69). Findings were analyzed as the percentage of subjects falling outside the 90th percentile of the upper limit of hearing. The percentages were 8.7 for the control group, 12.1 for the noise-exposed group, and 33.3 for the solvents and noise-exposed group. In the combined exposure group, styrene was the only solvent likely to be ototoxic. However, the combination of any of the solvents, or noise and solvents, could have played an important role in causing this effect. A more recent study explored the relationship between hearing loss, age, and exposures to noise and styrene (70). The exposures were assessed for 299 workers in the glass-reinforced plastics industry in Canada. No consistent relationship was found between cumulative noise or styrene exposure and audiometric thresholds. Age, however, showed a strong association even after an exclusion of individuals over 50, and a positive correlation with age and both cumulative exposures was noted. Age as a possible confounder may be a problem in studies of occupational hearing loss, and treatment of the age factor in the analysis of the outcome of these studies may be handled in different ways (71).

In summary, most of these reports and studies strongly indicate that chemicals, in different ways, can interact with noise to cause hearing loss.

2.1.3.2 Carbon Monoxide and Noise Carbon monoxide (CO) in high concentrations has ototoxic effects in humans and experimental animals (72). The mechanism is postulated to be an impairment of the normal oxidative metabolism in the inner ear. Later findings suggest involvement of free radical generation since the effect of CO is blocked by free-radical blockers (73). Combined exposure of rats to CO and noise showed a synergistic effect on auditory thresholds that was also confirmed by exaggerated loss of outer hair cells in rats exposed to the combination (74). Short-term exposure to a combination of impulse noise and CO (3 h) in guinea pigs showed no interaction between the exposures. This can be interpreted as a counteracting effect in the cochlear blood flow, which was reduced by impulse noise and increased by CO (75). In a big hearing conservation program in Germany, a subgroup of workers exposed to ototoxic factors such as carbon monoxide, lead, and carbon disulfide suffered from a slightly higher risk of hearing loss (odds ratio 1.5) (76). In a human experimental study, the amount of noise needed to produce a temporary threshold shift (TTS) was not altered at simultaneous exposure to 200 ppm CO (77).

2.1.3.2.1 Smoking and Noise The interaction between noise and CO is of interest when studying noise-induced hearing loss and smoking. Several studies have reported that heavy smoking interacts synergistically with noise, thus causing a more severe hearing loss in humans (78–80).

2.1.3.3 Metals and Noise 2.1.3.3.1 Lead Lead has been proposed to cause hearing loss especially in children with high blood levels of lead (81–83). However, in later studies of children in remote areas with really high blood levels of lead no effect on hearing thresholds or auditory brainstem responses were found (84, 85). No interaction with noise has been reported in these studies. Forst et al. (86) found a relationship between blood lead levels and the hearing threshold at 4 kHz in workers. Even if no excessive noise exposure were present, the effect at 4 kHz might implicate an interaction since this frequency is the one most commonly associated with noise-induced hearing loss.

2.1.3.3.2 Manganese Effects on hearing and the vestibular system have been seen after occupational exposure to manganese. Hearing thresholds are elevated at all frequencies. Simultaneous or subsequent noise exposure has also been shown to interact with the hearing loss caused by manganese (36).

2.1.3.3.3 Other Metals In humans, early signs of mercury poisoning have been associated with cochlear damage. In contrast, the hearing loss after progressive or heavy exposure is due to the neurotoxic effects of mercury. In animal experiments a loss of outer hair cells has been shown in the middle region of the cochlea (36). Trimethyltin and triethyltin have been shown to cause a rapid hearing loss affecting the cochlear inner hair cells (87).

A protection from noise-induced hearing loss has been shown in humans treated with magnesium (88). Rats kept on a magnesium-deficient diet and exposed to noise stress showed elevated systolic and diastolic blood pressure and increased vascular calcium levels, which were more pronounced after the combined "exposure" to magnesium deficiency and noise (89).

2.2 Interactions between Chemical Agents and Noise: Nonauditory effects

Noise exposure in the work environment can cause effects other than hearing loss. Best known is perhaps the disturbing effect caused by low frequency noise from equipment such as ventilation systems, engines, or computers that can cause mainly stress reactions. These effects caused by noise are not discussed in detail here, but disturbing noise may cause many types of physiological reactions in humans. Nonauditory effects of noise are different from noise-induced hearing loss since they are not specific for noise exposure but may be caused by other stress situations. Also, the ability to compensate for these effects is more pronounced. Effects seen are peripheral vasoconstriction, changes in catecholamine levels and metabolism, as well as different cardiovascular signs such as blood pressure elevations or pulse rate changes (90, 91). Some of these effects have been found also after exposure to noise in combination with chemical factors.

2.2.1.1 Solvents and Noise When rats were exposed to various solvents (acetone, carbon disulfide, and trichloroethylene) in combination with noise, effects were found in the nervous, cardiovascular, endocrine, and immune systems. The interaction noted was, however, of an antagonistic type meaning that noise exposure minimized the effects of the solvents in these biological parameters (92). In rats exposed to noise and/or 1,1,1-trichloroethane, no specific effects were found except for some changes in liver weight/body weight relationship after the combined exposure (91). Exposure to alcohol in drinking water and/or noise modified the a-adrenergic effects of noradrenaline in rats (93). In rats, disturbances of the metabolism in the myocardium have also been found after exposure to noise in combination with dimethylformamide or xylene (94). Effects on mutagenicity in rats were investigated after exposure to several solvents (acetone, carbon disulfide, and trichloroethylene) in combination with noise, and it was found that noise exposure does not aggravate the mutagenicity of these chemicals (95).

2.2.1.2 Other Chemicals and Noise Ozone is an environmental pollutant that causes airway toxicity especially affecting the lower respiratory tract. Effects include appearance of plasmamarkers, edema, and inflammation (90). In a study on rats exposed to noise and/or ozone, the effect parameters shown after exposure to ozone alone were modulated in both directions by the noise exposure. The overall toxicity was not increased but the modulation may be important after repeated ozone exposure (96).

The teratogenicity of combined exposure to noise and cadmium was studied in mice. The combined exposure resulted in an increase of total percentages of malformed fetuses compared to the same dose of cadmium alone, but the interactions between cadmium and noise showed no synergistic effect on teratogenicity. Also in the groups exposed to noise alone, the total percentages of malformed fetuses were significantly higher than those in the control group (97).

Different effects of smoking and nicotine on the nervous system, including EEG, mood, b-endorphine, cortisol, and ACTH, where investigated also in combination with noise exposure. Even if several effects were found after smoking alone, no sign of interaction between noise and nicotine

could be demonstrated (98, 99).

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3 Vibrations
Both whole-body and hand–arm vibrations affect a vast number of workers. A common deleterious effect from vibration exposure is the white-finger syndrome, which includes disturbances in both nerve and blood vessels. Since drugs and chemicals can also alter the function of these structures, it is of interest to what degree vibrations and chemicals interact at simultaneous or subsequent exposure.
3.1 Smoking and Vibrations
Heavy smoking can induce white-finger symptoms (100). After investigation of single and combined exposure to hand–arm vibrations and duration of heavy smoking in 2705 workers, a hyperadditive effect was seen on white-finger symptoms (101). It was pointed out that vibrations and smoking have effects in common, such as disturbances in sympathetic nervous system and obstructive lesions in vessels; but the agents also have different degenerating effects such as increased risk of thrombosis (smoking) and functional changes in arteries (vibrations).
3.2 Arsenic and Vibrations
Exposure to inorganic arsenic can cause Raynaud's phenomenon, acrocyanosis, and gangrene of the lower legs (“black foot” disease). Smelters and miners are workers who might be exposed to arsenic dust, the latter group also to considerable vibration. A lower finger systolic pressure has been observed in arsenic-exposed workers at skin temperatures of 10 and/or 15°C expressed as a percentage of the pressure at 30°C (102). There was also a covariation between the duration of exposure to arsenic and the decrease in finger systolic pressure between the measurements at 30 and 10°C. The increased vasospastic reactivity in the fingers and Raynaud's phenomenon in smelter workers seems to be due to functional alterations in the vessels caused by inhalation of arsenic. In a later study the authors showed that the peripheral vascular disturbances caused by arsenic were dependent on long-term arsenic exposures and seemed to be independent of short-term fluctuations in arsenic exposure (103).

In a hygienic evaluation on gold miners (104), some workers were exposed to high levels of both vibration and arsenic, the latter seen as extensive arsenic accumulation in the hair and excretion with the urine. The vibration disease and sensory polyneuropathy in subjects exposed to both vibrations and arsenic were reported to be of a more severe course and were interpreted by the authors as results from synergistic-action between vibration and arsenic.

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4 Temperature
No occupational studies on thermal interaction with chemicals in workers have been found. Such temperature dependence has, however, been studied in human volunteers and in mice.

It is well known that body temperature of workers can vary by >1°C, depending on environmental temperature and physical intensity of the task. Thus, the impact of temperature on metabolic enzymatic velocity of chemical compounds and its impact on general health can be considered of interest (105).

Temperature changes in the environment may also alter physiological functions, which may, in turn, influence the chemical's toxicokinetics. Peripheral vasodilatation and sweating, which enhances skin hydration (see paragraph about humidity below), are responses that have been shown to increase percutaneous absorption (106). Temperature also affects respiratory rate, changes in volume and composition of blood and urine flow, and changes that may affect uptake, distribution, and elimination of chemical vapors (107). The percutaneous absorption of chlorinated solvents is accelerated by higher ambient temperature (108).

4.1 2-Butoxyethanol and Temperature

In volunteers dermally exposed to 2-butoxyethanol vapors, elevated ambient-air temperature and humidity resulted in higher blood solvent levels, which suggests an increased dermal uptake rate under these conditions (109). Skin heating, by hot showers or sauna baths taken after toluene exposure, did not, however, affect the solvent kinetics in blood (110).

Chemical exposure within a cold environment also can cause secondary responses in physiological functions such as shivering, peripheral vasoconstriction, elevated blood pressure, increases in respiratory rate and cardiac output, and a progressive fall in blood pH. Below a rectal temperature of ~35°C, the metabolic rate begins to decline. Subjects exposed to a cold environment (16°C, 2 h) had decreased plasma volume and increased urine flow (107).

4.2 Arsenic and Temperature

Arsenate-exposed hamsters produced synergistically greater percentages of malformed offspring when short-term hypertermia was added to the arsenate exposure (111). In another study on hamster, elevated arsenic concentrations were seen several hours after the cessation of heat exposure (112).

4.3 Ethanol and Temperature

Both maternal hypertermia and alcohol have been associated with birth defects in humans as well as mice. After combined exposure to both agents to doses at which teratogenicity could not be observed on day 8 of gestation, synergistic increase in resorption and frequency of externally malformed fetuses, skeletal malformations, and visceral variations were found (113).

4.4 Mercury, Ionizing Radiation, and Temperature

The effect of temperature on chemical toxicity has been studied on preimplantated mouse embryos exposed to mercuric chloride (3 mM, 10 mM), or to X-rays (1 Gy) or to a combination of the two agents (114). The embryos were cultured *in vitro* at 34–39°C with an increment of 1°C. A combined risk greater than expected from the sum of the individual effects was observed only (for a combination of 1 Gy+3 mM) in the range of the optimum temperature, that is, between 36 and 38°C (for a combination of 1 Gy+10 mM). Temperature and mercury tended to interact slightly, seen as a reduced number of cells per embryo at a 10 mM mercury chloride concentration. At binary exposure to X-rays and heat, a synergistic lowering in the latter parameter was indicated.

Combined postnatal effects were studied (115) after prenatal exposure to heat (42°C, 10 min a day) and methyl mercury (5 mg/kg, day 12). Heat alone affected postnatal open-field activity, response to diazepam, and spatial learning. The mercury exposure affected body temperature. No distinct interactions at combined exposure were recognized.

4.5 Formaldehyde and Temperature

Odors are a high priority problem in many industries. Odor intensity and sensory irritation was studied in 20 volunteers exposed to formaldehyde and radiant heat (116). The subjects estimated the odor intensity as higher when jointly being exposed to radiant heat on the face. Most volunteers also reported a change in the odor perception toward a more intense or pungent one at the strongest radiant-heat condition, a finding that indicates a possible combined effect according to the authors. It should be pointed out that the level of radiant heat used is rarely found in nonindustrial conditions, and thus less likely to contribute to sensations reported in connection with sick buildings.

5 Humidity
As mentioned in Section 4.2, humidity can indirectly interact with chemicals within the human body. The percutaneous absorption can be altered by humidity-induced changes in the hydration state of the skin and thereby alter the total uptake of a chemical. Volunteers exposed to 2-butoxyethanol vapor had blood concentrations, and hence presumably an uptake rate, that was 3–4 times higher during skin-only exposure than during mouth-only exposure (109).

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6 Dust and Particles
Toxic ions, molecules, and microscopic particles can be adsorbed on the surface of inhaled dust and particles, which increases the exposure of the respiratory tract. An increased forming of toxic reactive oxygen species on cobalt metal particles have been observed when these particles are associated with tungsten particles (117). An electrostatic field–mediated transport of dust and particles has also been suggested to deposit, and thus transport, chemicals to the skin of cathode ray tube (CRT) based videodisplay terminals (see Section 7).
6.1 Radon and Particles
The excess of lung cancer seen in miners has been assumed (118) to originate at least partly in an increased lung concentration of radon progeny adsorbed on inhaled particles although unattached progeny is believed to play the greater role.
6.2 Polyaromatic Hydrocarbons and Particles
Adsorption of polyaromatic hydrocarbons (PAHs) on dust similar to that of radon progeny described above has also been proposed (119). The activation of PAHs into reactive metabolites has also been reported to increase on the surface of asbestos fibers (120).
6.3 Smoking and Asbestos
The interaction between asbestos and tobacco smoking is perhaps the most commonly used example of occupationally relevant synergistic interactions. Asbestos includes several fibrous minerals, many being reported to be human carcinogens. At phagocytosis, the inflammatory processes alters growth and differentiation of target lung cells. As is also the case for tobacco smoke, asbestos is a complex carcinogen that can induce alterations at different levels of carcinogenesis (121). In one study, the death rate due to lung cancer was about fourfold higher than in smokers not exposed to asbestos and 12 times higher than in asbestos exposed nonsmokers (122). Most occupational studies on this combined exposure do in fact support a synergistic interaction between the two agents (123–125), but additive outcomes have also been indicated (126). A possible reason for observed differences in the degree of synergistic interaction might be the type of asbestos fibers the workers in question have been exposed to. Simultaneous smoking in the presence of asbestos does not increase the incidence of mesothelioma as compared to exposure to asbestos alone.
6.4 Smoking and Arsenic Dust
An overall comparison between studies on combined occupational exposure to arsenic dust and smoking has suggested a synergistic increase in the rate of lung cancer due to such exposure (127). The mechanism for the synergism was, however, unclear at the time.

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7 Electrostatic Fields
It has been proposed by several authors that electrostatic fields, originating from the CRT-based computer screen and induced by movements of the human subject (e.g. by friction against synthetic

cloths), can increase deposition of particles and chemical substances. Such hypothesis are discussed in relation to hypersensitivity to electricity as well as skin symptoms perceived at CRT computer screens. Chemical substances discussed are chlorinated substances, PCB (polychlorinated biphenyls), various flame retardants, contact allergens, radon progeny, and dust particles. A finding opposing that hypothesis is that a connection between the CRT screen and the operator to electric earth, which reduces the field considerably, does not seem to decrease the frequency of skin problems (128, 129). It is believed that a high static charge on the surface of the operator's body might increase the deposition on the skin of the operator; a process that thus could be unrelated to the potential charge from a computer screen.

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8 Electromagnetic Radiation and Fields
8.1 Low Frequency Fields and Thorium
In the search for treatment at accidental inhalation of thorium isotopes, both low frequency electromagnetic fields (EMFs) and the chelating agent CaDTPA have been found to decrease the retention of intravenously injected thorium. After ^{234}Th nitrate exposure, the effect of EMF alone (50 Hz, 10 mT) has been reported (130) to cause a substantial decrease in deposition in different parts of the body (23–59% remaining as compared to controls). Rather surprisingly, the combined exposure to the EMF and CaDTPA resulted in a considerably less effective decrease.
8.2 Radiofrequency Radiation and Fields
Workers within the plastic sealing and electrosurgical units of the microelectronics industry are often exposed to concurrent exposures to chemical and physical agents. Hyperthermia induced by radio-frequency (RF; 10 MHz) radiation can potentiate the toxicity and teratogenicity of some chemicals. 2-Methoxyethanol (2ME), an industrial solvent, produces enhanced teratogenicity in rats when combined with exposure to RF.

In a preliminary study (131), RF radiation exposure of rats for 30 min, which was sufficient to elevate rectal temperature to 42.0°C (4°C above normal for rats), and 2ME (150 mg/kg) were administered on gestation day 13. Pregnant rats were sacrificed on gestation day 20. Combined exposures enhanced the adverse effects produced by the experimental agent alone (no malformations were detected in a double-sham group). Mean fetal malformations per litter increased from 14% after 2ME and sham RF (15/26 litters affected, with an average of 2 fetuses/litter malformed) and 30% after RF radiation and water gavage (10/18 litters affected, with an average of 4 fetuses/litter malformed), to 76% after the combined treatment (18/18 litters affected, with an average of 12 fetuses/litter malformed). In addition to a significant increase in the frequency of malformations, the severity of malformations also was enhanced by the combination treatment (on a relative severity ranking scale, the 2ME-only severity score was <1, at RF only the score was 3, and at the combined exposure the score was 6).

In a later study (132), the authors investigated the interactive dose-related teratogenicity of RF radiation (sham exposure or maintaining colonic temperatures at 42.0°C for 0, 10, 20, or 30 min) and 2ME (0, 75, 100, 125, or 150 mg/kg) by administering various combinations of RF radiation and 2ME to groups of rats on gestation day 9 or 13. On gestation-day 20 fetuses were examined for external, skeletal, and visceral malformations. Exposure to 2ME, either by itself or in combination with RF radiation at gestation day 13, resulted in highly significant effects from both 2ME and RF radiation. The structures showing strong evidence of effects were the forepaw digits, forepaw phalanges, hindpaw digits, hindpaw phalanges, hind limbs, metacarpals, and metatarsals. Day 9 exposures generally evidenced little effect. Synergism was observed between RF radiation and 2ME for some, but not all, treatment combinations. In a subsequent study (133), it was shown that

concurrent RF radiation exposure can also change the shape of the dose–effect curve of 2ME.

In a third study (134), the same research group studied the effects of varying the degree and duration of hyperthermia induced by RF radiation (sufficient to maintain colonic temperatures at control, 38.5, 39.0, 40.0, or 41.0°C for ≤ 6 h) and 2ME (100 mg/kg) administered on gestation day 13 to rats. On day 20, fetuses were examined for external and skeletal malformations. Significant interactions were observed between 2ME and RF radiation sufficient to maintain colonic temperatures at 41°C for 1 h, but no consistent interactions were seen at lower temperatures even with longer exposure durations.

So far these studies have not demonstrated whether the found effects are induced primarily by the hyperthermia or by the non-temperature-related influences of the RF. In a more recent study (135), however, the authors attempted to determine whether altered environmental temperatures would affect the interactive developmental toxicity of RF and 2ME. RF radiation sufficient to maintain colonic temperatures at the control value (38°C), 39.0, or 40.0°C for 2 or 4 h combined with either 0 or 100 mg/kg 2ME at environmental temperatures of 18, 24, and 30°C were given on gestation day 13 to Sprague–Dawley rats. Dams were killed on gestation day 20. The environmental temperature did affect the specific absorption rate (SAR) necessary to maintain a specific colonic temperature, but it did not affect the interactive developmental toxicity of RF radiation and 2ME in rats. The findings support earlier evidence that the developmental toxicity of RF radiation (combined or alone) is associated with colonic temperature, and not with SAR.

8.3 Visible light

Several drugs have been shown to be phototoxic to the eye. These symptoms are, however, most pronounced in sunlight and thus not a specific occupational problem and therefore not discussed further here.

8.3.1 Solvents and Light Occupational exposures to chemicals have been associated with different kinds of visual disorders. The number of reports concerning reduced color discrimination ability has increased and the findings have been made after exposures that are around respective occupational exposure limit values levels in Canada, Finland, and Italy; above these levels in Russia, and of unknown levels in Taiwan (136–148). The main findings are reduced color discrimination ability, which is found in as much as 80% of the exposed workers, compared to 30% in unexposed workers.

More recent studies made on workers exposed to different classes of chemicals confirm earlier findings. A dose-related subclinical color vision impairment has been observed in two studies (149, 150) on mercury-exposed workers compared to referents matched for sex, age, tobacco smoking, and alcohol habits. A subclinical colour vision loss, mainly in the blue-yellow axis, was present in perchloroethylene exposed dry cleaners compared to controls matched for sex, age, alcohol consumption, and cigarette smoking (151). In a study on styrene-exposed workers (136) visual color impairment was reported from 4 ppm.

The impact of simultaneous exposure to ambient light was not included in these studies. Data on the light exposure would have been of considerable interest, since recent studies presented below show that combined exposure to fluorescent light and a *n*-hexane metabolite has a pronounced synergistic effect on the retinal function in the rat.

The conditions that usually produce light-induced damage to the retina are photochemical rather than thermal. The shorter the wavelength is, the greater the effectivity of damaging tissue. Therefore, violet and blue lights cause most retinal injury. In experimental studies it has been shown that blue light may damage the retina of rats in a dose-dependent manner. After exposure to light from fluorescent tubes, a decrease in the activity of cytochrome oxidases, a family of mitochondrial enzymes, has been observed in the rat retina (152). It is known that cytochrome oxidase activity is decreased after exposure to 2,5-hexanedion (2,5-HD). Cytochrome oxidase might therefore be site of interaction between light and 2,5-HD.

In rats exposed to 2,5-hexanediol (2,5-HDol) in both light and total darkness, the presence of light caused damage to the exposed rat retina, and the reduction in the number of photoreceptors progressed after termination of the exposure (153, 154). In darkness there was no loss of photoreceptor cells in the retina of the albino rats. After exposure to *n*-hexane metabolites in light or in total darkness, 2,5-HDol potentiated light-induced damage. In addition, the retinal damage caused by 2,5-HDol together with light exceeded a simple summation of the action of these two agents alone after the recovery periods. The 2,5-HDol-exposed group of albino rats in darkness showed no or minor loss of photoreceptor cells compared to the control group, strongly indicating that 2,5-HDol had no, or only a minor, toxic effect of its own on the retina.

8.4 Ultraviolet Radiation

8.4.1 Halogenated Hydrocarbons and UV Trichloroethylene, perchloroethylene, and methyl chloroform are examples of halogenated hydrocarbons often used as degreasing agents in the metal industry. The ultraviolet radiation emitted from welding arcs decomposes these hydrocarbons to phosgene and dichloroacetyl chloride, when welding is performed in such atmospheres (155–158). Phosgene, earlier used as a war gas, is a colorless gas or fuming liquid (boiling point 8°C). The substance yields an acidic solution when it decomposes in water and gives rise to pulmonary edema, which can be fatal at exposures of ~25–50 ppm for 0.5–2 h. The odor is said to be like new-mown hay, and the odor threshold is ~0.5 ppm (159). The highest amount of phosgene is produced by perchloroethylene, followed by trichloroethylene, whereas 1,1,1,-trichloroethane yields comparably small amounts. The amount of phosgene produced also depends on the amount of UV emitted by the welding method used. MIG welding on aluminum generates considerably more phosgene than, for example, the use of coated electrodes on mild steel (160).

8.4.2 Cuteaneous Phototoxic Substances and UV 8.4.2.1 Ultraviolet-Cured Ink and UV External exposure of skin to cuteaneous phototoxic chemicals and subsequent exposure to ultraviolet irradiation cause adverse dermal alterations such as intense burning sensations, blisters, dermatitis, and erythema. Occupational exposure to ultraviolet-cured ink (161) caused complaints from several workers concerning sensitivity to sunlight, including burning and later swelling of exposed areas within 5–10 min of sun exposure. Amyl dimethylaminobenzoate, a substance included in the ink, was found to produce diphasic phototoxic reaction *in vivo* after topical application on symptomatic workers, asymptomatic workers, and previously unexposed subjects.

8.4.2.2 Coal Tar Compounds and UV Wheal-and-flare formations, mediated by histamine released from dermal mast cells, are common symptoms of cutaneous phototoxicity from coal-tar compounds. Rat serosal mast cells were used as an *in vitro* model system to study the direct effect of phototoxic compounds on mast-cell degranulation. The coal-tar compounds studied included acridine and pyrene. Combined exposure of cells to acridine and UV-A (320–400 nm) radiation caused mast cells to degranulate (162).

Phototoxicity has also been associated with direct coal distillation (EDS liquids). Such liquid coal–based fuels with a boiling point above 200°C, which may be chemically similar to coal-tar products, were found to be phototoxic in guinea pigs (163).

Cuteaneous photosensitivity reactions were seen in 28 workers after exposure to bitumen, an impure mixture of hydrocarbons including known potent photosensitizers as anthracene and phenanthrene. The bitumen was included in a “hot-black” paint that was removed at a shipyard (164). Signs on sunlight- and dust-exposed skin varied from erythema, through marked erythema, to vesiculation and exudation in three cases. Symptoms resolved normally over 7–10 days.

8.4.2.3 Vegetables and UV Potent photosensitizers can also be found in raw common vegetables (165). Two cases exposed to raw parsnip juices while peeling, and subsequent UV-A irradiation a few hours later suffered from blisters at the site of substantial parsnip contact. Celery has also been reported to have phototoxic properties (166).

8.5 Ionizing Radiation

High level exposures to ionizing radiation due to accidents or serious human mistakes and

mishandling have occurred but are rare. Low level exposures are, however, fairly common in occupations such as mining, nuclear therapy, dental care, research, and nuclear plants. In this respect, it is of occupational health interest that interactions between ionizing radiation and chemicals have been reported.

8.5.1 Smoking and Radon Data concerning combined exposure to radon and smoking covers a wide span of both qualitatively and quantitatively different interaction outcomes ranging from strong synergism to a kind of relative protection (167, 168). Most of the studies on miners have indicated a strong synergistic interaction between the two agents (169), thus providing results often used to illustrate synergistic exposure interactions in occupational health. There are some divergent observations from the past, however, that have also led to a suggestion that high concentrations of dust and particles in older mines together with active smoking may increase mucus secretion and thereby somewhat reduce the short-ranging a-radiation to the epithelium and consequently also the absorbed dose. An increase of just 10 mm, of a mucous sheath can be calculated to reduce deposited energy from the poorly penetrating a-particles to the bronchia by as much as ~ 50%. This shielding mechanism, possibly together with increased coughing, was considered to contribute a somewhat protective effect from smoking at radon exposure in an early study on miners (170). A corresponding protective phenomenon also has been noted experimentally in smoke-exposed dogs with exposure to uranium ore dust and radon progeny (171). However, in reports on lung cancer in miners from modern and low dust mines, as well as regarding indoor exposure to radon progeny, a generally multiplicative interaction between smoking and radon progeny has been explained by the mutagenic action of the smoke chemicals and the irradiation.

Radon progeny, much of which is normally deposited on physical surfaces such as walls and furniture in the room, can attach to the surface of tobacco smoke particles. This phenomenon has been proposed to increase the amount of radon progeny available in the air for respiration (172). However, this particleborne “attached” fraction is usually given less emphasis than the unattached radon progeny in calculations of the dose delivered to the epithelium. Furthermore, an increased air turbulence in a room tends to lower the radon progeny levels through enhancing attachment of radon progeny to surfaces, but this plating out of radon progeny is reduced in the presence of smoke by providing the most nearby surfaces for attachment. Findings obtained in an office study corroborate this view (173), as a smoke-free environment and prolonged daily air conditioning were found to lower the annual effective lung exposure dose. As a consequence of these findings, smoking in a room has also been proposed to potentially bias retrospective glass-based radon assessment through a reduction of the plating out of radon progeny on glass (and other) surfaces (174).

A study with some bearing on the interaction between radon progeny exposure and other agents was based on an ongoing lung cancer screening program among 8346 radon- and arsenic-exposed tin miners. A total of 243 new lung cancer cases were identified in this study and radon and arsenic exposures were determined to be the predominant risk factors (175). Increased lung cancer risk was also associated with chronic bronchitis and silicosis, as well as with exposure to tobacco smoke, including smoking from an early age, duration, and cumulative exposure.

8.5.2 Caffeine and Ionizing Radiation Studies have shown combined effect of radiation (0.5–2.5 Gy) and caffeine (100 and 250 mg/kg maternal body wt) on day 11 of gestation in mouse embryos (176). The intrauterine mortality and frequencies of cleft palate and defects of forelegs and hindlegs were higher than the sum of the single exposures.

8.5.3 Mercury Chloride and Ionizing Radiation In a number of studies (177–179) on early mouse embryos *in vitro*, the risk from combined exposure to ionizing radiation and mercuric chloride was observed to be higher than that expected from either of these agents individually. To achieve an enhanced risk, the mercury exposure had to start as soon as possible after irradiation and then maintained as long as possible. The authors conclude that if inhibition of DNA repair is involved in the mechanism of interaction at all, an additional late process induced by mercury must also be involved.

8.5.4 Arsenic, Cadmium, Caffeine, Lead or Mercury, and Ionizing Radiation The influence of arsenic, cadmium, lead, or mercury at combined exposure to ionizing radiation in terms of risk to preimplantation mouse embryos *in vitro* was studied under various conditions (180). Morphological development, cell proliferation, and formation of micronuclei were used as endpoints. Arsenic did not alter the radiation risk. After cadmium and radiation exposure, only a few results indicated that the morphological development might have been impaired more strongly after exposure to two or more of these substances combined. Lead enhanced the radiation risk only with regard to micronucleus formation. Mercury had the greatest potential for enhancement of radiation risk, when morphological development and cell proliferation were studied. The observed combination effects exceeded even those effects that were calculated by taking factoring in the shape of the dose–effect curves (isobologram analysis, envelope of additivity). Mercury neither induced micronuclei nor enhanced their formation in combination experiments.

The effects of various doses of X-rays (0.25–2 Gy, given immediately before the chemicals) and to different concentrations of two chemicals—caffeine (0.5–2 mM) and mercury (0.5–5 mM)—on preimplanted mouse embryos *in vitro* have been studied (181). Morphological, proliferative, and cytogenetic endpoints were used. No synergistic enhancement in risk was observed after exposure to the three agents as compared to the interactions already detected at the level of a combined exposure to only two agents. Binary exposure to X-rays and caffeine, or to X-rays and mercury (but not to caffeine and mercury), caused synergistic increases in the percentage of alterations in various morphological stages of early mouse embryonic development.

8.5.5 Paraquat and Ionizing Radiation Lung changes have been observed in rats (n = 160) after combined exposure to the common herbicide paraquat (0.46 mg/kg bw, 5 times per week for 4 months) and ionizing radiation (4 Gy; directly on termination of paraquat intake) (182). The combined exposure induced more marked and more prolonged depression of the three parameters (superoxide dismutase, catalase, and nonprotein sulfhydrylgroups) of lung antioxidant defense and synergistic increase in bronchoalveolar lavage fluid content of thiobarbituric acid reactants and lactate dehydrogenase activity than did the single-factor exposures.

8.5.6 1,2-Dibromoethane and Ionizing Radiation Somatic mutations in the stamen hair cells of Tradescantia KU 9 (183) can be induced by combined exposure to 1,2-dibromoethane (DBE) and X rays. Synergistic interaction at low radiation doses has been found between the two agents for both DBE exposure followed by acute X-rays and chronic simultaneous exposures (184). An interaction of single strand lesions in the DNA as a cause of the synergism was discussed by the authors.

8.5.7 Caffeine, Mercaptoethylamine, and Ionizing Radiation After low doses of g-radiation (dose range 5–50 cGy), supersensitivity of Chinese hamster cells was revealed as studied by the cytokinesis block micronucleus test. Treatment with caffeine (repair inhibitor) and mercaptoethylamine (radioprotector) and the exposure to secondary radiation emitted by protons with an energy of 70 GeV revealed that the supersensitivity was associated with the absence of cytogenetic repair (185).

8.5.8 N-Nitroso-N-methylurea and Ionizing Radiation In a study on cultured Chinese hamster V79 cells (186), the toxicity and mutagenicity of formaldehyde with or without previous exposure to ionizing radiation was investigated. Both agents caused a dose-dependent decrease in colony-forming efficiency and a parallel increase in 6-thioguanine-resistant colonies. Mutant frequencies were induced by 0.3–1 mM formaldehyde, and by 2 and 4 Gy of radiation. As compared with the corresponding separate effects caused by single exposures, ionizing radiation followed by submutagenic concentrations of formaldehyde potentiated both the cytotoxicity and the mutagenicity.

8.5.9 Acrylamide and Ionizing Radiation Mutations induced by combined treatment with acrylamide and X-rays have been studied using the dominant lethal mutation test in male mice (187). Both doses

at which mutagenicity was found and was not found of both agents (1.00 Gy, 125 mg/kg bw and 0.25 Gy, 25 mg/kg bw, respectively) were used. After combined exposure at nonmutagenic doses, enhanced risk was observed in late spermatids, whereas exposure to mutagenic doses induced an enhanced risk in spermatozoa, spermatids, and late spermatocytes.

8.5.10 Biochemical Modulation of Ionizing Radiation Treatment The development of biochemical radiobiology includes a growing number of studies concerning biochemical modulation of ionizing radiation treatment (188). Even though substantial exposure to the chemical agents studied (e.g. non-nitro- compounds, pyrimidine analogs, misonidazole) are rarely found within industrial plants, such modulations are interesting regarding mechanistic aspects of occupationally found interaction between ionizing radiation and chemical factors.

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Populations at Risk
David H. Pedersen, Ph.D., Randy O. Young, and Vernon E. Rose, Dr.P.H., CIH

Introduction
The practice of industrial hygiene and toxicology both involve recognition, as well as anticipation of the potential for occupational health problems (1). In the anticipation and/or recognition phase, an assessment of the risk to health or well-being resulting from exposure to an agent (chemical, physical, or biological) is made. This phase usually involves identifying the agents to which workers are or might be exposed; assessing the agents' properties, including toxicity; and understanding the conditions surrounding the use of, or interaction with, the agents. This information allows occupational health and safety professionals to make a preliminary assessment of occupational health risk based on the inherent properties of chemical, physical, or biological agents combined with the potential for contact or exposure under actual use conditions, including environmental level and in-use exposure control measures. The two basic applications of the anticipation/recognition process can be classified as either individual or aggregate.

The individual process is used by occupational health and safety practitioners who apply anticipation and recognition techniques to the exposure and conditions of exposure prevalent in a single facility or group of facilities under his or her professional jurisdiction. In that process, the individual professional needs an understanding of the toxic properties of those agents associated with these specific workplaces or processes and an understanding of the conditions of exposure existing in those situations. The data necessary for the individual process have been available to the practitioner for quite some time, either through the scientific literature or through investigation in the workplaces under his or her jurisdiction, with the possible historical exception of accurate information regarding the formulation of trade-named products.

The broader aggregate process of anticipation and recognition is applicable to definable industrial or occupational populations, and is an assessment of the potential risk of these populations for adverse health effects due to occupational exposure to chemical, physical, or biological agents in the workplace. The aggregate approach is common to occupational health and safety researchers, regulatory bodies, and others interested in the extent of exposure to a specific agent or list of agents with known adverse health effects. For example, in the initial stages of an epidemiologic study, researchers might wish to identify populations of workers who are exposed to a specific agent or group of agents. Government agencies need a measure of the potential impact of research or regulatory efforts based on the number of industries and workers impacted when they decide on the priorities to assign to research or regulatory efforts or the development of occupational health standards. This type of data was not available until after the implementation of the Occupational Safety and Health Act of 1970, and required several efforts by the federal government.

This aggregate approach to the identification of worker populations at risk due to their occupational exposures to specific individual or grouped chemical agents also serves the general occupational health community by profiling the industries in which exposure may occur, thereby permitting an assessment of the relative potential for specific adverse health effects in selected industries. This type of broad overview is not normally available to the individual occupational health practitioner, and has the potential for improving the practitioner's initial assessment of occupational risk in his or her area of responsibility. This was recognized, prior to his untimely death, by Dr. Charles H. Powell (2), whose original suggestion prompted this effort to provide aggregate analyses of the industrial distribution of chemical exposure for consideration by the professional community.

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Background
In the early 1960s, the Occupational Health Program of the U.S. Public Health Service (the forerunner to the National Institute for Occupational Safety and Health) constantly received requests for assistance from state and local health departments interested in establishing or expanding their occupational health programs (3). A typical question asked might have been “What is the extent of exposures in the workplaces for which we have responsibility?” The data needed to answer this question include: (*1*) the prevalence of exposure to specific agents in the nation; (*2*) the types of workplaces (industries) in which exposure to these agents occurs; (*3*) the number of workplaces in which such exposure takes place; (*4*) the number of workers exposed to specific agents; and (*5*) the extent to which these exposures are controlled. Unfortunately, the Public Health Service could not provide answers to these questions because such data did not exist.

This lack of knowledge was strongly addressed in a 1966 report to the Surgeon General of the United States (commonly known as the Frye Report), which stated, “It is almost inconceivable that this nation, with its vast resources and technical skills, has never developed a comprehensive picture of the work environment to determine the relationship with the health status of its productive work

force” (4). The Frye Report went on to identify three major steps necessary for assessment of the national occupational health situation, which included the establishment of continual surveillance of: (*1*) the incidence and prevalence of occupational disease; (*2*) aspects of the work environment responsible for, or contributing to, occupational disease; and (*3*) the relationship between disease and the work environment to enhance the “preventive” aspects of occupational health (5). These concepts, as described later, were addressed in the federal surveillance efforts that eventually provided most of the data needed for the aggregate process of anticipation and recognition of occupational hazards.

Despite a lack of available data, the Occupational Health Program did address the questions from states and municipalities through a program that involved limited study of the extent of hazards in defined working populations in city or metropolitan areas (6). The program identified industries of interest, usually in the manufacturing sector, plus other identified workplaces, and selected a sample of workplaces to be visited for purposes of cataloging predetermined information of interest. The data collected included basic background information about specific plants, including availability of occupational health and safety services and specific information on the hazardous agents observed, the number of workers exposed, and estimates of the degree to which these hazards were controlled. The results obtained from the sample of workplaces visited were extrapolated to a larger population base and used to determine the need for occupational health specialists, and identifying industry-specific priorities for inspection and consulting programs.

Another federal effort by the Bureau of Occupational Safety and Health of the U.S. Public Health Service, reported in 1970, developed the “environmental” segment of the National Surveillance Network (NSN), which was also directed at survey activity in limited geographical areas. This network was intended to collect environmental and medical control data on specific plants, their workers, and the working environment. There were three intended uses for these data, addressing the need to: (*1*) provide information to participating agencies by projecting local data to the geographical areas of concern; (*2*) supplement projected data as necessary with data from participating agencies; and (*3*) estimate the scope of national health problems to “give input and direction to federal projects, such as the development of criteria and standards” (5).

Building upon the principles of the NSN, the National Institute for Occupational Safety and Health (NIOSH) conducted the National Occupational Hazard Survey (NOHS) from 1972 to 1974. This study involved the administration of a standardized questionnaire to facility management and a traditional industrial hygiene walkthrough in 4636 randomly selected workplaces in the United States. This statistical sample of the U.S. workplace was designed to be representative of all nonagricultural businesses covered under the Occupational Safety and Health Act of 1970 and employing eight or more workers. A team of 20 extensively trained surveyors visited the selected workplaces, recording potential exposure agents, duration of exposure, and controls in place (7–9). One of the major surprises of the survey was documentation of the extent of use of trade-name products in the workplaces and the lack of information about the ingredients of these products. An amazing 70% of the observed and recorded exposures in the NOHS involved trade-name products. It required several years for NIOSH to contact manufacturers to identify the ingredients or components of their products so that actual chemical names could be entered into the database in place of the unresolved trade names. When completed, the NOHS provided the first comprehensive national view of the chemical, physical, and biological agents to which American workers were potentially exposed, and the degree to which these exposures were controlled.

A second national survey, the National Occupational Exposure Survey (NOES), was initiated in 1981. A team of 15 trained surveyors conducted standardized management interviews and walkthrough surveys in 4490 workplaces from 1981 to 1983. The NOES was similar in design to the earlier NOHS survey, but specifically excluded most Agricultural, Mining, Wholesale, Retail, and Finance/Real Estate facilities. These deliberate exclusions were made either because other surveys were planned (Mining) or to focus survey resources on those industrial sectors believed to present the greatest potential hazard to the workforce (e.g., Construction, Manufacturing, and Services). The

data collected were quite similar to that in the NOHS, with the notable addition of gender-specific information on workers potentially exposed to chemical, physical, or biological agents, and data on the exposure of workers to ergonomic stress (10–12). Again, approximately 70% of the observed occupational exposures involved trade-name products, and extensive efforts were required to replace more than 100,000 observed trade names with their actual chemical constituents in the NOES database.

The information from the two surveys has been combined into one database with six interactive data files for ease of retrieval (13). These files include:

1. *The Industrial Classification File* This file, contains the 1972 Standard Industrial Classification (SIC) system codes and titles used to code the establishments visited during the surveys.
2. *The Occupational Codes File*. This file contains the Bureau of the Census occupation codes and titles used to code the job titles of workers observed in the walkthrough surveys.
3. *The Chemical Master File*. This file contains a listing of all the agents (hazards) in the survey databases. Each hazard observed was assigned a unique code by NIOSH, and these codes were cross-referenced to Chemical Abstracts Service (CAS) (14) numbers and identification codes from the Registry of Toxic Effects of Chemical Substances (RTECS) (15).
4. *The Facilities File*. This file contains all information collected for each facility surveyed except for exposure data and facility name and address. This information includes the type of industrial hygiene, safety, and medical services at the facility.
5. *The Exposure File*. This file contains all observations made by the surveyors during the walkthrough survey. Included is information on the use of personal protective equipment, engineering controls present, number of workers exposed, gender (for the NOES), and the occupations of observed worker groups.
6. *The "Trade Named" Ingredients File*. This file contains the ingredients for the trade-name products observed during each survey.

The data from the NOHS and NOES surveys are obviously useful in the broad aggregate process of anticipation and recognition, and represent a major step toward the national occupational health surveillance goals established in the 1966 Report to the Surgeon General (4). Evidence of the usefulness of these data in planning and prioritizing occupational health and safety research, regulation, and standards setting is demonstrated in extensive use by federal agencies. A partial list of these agencies includes the National Institute for Occupational Safety and Health, the Occupational Safety and Health Administration, the National Institute for Environmental Health, the Environmental Protection Administration, the Centers for Disease Control and Prevention, the National Cancer Institute, the National Toxicology Program, and the National Institutes of Health. In addition, labor organizations, academic researchers, state and local governments, industrial associations, and citizen's groups have made extensive use of the survey data in their efforts to identify occupational health problems and propose possible solutions.

The utility of the NOHS/NOES data is also demonstrated in its use as the basis for related research work that illustrates occupational health trends and identifies specific possible problem areas. Examples from NIOSH publications and the peer-reviewed literature include: computer modeling of relative health risk due to occupational exposures (16), mapping of the distribution of occupational chemical exposures (17), industrial compliance with OSHA record-keeping requirements (18), analyses of worker access to medical care (19, 20), identification and location of possible occupational asthma cohorts (21), and estimation of the number of workers potentially exposed to carcinogens (22, 23).

Perhaps the best evidence of the continuing need for this type of data is the effort by NIOSH to develop and conduct a successor to the NOES survey. This project (the National Occupational Exposure Survey for the 21st Century) is the current responsibility of a NIOSH team whose charge

includes working collaboratively with other federal agencies and nongovernmental partners to plan for and conduct a new national survey. This survey is to be complementary to both the NOHS and NOES, address the known data needs of NIOSH and its partners, allow for known changes in the American industrial universe since 1983, and permit a detailed examination of occupational health and safety problem areas that have emerged since the NOES was conducted (24).

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Data Source Considerations

The NOES data files were used to develop the tables in this chapter that identify populations at potential risk of exposure to many of the chemical hazards reviewed in this publication. However, readers should be aware that there are definite limitations to the survey data that are related to its statistical design or to survey protocols, and should take these into account when reviewing the data displays.

These limitations include a lack (except for observed noise) of environmental level information, the accuracy of the estimates of the number of workers potentially exposed to specific agents, the age of the survey data, a bias towards larger (by employment size) facilities, the use of trade-name ingredient data in the estimation process, and the "provisional" nature of the data. Finally, readers should be aware that if they combine the estimates for individual agents to derive an estimate of the number of workers exposed to a list of agents, the estimate will be inflated, since at least some workers would be counted multiple times. This practice is discouraged. A brief explanation of the NOES limitations follows.

The NOES survey protocol did not allow for the measurement of environmental agent exposure levels for a variety of practical reasons, including the lack of available tests for the environmental concentration of the approximately 12,000 chemical, physical, or biological agents in the NOES database. In essence, simple logistical difficulties and constrained resources would not permit the standardized sampling of environmental concentrations of all observed exposures. For this reason, all NOES estimates of the number of workers exposed to specific agents are regarded as "potential exposures."

One of the fundamental factors considered in the design of the NOES survey was the relative accuracy of the estimates associated with facility totals and potentially exposed worker totals. Since survey design and sampling considerations made it impossible to achieve equal accuracy for both, it was decided that the accuracy of the estimates of the number of workers was the more important of the two estimates. Therefore, given that the majority of the U.S. workforce is employed in larger facilities (measured by employment totals), the survey data are biased towards larger plant workforces, and may under-represent workers in smaller plant workforces. In addition, NOES estimates may be associated with large standard errors, and should not be regarded as absolutes. Complete documentation of the sources of error in the NOES estimates is found in the NIOSH NOES Sampling Methodology publication (11).

The age of the NOES data is an obvious drawback, and means that the data may not accurately reflect current conditions or industrial worker and occupational exposure distribution in the national workplace. The long delay in updating this survey is a problem that the current NIOSH working committee is attempting to address through the establishment of external partnerships with other agencies with an interest in this type of data (24).

The NOES estimates are based upon the observed number of workers at the facility level exposed to specific agents projected to the national universe (11). In the NOES, such observations consisted of

"actual" and "trade-name" exposures, with "actual" exposures being those that were immediately recognizable on site (e.g., a drum labeled benzene), and a "trade name" exposure being an observed use and occupational contact with a trade-name product (12). However, as noted, approximately 70% of all occupational exposures are to trade-name compounds, and the exact nature of the resultant chemical exposures is not always clear at the actual user level. Therefore, as the composition of individual trade-name compounds became known, their component list was substituted for that trade name in the electronic database, and the NOES estimates of workers potentially exposed were generally based on both sources of exposure identification. This was because estimates based only on "actual" observation would have grossly underestimated the number of workers exposed. The practice of using both "actual" and "trade-name" sources of data in deriving the NOES estimates was followed in generating the tabular estimates presented in this chapter.

Finally, the NOES data presented in this chapter should be regarded as "provisional." This is because the NOES trade-name ingredient clarification effort was never completed. Of the approximately 100,00 trade names observed during the NOES survey, a 5-year communications effort ultimately resulted in the resolution of approximately 80,000 trade names. Since the addition of the missing data would change the NOES chemical inventory and the estimates of the number of workers potentially exposed, the data must be technically regarded as "provisional."

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Data Display Considerations

Chemicals were selected for tabular display in this chapter in a two-stage process. First, the list of agents in the threshold limit values for Chemical Substances and Physical Agents (25) was searched, and the cited Chemical Abstracts Service (CAS) (14) numbers for specific chemicals were used to search the CAS file in the NOES database for a match. Three situations were immediately evident. In most cases, the cited CAS number was used to represent a single, specific chemical agent. But, in some cases, such as nickel, a number of different agents were represented by a single CAS number. In these cases, a special aggregated estimate of the number of workers potentially exposed was derived from the NOES data, and the tabular display was entitled in similar fashion to the display in threshold limit values for Chemical Substances and Physical Agents. For both of these cases, a single CAS number is cited in the table title. In the third case, a grouping of chemicals with different CAS numbers had been established under a common name for the threshold limit values publication. In this case, a special aggregated estimate of the number of workers potentially exposed was derived from the NOES data, the tabular display was entitled in similar fashion to the display in the TLV book, and multiple CAS numbers are cited in the table title.

Second, if a match (by CAS number) between the threshold limit values booklet (TLV) and the NOES database was observed, the NOES file was queried for the overall estimate (without regard to industry) of the number of workers potentially exposed. As previously mentioned, NOES estimates of the number of workers potentially exposed to an agent are subject to a degree of standard error, and estimates of less than 8000 may have unacceptable standard error. Accordingly, NOES data presented in tabular form in this chapter are restricted to those chemical agents for which the overall NOES estimate of workers potentially exposed exceeds 8000.

Considerable thought was given to the generation of estimates from the NOES database for this publication, given the wide variety of information and the space available. It was decided that the interests of the general audience could best be served by producing estimates of the workers potentially exposed to the agents identified in the TLV book/NOES search, and stratifying these estimates by the 1972 Standard Industrial Classification (SIC) (26) used in the NOES and by facility employment size. Readers interested in other analysis from the NOES database should contact

coauthor Randy Young at NIOSH.

The NOES database contains information on total employment in the surveyed facilities, and on the total number of workers who were observed to be potentially exposed to some agent by NOES survey protocol. This latter group can be referred to as "production workers," since their employment involved occupational exposure to at least one agent. There is a considerable difference between these groups. NOES estimates show that approximately 33 million workers were employed in the industrial universe surveyed during the NOES in 1981–1983 (12). Of these, approximately 19 million were observed (by NOES protocol) to be potentially exposed to some chemical, physical, or biological agent. Since, from an industrial hygiene viewpoint, the group of workers potentially exposed to at least some agent is of greater professional immediacy, it was decided that all NOES estimates provided here should profile these "production workers" rather than the total employed workforce.

Table 1 of this chapter provides the NOES estimates of the number of "production workers" for 38 two-digit SIC groups, stratified by facility employment size. The reader should note that there are "cells" (e.g., facilities employing 500 or more in SIC 07 [Agricultural Services]) in this table labeled with a "···" notation rather than containing estimates. This is because the statistical nature of the survey sampling procedure (11) resulted in failure to identify a number of facility employment strata within SIC for survey due to their sparsity in the national universe, and there are no NOES data for these cells. This "···" identification of an empty cell (no NOES data) has been carried over into the tabulations presented here, to distinguish between *no data* and data that indicate *no potential exposures* (zeros).

Table 110.1. Estimated Production Employees by SIC and Facility Employment Size (1981–1983 National Occupational Exposure Survey)

Another function of Table 1 is to display the 38 SIC groups, by code number and industry title, (26) to be profiled in the NOES estimates provided here. It should be noted that the actual survey design of the NOES called for survey activity in 43 two-digit SICs (11, 12). However, as documented in the third NOES publication, (12) five of these SICs contained so little survey data that estimates of the number of potentially exposed workers in them was felt to be associated with unacceptably high standard error. Therefore, they are not represented in Table 1, or in any of the agent specific tabulations presented here.

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Calculation and Display of Estimates

The estimates of potentially exposed workers displayed in this chapter were generated using the inverse inclusion probability of the facilities surveyed in the NOES. These weights were used to project facility-specific numbers of observed workers potentially exposed to *any* NOES agent ("production workers") to the national NOES universe, as documented in the second of the NIOSH publications on the NOES (11). As previously mentioned, these data are shown in Table 1.

Estimates of the number of production workers potentially exposed to *specific* agents by SIC and facility employment size strata *and* for all industries without regard to facility employment size were generated in a similar fashion and are displayed in the Appendix to this Chapter. Note that only those industries for which there were observations of exposure to the specified agent are listed in each table. In other words, the number of two-digit SIC industries cited in a specific table will not exceed 38, but may well be less, depending on the distribution of observed potential exposure.

In addition to these estimates of the number of workers potentially exposed, the tables in this chapter provide estimated proportion data, expressed as percent values for each facility employment size strata (small, medium, and large) within each SIC profiled. These values were generated by dividing the estimated number of workers potentially exposed to *specific NOES agents* by the estimated number potentially exposed to *any NOES agent* for that particular industry—facility employment size or industry "cell" in the tables (see Table 1). These percent values are used to convey three types of information:

1. *Industry-Specific Exposure Concentration by Facility Employment Size*. Percent values in the industry–facility employment size "cells" indicate the proportion of *all* potentially exposed workers in that cell who are potentially exposed to a specific agent. For example, in a table profiling potential exposure to agent *X*, a value of 4.1% in the SIC 28 small (employing fewer than 100 workers) facilities cell would indicate that 4.1% of all workers potentially exposed to *any* NOES agent in small facilities in SIC 28 are potentially exposed to agent *X*. Therefore, these data provide a proportional estimate of the relative concentration of worker exposure to a specified agent by employment size strata within specified industries.
2. *Industry-Specific Exposure Concentration*. Percent values in the industry–total "cells" indicate the proportion of all workers potentially exposed to a specific agent who are employed in that industry. For example, in a table profiling potential exposure to agent *X*, a value of 4.1% in the SIC 28 total cell would indicate that 4.1% of all workers potentially exposed to agent *X* are employed in SIC 28. Therefore, these data provide a proportional estimate of all worker exposure to a specified agent by listed industry.
3. *All Industries Exposure Concentration by Facility Employment Size*. Percent values displayed by facility employment size strata in the all industries facility employment strata "cell" displays indicate the proportion of all workers potentially exposed to any NOES agent who are potentially exposed to a specific agent in small, medium, and large facilities, without regard to industry. For example, in a table profiling potential exposure to agent *X*, a value of 4.1% in the all industries–small facilities cell would indicate that 4.1% of all small facilities workers exposed to any NOES agent are potentially exposed to agent *X*. Therefore, these data provide a proportional estimate of the relative concentration of worker exposure to a specific agent by facility employment size without regard to industry.
4. *Summary Estimate*. The value in the all industry total "cells" in the summary estimate of all workers potentially exposed to the agent specified in the table title without regard to facility employment size or industry of employment. Note that the percent data will always equal 100%.

These data points are further illustrated in Figure 1.

SIC Code	Industry	Workers by Facility Employment Size			
		Small (8–99)	Medium (100–499)	Large (500+)	Total
XX	Xxxxxxx	Est. %	Est. %	Est. %[c]	Est.[b–d] Col %[f]
•					
•					
All Industries		Est. T%	Est. T%	Est. T%[h]	Est.[g] All %[i]

[a]All specific chemical names are in NOES format, which generally follows the nomenclature used in the Registry of Toxic Effects of Chemical Substances (RTECS).[15]

[b]NOES estimates of the number of workers potentially exposed are presented by two-digit 1972 Standard Industrial Classification (SIC) and for all (all industries) NOES industries. Note that only those SICs for which there are survey data will be displayed, and that there are a maximum of 38 SIC groups in any table.

[c]NOES estimates of the number of workers potentially exposed (est. values) are presented by facility employment size and for all facilities within an SIC. A lack of NOES survey observations in an individual cell of the table is denoted with "…", and no estimates are provided.

[d]The first row of data (est. values) in each SIC cluster in the table presents the NOES estimates of the number of workers potentially exposed to the specified agent in small, medium, large, and all facilities in that SIC.

[e]The first three elements in the second row of data in each SIC cluster (% values) in the table presents the number of workers potentially exposed to the specified agent as the percent of all workers potentially exposed to any NOES agent in small, medium, and large facilities in that SIC. All percent values are expressed to the nearest tenth of a percent.

[f]The fourth element in the second row of data in each SIC cluster (Col % values) presents the number of all potentially exposed workers in that SIC as the proportion (as a percent) of all workers (regardless of industry of employment) potentially exposed to the specified agent. This datum displays the proportion of all workers potentially exposed to the specified agent within the cited industry.

[g]The first line (est. values) of the all industries data presents the NOES estimates of all workers potentially exposed to the specified agent, in small, medium, large, and total facilities regardless of industry of employment.

[h]The second line of the all industries data (T% values) presents the number of workers potentially exposed to the specified agent as the percent of all workers potentially exposed to any agent in small, medium, and large facilities without regard to industry.

[i]The all industries data (all % values) in the second data line represent the summary percentage value for all industry-specific observations. This number will always equal 100%.

Figure 110.1. Explanation of Tabular Format. 1981–1983 NOES Estimated Number of Workers Potentially Exposed to Defined Agent Name (CAS #)[a]

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Appendix
This appendix displays the tabular information on the industrial distribution of potential occupational exposures to 289 selected chemical agents or groups of agents in Tables 2 through 291. These tables are essentially in alphabetical order by RTECS (15) naming convention, and the page number in the appendix for specific chemical agents are referenced by Chemical Abstract Service (14) (CAS) number in the overall Patty's index and in the CAS numbers cited in the various chapters of Patty's.

Table 2

Table 110.2. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACETALDEHYDE (CAS# [*75-07-0*])

Table 3

Table 110.3. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACETIC ACID (CAS# [*64-19-7*])

Table 4

Table 110.4. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACETIC ANHYDRIDE (CAS# [*108-24-7*])

Table 5

Table 110.5. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACETONE (CAS# [*67-64-1*])

Table 6

Table 110.6. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACETONITRILE (CAS# [*75-05-8*])

Table 7

Table 110.7. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACETOPHENONE (CAS# [*98-86-2*])

Table 8

Table 110.8. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACETYLENE (CAS# [*74-86-2*])

Table 9

Table 110.9. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SALICYLIC ACID, ACETATE (CAS# [*50-78-2*])

Table 10

Table 110.10. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACRYLAMIDE (CAS# [*79-06-1*])

Table 11

Table 110.11. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACRYLIC ACID (CAS# [*79-10-7*])

Table 12

Table 110.12. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACRYLONITRILE (CAS# [*107-13-1*])

Table 13

Table 110.13. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ADIPIC ACID (CAS# [*124-04-9*])

Table 14

Table 110.14. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ALUMINUM (CAS# [*79-10-7*])

Table 15

Table 110.15. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ALUMINUM OXIDE (CAS# [*1344-28-1*])

Table 16

Table 110.16. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: AMMONIA (CAS# [*7664-41-7*])

Table 17

Table 110.17. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: AMMONIUM CHLORIDE (CAS# [*12125-02-9*])

Table 18

Table 110.18. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: AMMONIUM SULFAMATE (CAS# [*7773-06-0*])

Table 19

Table 110.19. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACETIC ACID, PENTYL ESTER (CAS# [*628-63-7*])

Table 20

Table 110.20. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ANILINE (CAS# [*62-53-3*])

Table 21

Table 110.21. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ANTIMONY (CAS# [*7440-36-0*])

Table 22

Table 110.22. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ANTIMONY TRIOXIDE (CAS# [*1309-64-4*])

Table 23

Table 110.23. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ARGON (CAS# [*7440-37-1*])

Table 24

Table 110.24. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ARSENIC (CAS# [*7440-38-2*])

Table 25

Table 110.25. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ASBESTOS (CAS# [*1332-21-4*])

Table 26

Table 110.26. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ASPHALT (CAS# [*8052-42-4*])

Table 27

Table 110.27. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: BARIUM (CAS# [*7440-39-3*])

Table 28

Table 110.28. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: BARIUM SULFATE (CAS# [*7727-43-7*])

Table 29

Table 110.29. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: BENZENE (CAS# [*71-43-2*])

Table 30

Table 110.30. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: BENZOYL PEROXIDE (CAS# [*94-36-0*])

Table 31

Table 110.31. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: BENZYL ACETATE (CAS# [*140-11-4*])

Table 32

Table 110.32. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: BENZYL CHLORIDE (CAS# [*100-44-7*])

Table 33

Table 110.33. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: BERYLLIUM (CAS# [*7440-41-7*])

Table 34

Table 110.34. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: PROPANE, 1-BUTOXY-2,3-EPOXY- (CAS# [*2426-08-6*])

Table 35

Table 110.35. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CADMIUM (CAS# [*7440-43-9*])

Table 36

Table 110.36. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: LIMESTONE (CAS# [*1317-65-3*])

Table 37

Table 110.37. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CALCIUM CHROMATE (CAS# [*13765-19-0*])

Table 38

Table 110.38. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CALCIUM OXIDE (CAS# [*1305-78-8*])

Table 39

Table 110.39. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SILICIC ACID, CALCIUM SALT (CAS# [*1344-95-2*])

Table 40

Table 110.40. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CALCIUM SULFATE (CAS# [*7778-18-9*])

Table 41

Table 110.41. 1981-83 NOES Estimated Number of Workers Potentially

Exposed to: CAMPHOR (CAS# [*76-22-2*])

Table 42

Table 110.42. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: AZEPIN-2-ONE, HEXAHYDRO-, 2H- (CAS# [*105-60-2*])

Table 43

Table 110.43. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CARBAMIC ACID, METHYL-, 1-NAPHTHYL ESTER (CAS# [*63-25-2*])

Table 44

Table 110.44. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CARBON BLACK (CAS# [*1333-86-4*])

Table 45

Table 110.45. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CARBON DIOXIDE (CAS# [*124-38-9*])

Table 46

Table 110.46. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CARBON DISULFIDE (CAS# [*75-15-0*])

Table 47

Table 110.47. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CARBON MONOXIDE (CAS# [*630-08-0*])

Table 48

Table 110.48. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CARBON TETRACHLORIDE (CAS# [*56-23-5*])

Table 49

Table 110.49. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: PYROCATECHOL (CAS# [*120-80-9*])

Table 50

Table 110.50. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CHLORINE (CAS# [*7782-50-5*])

Table 51

Table 110.51. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CHLOROBENZENE (CAS# [*108-90-7*])

Table 52

Table 110.52. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: METHANE, CHLORODIFLUORO- (CAS# [*75-45-6*])

Table 53

Table 110.53. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CHLOROFORM (CAS# [*67-66-3*])

Table 54

Table 110.54. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ETHANE, CHLOROPENTAFLUORO- (CAS# [*76-15-3*])

Table 55

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Table 110.223. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: PROPANOL, 2-, 1-METHOXY- (CAS# [1079-82-])

Table 224

Table 110.224. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: PROPYLENE OXIDE (CAS# [*75-56-9*])

Table 225

Table 110.225. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: PYRETHRUM (CAS# [*8003-34-7*])

Table 226

Table 110.226. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: PYRIDINE (CAS# [*110-86-1*])

Table 227

Table 110.227. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: BENZOQUINONE, PARA- (CAS# [*106-51-4*])

Table 228

Table 110.228. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: RESORCINOL (CAS# [*108-46-3*])

Table 229

Table 110.229. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: RHODIUM (CAS# [*7440-16-6*])

Table 230

Table 110.230. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ROSIN (CAS # 8050-09-7)

Table 231

Table 110.231. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ROTENONE (CAS# [*83-79-4*])

Table 232

Table 110.232. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: NAPHTHA (CAS# [*8030-30-6*])

Table 233

Table 110.233. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SELENIUM (CAS# [*7782-49-2*])

Table 234

Table 110.234. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: KIESELGUHR (CAS# [*61790-53-2*])

Table 235

Table 110.235. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: FUMES, SILICA (CAS# [*69012-64-2*])

Table 236

Table 110.236. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SILICA, FUSED (CAS# [*60676-86-0*])

Table 237

Table 110.237. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CRISTOBALITE (CAS# [*14464-46-1*])

Table 238

Table 110.238. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: QUARTZ (CAS# [*14808-60-7*])

Table 239

Table 110.239. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TRIPOLI (CAS # 1317-95-9)

Table 240

Table 110.240. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SILICON (CAS # 7440-21-3)

Table 241

Table 110.241. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SILICON CARBIDE (CAS # 409-21-2)

Table 242

Table 110.242. 1981-83 NOES Estimated Number of Workers Potentially

Exposed to: SILANE (CAS# [*7803-62-5*])

Table 243

Table 110.243. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SILVER (CAS # 7440-22-4)

Table 244

Table 110.244. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SODIUM AZIDE (CAS# [*26628-22-8*])

Table 245

Table 110.245. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SODIUM BISULFITE (CAS# [*7631-90-5*])

Table 246

Table 110.246. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SODIUM HYDROXIDE (CAS # 1310-73-2)

Table 247

Table 110.247. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: PYROSULFUROUS ACID, DISODIUM SALT (CAS# [*7681-57-4*])

Table 248

Table 110.248. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: STARCH (CAS# [*9005-25-8*])

Table 249

Table 110.249. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: STODDARD SOLVENT (CAS# [*8052-41-3*])

Table 250

Table 110.250. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: CHROMIC ACID, STRONTIUM SALT (1:1) (CAS# [*7789-06-2*])

Table 251

Table 110.251. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: STYRENE (CAS# [*100-42-5*])

Table 252

Table 110.252. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SUCROSE (CAS# [*57-50-1*])

Table 253

Table 110.253. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: THIOPYROPHOSPHORIC ACID(((HO)2PS)20), TETRAETHYL ESTER (CAS# [*3689-24-5*])

Table 254

Table 110.254. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SULFUR DIOXIDE (CAS# [*7446-09-5*])

Table 255

Table 110.255. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SULFUR HEXAFLUORIDE (CAS# [*2551-62-4*])

Table 256

Table 110.256. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SULFURIC ACID (CAS# [*7664-93-9*])

Table 257

Table 110.257. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SULFUR CHLORIDE(S2CL2) (CAS# [*10025-67-9*])

Table 258

Table 110.258. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TELLURIUM (CAS# [*13494-80-9*])

Table 259

Table 110.259. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TERPHENYL (CAS# [*26140-60-3*])

Table 260

Table 110.260. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: PLUMBANE, TETRAETHYL- (CAS# [*78-00-2*])

Table 261

Table 110.261. 1981-83 NOES Estimated Number of Workers Potentially

Exposed to: FURAN, TETRAHYDRO (CAS# [*109-99-9*])

Table 262

Table 110.262. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: SODIUM PYROPHOSPHATE, TETRA (CAS# [*7722-88-5*])

Table 263

Table 110.263. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: THIOBIS(6-TERT-BUTYL-META-CRESOL), 4,4- (CAS# [*96-69-5*])

Table 264

Table 110.264. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: THIOGLYCOLIC ACID (CAS# [*68-11-1*])

Table 265

Table 110.265. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: DISULFIDE, BIS(DIMETHYLTHIOCARBAMOYL) (CAS# [1372-68-])

Table 266

Table 110.266. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TIN (CAS # 7440-31-5)

Table 267

Table 110.267. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TITANIUM OXIDE (TIO2) (CAS# [*13463-67-7*])

Table 268

Table 110.268. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: BENZIDINE, 3,3-DIMETHYL- (CAS# [*119-93-7*])

Table 269

Table 110.269. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TOLUENE (CAS# [*108-88-3*])

Table 270

Table 110.270. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TOLUENE-2,4-DIISOCYANATE (CAS# [*584-84-9*])

Table 271

Table 110.271. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TOLUIDINE, ORTHO- (CAS# [*95-53-4*])

Table 272

Table 110.272. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TRIBUTYL PHOSPHATE (CAS# [*126-73-8*])

Table 273

Table 110.273. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TRICHLOROACETIC ACID (CAS# [*76-03-9*])

Table 274

Table 110.274. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ETHYLENE, TRICHLORO- (CAS# [*79-01-6*])

Table 275

Table 110.275. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: METHANE, TRICHLOROFLUORO- (CAS# [*75-69-4*])

Table 276

Table 110.276. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ETHANE, 1,1,2-TRICHLORO-1,2,2-TRIFLUORO- (CAS# [*76-13-1*])

Table 277

Table 110.277. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: NITRILOTRIETHANOL, 2,2,2"- (CAS# [*102-71-6*])

Table 278

Table 110.278. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TRIETHYLAMINE (CAS# [*121-44-8*])

Table 279

Table 110.279. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TRIMELLITIC ANHYDRIDE (CAS# [*552-30-7*])

Table 280

Table 110.280. 1981-83 NOES Estimated Number of Workers Potentially

Exposed to: TRIMETHYL PHOSPHITE (CAS# [*121-45-9*])

Table 281

Table 110.281. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TRIPHENYL PHOSPHATE (CAS# [*115-86-6*])

Table 282

Table 110.282. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TUNGSTEN (CAS # 7440-33-7)

Table 283

Table 110.283. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: TURPENTINE (CAS # 8006-64-2)

Table 284

Table 110.284. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ACETIC ACID ETHENYL ESTER (CAS# [*108-05-4*])

Table 285

Table 110.285. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ETHYLENE, CHLORO- (CAS# [*75-01-4*])

Table 286

Table 110.286. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: VINYLTOLUENE (CAS# [*25013-15-4*])

Table 287

Table 110.287. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: LIGROINE (CAS# [*8032-32-4*])

Table 288

Table 110.288. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: XYLENE AND ISOMERS (CAS #'S 1330-20-7, 95-47-6, 108-38-3, 106-42-3)

Table 289

Table 110.289. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ZINC CHLORIDE (CAS# [*7646-85-7*])

Table 290

Table 110.290. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ZINC CHROMATES (CAS #'S 13530-65-9, 11103-86-9, 37300-23-5)

Table 291

Table 110.291. 1981-83 NOES Estimated Number of Workers Potentially Exposed to: ZINC OXIDE (ZNO) (CAS# [*1314-13-2*])

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Carbon Black

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1 Introduction

Carbon black is a powdered form of elemental carbon in the form of near-spherical colloidal

particles and coalesced particle aggregates of colloidal size, obtained by partial combustion or thermal decomposition of hydrocarbons (1). It is distinguishable from other commercial carbons, such as charcoal, by its fine particulate nature and the shape, structure, and degree of fusion of the particles observed with the electron microscope. The fundamental unit of a carbon black particle is the aggregate (2). Although carbon black is often equated with soot, it differs markedly from the unwanted, uncontrolled by-products of combustion found in chimneys and the ambient air. The contrast between carbon blacks, soots, and diesel particulate is discussed in more detail in the following.

Carbon black is the earliest known synthetic pigment, having been produced by the Chinese more than 1500 years ago. They made the ink pigment lampblack by burning purified animal or vegetable oils in small lamps with the flames impinging on cool porcelain surfaces on which the carbon black collected.

Carbon black has been commercially produced in the United States for more than 100 years. Although it is still used as a pigment in printing inks, paints, and lacquers, its major use over the past 50 years has been as a reinforcing agent in rubber, particularly in tires. It is also used in plastics, to which it imparts weathering resistance, antistatic, and electrically conductive properties.
1.0 Carbon Black
1.0.1 CAS Number: [*1333-86-4*]

1.0.2 Synonyms: Carbon Lampblack; Acetylene black; Lampblack; Thermal black; Channel black

1.0.3 Trade Names: NA

1.0.4 Molecular Weight: 12.0

1.0.5 Molecular Formula: C
1.1 Production and Use
From the primitive Chinese process mentioned, the production of carbon black has evolved into a high-volume, continuous process in which carefully controlled conditions determine the final characteristics of the product. Channel black manufacture started in the United States in the 1870s with plants located close to sources of the feedstock, natural gas. The introduction of the higher-yielding oil furnace process in the 1940s, the high level of smoke pollution, and the increasing cost of natural gas caused a steady decline in channel black production. The last channel black plant in the United States closed in 1976. Now over 95% of carbon black worldwide is produced by the oil furnace process. The unique association between the physicochemical characteristics of carbon blacks and their performance in various applications has, however, ensured the continued production of small quantities of blacks by the thermal, lampblack, channel, and acetylene black processes.

Carbon Black

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