EMERGENCY AND CONTINUOUS EXPOSURE LIMITS FOR SELECTED AIRBORNE CONTAMINANTS

Volume 2

COMMITTEE ON TOXICOLOGY
Board on Toxicology and Environmental Health Hazards
Commission on Life Sciences
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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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The document has been evaluated in total by the current members of the Committee; however, much of the work was initially done by former members. The contributions of the following are particularly noted: Richard R. Bates, Health Effects Institute, Cambridge, Mass.; Donald Ecobichon, McGill University; Lawrence Fishbein, National Center for Toxicological Research, Jefferson, Ark.; Peter Greenwald, National Cancer Institute, Bethesda, Md.; Ian Higgins, University of Michigan, Ann Arbor, Mich.; Wendell Kilgore, University of California, Davis, Cal.; Leonard T. Kurland, Mayo Clinic, Rochester, Minn.; Howard Maibach, University of California, San Francisco, Cal.; H. George Mandel, The George Washington University, Washington, D.C.; Robert E. Menzer, University of Maryland, College Park, Md.; Charles Reinhardt, E.I. duPont de Nemours and Company, Newark, Del.; Joseph Rodricks, Environ Corporation, Washington, D.C.; Ronald C. Shank, University of California, Irvine, Cal.; Edward A. Smuckler, University of California, San Francisco, Cal.; Robert Snyder, Rutgers University, Piscataway, N. J.; Peter Spencer, Albert Einstein College of Medicine, Bronx, N. Y.; and Philip Watanabe, Dow Chemical USA, Midland, Mich.

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INTRODUCTION

The National Research Council's Committee on Toxicology recommends emergency exposure limits (EELs), short-term public limits (STPLs), and short-term public emergency limits (SPELs--formerly called public emergency limits, or PELs) for a variety of chemicals of concern to its sponsoring agencies. The definitions and applicability of these limits and the criteria used to establish them were originally outlined in two documents prepared by the Committee (National Research Council, 1964, 1971). In a revision of these documents (National Research Council, 1979), the Committee summarized the principles used to establish exposure limits for short durations. The Committee has also recommended continuous exposure limits (CELs) in response to specific sponsor requests.

This document is one in a series prepared by the Committee that form the basis of the recommendations for EELs and CELs for selected chemicals. Since the Committee began recommending EELs and CELs for its military sponsors (U.S. Army, Navy, and Air Force), the scope of its recommendations has been expanded in response to requests by the U.S. Coast Guard and the National Aeronautics and Space Administration. The CELs grew out of a Navy request for exposure limits for atmospheric contaminants in submarines. The EELs and CELs have been used as design criteria by the sponsors in considering the suitability of materials for particular missions (as in a submarine or a spacecraft) and in assessing the habitability of particular enclosed environments. They are recommended for narrowly defined occupational groups and are not intended for application in general industrial settings or as exposure limits for the general public. These recommended values do not take into consideration the possible effects of exposure of hypersensitive persons.

The EEL is defined as a ceiling limit for an unpredictable single exposure, usually lasting 60 min or less, and never more than 24 h--an occurrence expected to be rare in the lifetime of any person. It reflects an acceptance of the statistical likelihood of the occurrence of a nonincapacitating, reversible effect in an exposed population. It is designed to avoid substantial decrements in performance during emergencies and might contain no uncertainty factor.

The CEL is recommended in specific situations where there may be exposure to a chemical continuously for up to 90 d. It is defined as a ceiling limit designed to avoid adverse health effects, either immediate or delayed, and to avoid degradation in crew performance that might endanger the objectives of a particular mission. Because human data on continuous exposures are rarely available, uncertainty factors might be used, the magnitude depending on the judgment of the Committee.

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National Research Council,Committee on Toxicology. 1971. Basis for Establishing Guides for Short-Term Exposures of the Public to Air Pollutants. Washington, D.C.: National Academy of Sciences. [15 p.]

National Research Council,Committee on Toxicology. 1979. Criteria for Short-Term Exposures to Air Pollutants. Washington, D.C.: National Academy of Sciences. [15 p.]

SUMMARY

Because this report deals with diverse substances, a conventional summary would be inappropriate. Table 1 summarizes previously recommended and currently recommended emergency exposure limits (EELs) for up to 24 h and continuous exposure limits (CELs) for 90 d for chemicals suggested for review by military sponsors of the Committee on Toxicology.

TABLE 1 Emergency and Continuous Exposure Limits

	Duration of Exposure	Previous Recommendations		Current Recommendations
Substance		Year	Limit	
Chlorine	60 min	1971	3 ppm	3 ppm
	24 h		1 ppm	0.5 ppm
	90 d		0.1 ppm	0.1 ppm
Chlorine trifluoride	10 min	1968	7 ppm	7 ppm
	30 min		3 ppm	3 ppm
	60 min		1 ppm	1 ppm
Ethanolamine	60 min	1967	50 ppm	50 ppm
	24 h		3 ppm	3 ppm
	90 d		0.5 ppm	0.5 ppm
Trichlorofluoromethane (FC 11)	60 min	1966	30,000 ppm	1,500 ppm
	24 h		20,000 ppm	500 ppm
	90 d		1,000 ppm	100 ppm
Dichlorodifluoromethane (FC 12)	60 min	1966	30,000 ppm	10,000 ppm
	24 h		20,000 ppm	1,000 ppm
	90 d		1,000 ppm	100 ppm
Dichlorofluoromethane (FC 21)	60 min	--	--	100 ppm
	24 h		--	3 ppm
	90 d		--	1 ppm
Trichlorotrifluoroethane (FC 113)	60 min	1969	1,500 ppm	1,500 ppm
	24 h		200 ppm	500 ppm
	90 d		100 ppm	100 ppm
Dichlorotetrafluoroethane (FC 114)	60 min	1966	30,000 ppm	10,000 ppm
	24 h		20,000 ppm	1,000 ppm
	90 d		1,000 ppm	100 ppm

Isopropyl alcohol	60 min	1966	400 ppm	400 ppm
	24 h		200 ppm	200 ppm
	90 d		50 ppm	1 ppm
Phosgene	60 min	1966	1 ppm	0.2 ppm
	24 h		0.1 ppm	0.02 ppm
	90 d		0.05 ppm	0.01 ppm
Sodium hydroxide	10 min	1965	4 mg/m^3	2 mg/m^3
	30 min		4 mg/m^3	2 mg/m^3
	60 min		2 mg/m^3	2 mg/m^3
Sulfur dioxide	10 min	1966	30 ppm	30 ppm
	30 min		20 ppm	20 ppm
	60 min		10 ppm	10 ppm
	24 h		5 ppm	5 ppm
	90 d		1 ppm	1 ppm
Vinylidene chloride	24 h	1966	25 ppm	10 ppm
	90 d		2 ppm	0.15 ppm
Xylene	60 min	1966	200 ppm	200 ppm
	24 h		100 ppm	100 ppm
	90 d		50 ppm	50 ppm

CHLORINE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	Cl_2
Molecular weight:	70.906
CAS number:	7782-50-5
Boiling point:	−34.05°C
Density:	1.4085 (20°C)
General characteristics:	Greenish-yellow gas with suffocating odor
Conversion factors:	1 ppm = 2.89 mg/m^3 1 mg/m^3 = 0.34 ppm

OCCURRENCE AND USE

Chlorine is abundant in combined form in the earth's crust (0.19%) and in seawater (3%). It is usually produced by electrolysis of chlorides. Contaminants include hexachloroethane, hexachlorobenzene, and water. Chlorine was among the first of the war gases used in World War I. It is now used as a bleaching agent, as a germicidal agent for purifying water, and in the manufacture of chlorinated hydrocarbons and chlorine-containing chemicals. About 10 million tons of chlorine is produced annually for industrial use. Massive exposure to fumes may occur during transportation accidents, but the development of treatment procedures has resulted in low incidences of morbidity and mortality in industrial operations, as opposed to nonindustrial exposures (ACGIH, 1980; Lawson, 1981; Stecher et al., 1968; Ploysongsang et al., 1982).

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

An epidemiologic study by Patil et al. (1970) evaluated a population of 500 diaphragm-cell workers exposed to chlorine at a ime-weighted average concentration of 0.146 ± 0.287 ppm (range, 0.006-1.42 ppm). It was concluded that results of chest x rays, ECGs, and pulmonary-function tests were no different between exposed and 382 control workers.

A chlorine study performed on 30 students at the University of Michigan by Anglen et al. (1980) disclosed some sensation of odor, throat irritation, and urge to cough in subjects exposed for 4 h at 0.5 and 1.0 ppm. Exposure at 2 ppm was reported to be much more irritating than that at 0.5 and 1.0 ppm for the same period. The effects were confirmed by a physician.

A study of pulmonary function on four healthy adults accidentally exposed for 2-5 min to chlorine (at unknown concentrations) showed

temporary lung-function impairment, which cleared, with no residual lung damage, after 1 mo. Fourteen to sixteen hours after exposure, patients were symptomatic, with cough, chest tightness, and shortness of breath. All had restrictive ventilating defects with impaired diffusing capacity and evidence of obstruction of small airways (Ploysongsang et al., 1982).

Results from a study sponsored by the Chlorine Institute (Rotman et al., 1983) indicate that an 8-h exposure of humans to chlorine at 1 ppm resulted in sensory irritation and changes in pulmonary functions. The literature on the health effects of chlorine has recently been reviewed (National Research Council, 1975).

Data published on airborne exposures of humans to chlorine are summarized in Table 2.

EFFECTS ON ANIMALS

Barrow and Smith (1975) and Barrow et al. (1977) demonstrated that chlorine exposure caused alterations of pulmonary function in rabbits and reduced respiratory rate in mice. The concentration of chlorine to which exposure for 10 min was required to decrease respiratory rate in mice by 50% (RD_{50}) was about 10 ppm. The authors suggested that exposure to a chemical at a concentration that reduced respiratory rate in mice by 50% would be intolerable and incapacitating to humans and that one-tenth of the RD_{50} might create some discomfort, but would be tolerable. Although this assumption appears to be true for chlorine, studies with other substances have challenged its general applicability. Potts and Lederer (1978) have shown that the pyrolysis products of red oak at concentrations that reduced respiratory rate in mice by 50% did not incapacitate humans. Therefore, use of the RD_{50} in mice for predicting sensory irritation in humans may very well be compound-specific.

Barrow et al. (1978) also reported studies of male and female Fischer 344 rats (10 of each sex) exposed to chlorine at 1, 3, or 9 ppm for 6 h/d, 5 d/wk, for 6 wk. The results showed decreased body weights in females at all concentrations and in males at 3 and 9 ppm. Three females died before the end of the study. Urinalysis, hematologic tests, and clinical-chemistry measurements were completed for the surviving animals. The urinary specific gravity was increased in females at all exposure concentrations and in males at 3 and 9 ppm. The hematocrit and white-blood-cell count were increased in females exposed at 9 ppm. Clinical-chemistry results included increases in alkaline phosphatase, blood urea nitrogen (BUN),γ-glutamyl transpeptidase (GGTP), and serum glutamic pyruvic transaminase (SGPT) at 9 ppm and in alkaline phosphatase at 3 ppm.

Pathologic examination of rats exposed at 9 ppm showed gross evidence of inflammatory reactions of the upper and lower respiratory tract, including hyperemia and accumulation of inflammatory material in the nasal passages. There were also various degrees of pulmonary atelectasis or consolidation. These observations were also made, but to a much smaller degree, in rats exposed at 3 ppm. The kidneys of rats exposed at 9 ppm were found to be darkened. These data indicated that repeated exposures of rats to chlorine at 3 and 9 ppm resulted in gross pathologic changes of the respiratory tract, significantly

decreased body weight, and altered kidney function and revealed a greater sensitivity of females. Although the results suggested that repeated exposure to chlorine at 1 ppm may have produced some toxicity, personal communication with the authors has revealed that chloramine may have been formed from chlorine and ammonia in the inhalation chamber during exposure. Thus, it was not certain whether repeated exposure to chlorine at 1 ppm alone was responsible for the toxic effects observed.

Chlorine itself is not absorbed. The chloride content of the plasma increases for a few hours after gassing, and urinary chloride excretion is increased on the second day after gassing.

In living tissues, chlorine rapidly converts to hypochlorous acid (Zillich, 1972), which easily penetrates the cell wall and reacts with cytoplasmic proteins to form N-chloro derivatives that destroy cell structure (National Research Council, 1975).

Data on animals exposed to chlorine are summarized in Table 3.

INHALATION EXPOSURE LIMITS

The American Conference of Governmental Industrial Hygienists (1980, 1983) has established a TLV-TWA for chlorine of 1 ppm and a 15-min TLV-STEL of 3 ppm. The TLV-TWA of 1 ppm was recommended "to minimize chronic changes in the lungs, accelerated aging, and erosion of the teeth." The Occupational Safety and Health Administration (1983) adopted a ceiling limit of 1 ppm as the federal workplace standard for chlorine.

COMMITTEE RECOMMENDATIONS

Emergency exposure limits were set by the Committee in 1966 and 1971 primarily on the basis of the chlorine concentrations that produced nasal and eye irritation. Having reviewed available toxicity data on chlorine, the Committee believes that no compelling new information warrants revision of the previously established 60-min EEL and 90-d CEL. However, on the basis of human data that suggest sensory irritation and changes in pulmonary function as results of 8-h exposure to chlorine at 1 ppm, the Committee believes that the 24-h EEL should be lowered to 0.5 ppm.

The present Committee's recommended EELs and CEL for chlorine and the limits proposed in 966 and 1971 are shown below.

	1966/1971	1984
60-min EEL	3 ppm	3 ppm
24-h EEL	1 ppm	0.5 ppm
90-d CEL	0.1 ppm	0.1 ppm

TABLE 2 Human Exposure to Chlorine

Concentration, ppm	Comments	Reference
34-51	Lethal in 1-1.5 h	Freitag, 1941
14-21	Dangerous within 0.5-1 h	Heyroth, 1963
7	Recommended 5-min EEL[a]	Zielhuis, 1970
5	Severe irritation of eyes, nose, and respiratory tract; intolerable after a few minutes	Zielhuis, 1970
3-6	Stinging or burning in eyes, nose, and throat; perhaps headache due to sinus irritation; watering of eyes; sneezing; coughing; bloody nose; blood-tinged sputum	Heyroth, 1963
5	Recommended 15-min EEL[a]	Zielhuis, 1970
4	Recommended 30-min EEL[a]	Zielhuis, 1970
3.5	Odor threshold	ACGIH, 1980
3	Short-term (5-min) limit	Pa. Dept. of Health undated
3	Permissible exposure (15 min)	ACGIH, 1983
3	Recommended 60-min EEL[a]	Zielhuis, 1970
1-3	Slight irritation	Zielhuis, 1970
1-2	Men can work without interruption	Heyroth, 1963
1	ACGIH TLV-TWA and OSHA standard	ACGIH, 1983 OSHA, 1983
0.146 (mean)	No effects on chest x ray, ECG, or pulmonary-function after 30 yr of exposure	Patil et al., 1970

[a] For emergency in manufacturing area and its neighborhood, in storage facilities and surrounding areas, and during transport; suggested by Zielhuis in 1970.

TABLE 3 Animal Exposure to Chlorine

Species	Concentration, ppm	Duration	Effects	Reference
Rabbit	50, 100, 200	30 min	Alteration of pulmonary function	Barrow and Smith, 1975
Mouse	0.7, 38.4	10 min	RD_{50}: 10 ppm	Barrow et al., 1977
Rat	9	6 h/d, 5 d/wk, 6 wk	Decreased body weight; increased urinary specific gravity; increased alkaline phosphatase, GGTP, SGPT, and BUN; increased hematocrit and WBC (females only); pulmonary inflammation and darkened kidneys at autopsy	Barrow et al., 1978
Rat	3	6 h/d, 5 d/wk, 6 wk	Decreased body weight; increased urinary specific gravity; increased alkaline phosphatase; less pulmonary inflammation than at 9 ppm	Barrow et al., 1978
Rat	1	6 h/d, 5 d/wk, 6 wk	Decreased body weight (females only); increased urinary specific gravity (females only)[a]	Barrow et al., 1978

[a] Whether effects are due to chlorine is questionable, in that chloramine may have been present in inhalation chambers.

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CHLORINE TRIFLUORIDE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	ClF_3
Molecular weight:	92.46
CAS number:	7790-91-2
Melting point:	−80 to −83°C
Boiling point:	11.2-11.75°C
Density:	1.8403 g/ml (15°C)
General characteristics:	May exist as white solid, colorless to pale yellow-green liquid, or practically colorless gas; sweet suffocating odor; odor threshold very low, but not accurately known (Cloyd and Murphy, 1965); vapor phase decomposes into Cl_2, ClF, ClOF, ClO_2, and HF, depending on availability of water
Conversion factors:	1 ppm = 3.78 mg/m^3 1 mg/m^3 = 0.26 ppm

OCCURRENCE AND USE

Chlorine trifluoride is used as a fluorinating agent, in nuclear-fuel processing, as an incendiary, and as an igniter and propellant for rockets (Windholz et al., 1976). It is prepared by reaction of chlorine and fluorine at 280°C and condensation of the product at −80°C. The product obtained is 99.0% pure (Hawley, 1977). Dost et al. (1974) noted the instability of chlorine trifluoride and the potential diversity of its hydrolysis products.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

At high concentations (detectable by odor), exposure can cause gasping, swelling of the eyes and eyelids, cloudiness of the cornea, lacrimation, severe salivation, coughing, breathing difficulties, and convulsions within a few minutes (Cloyd and Murphy, 1965). Damage to the eyes is said to be permanent (Leins, undated). Concentrations high enough to be fatal would be so irritating to eyes, throat, and lungs as to be intolerable. The halogen-pungent odor of chlorine trifluoride can be detected at sufficiently low concentrations that exposed personnel may not experience adverse effects if they evacuate the area immediately (Cloyd and Murphy, 1965). Contact with skin causes severe burns and ulcers that are difficult to heal (Cloyd and Murphy, 1965; Leins, undated). The tissue destruction is caused by

oxidation of tissues, thermal damage from the heat of oxidation, and the effects of HF formed (Cloyd and Murphy, 1965).

In the only documented human exposure, a worker was exposed to the effluent of a chlorine trifluoride-charcoal reactor when he was eating lunch approximately 200 ft downwind from the disposal system. The exposure lasted about 1-2 min. He reported to the medical clinic with symptoms of frontal headache, a bad taste, abdominal pain, and breathing difficulty that persisted for some 2 h. A physician treated him with oxygen therapy for 0.5 h and with APCs (a mixture of aspirin, phenacetin, and caffeine) and the symptoms were relieved. No systemic or local effects were found. The patient reported for work the next day, with no apparent after-effects except fatigue (Longley et al., 1965).

EFFECTS ON ANIMALS

Rats exposed in a dynamic-flow chamber to chlorine trifluoride at 400 ppm died within 40 min; at 800 ppm, the LT_{50} (lethal time for 50% of the animals) was 15 min. Inhalation exposure of rats at 800 ppm for 15 min was always lethal, whereas exposure at 400 ppm was usually lethal after 35 min of exposure (Dost et al., 1974). In another experiment, 1-h exposure to chlorine trifluoride led to $LC50^s$ of 299 (260-344) ppm in male rats and 178 (169-187) ppm in mice (Vernot et al., 1977).

In extensively described experiments, rats were exposed at 480, 96, and 21 ppm; two dogs were also exposed at 21 ppm (Horn and Weir, 1955). The LT_{50} at 480 ppm was 40 min; at 96 ppm, it was 3.7 h. At 480 ppm, the rats immediately exhibited increased activity. After 2 min, rhinorrhea was noted. From then on, symptoms of respiratory difficulty, eye irritation, and excessive salivation developed. Within 20 min, all were in “acute distress.” In several rats, the cornea looked dull and milky-white where it was not protected by the eyelid. All rats died within 70 min; death was usually preceded by excitement and occasionally by convulsions and coma. The same signs developed, at a lower rate, in the rats exposed at 96 ppm. After 4.5 h of exposure, 70% of the animals were dead. Shortly after the survivors were removed from the chamber, two more died (total mortality, 80%). Some showed excitement and “tonic movements” before death. The gross pathology of the lungs from the animals exposed at 480 and 96 ppm was the same: emphysema, pulmonary edema, vascular congestion, and fusion of the lining cells of the bronchi into a hyaline membrane. The livers exhibited hydropic degeneration and marked vascular congestion. In the 96-ppm group, only the gastrointestinal tract was markedly distended with gas.

Rats and dogs were exposed at 21 ppm 6 h/d for 2 d. About 10 min after exposure began, the dogs had rhinorrhea and lacrimation and kept their eyes tightly closed. During the first day, they coughed up mucous material and had rapid respiration and excessive salivation. When removed from the chamber, they refused to eat or drink, and they kept their eyes tightly closed. The conjunctivae were markedly injected. The animals' fur felt as though it had been “singed.” Toxic signs also appeared early in the rats, with preening and rhinorrhea. By the end of the first day, rhinorrhea and lacrimation

were observed. By the next morning, the animals were essentially normal, except that the dogs' eyes were still markedly inflamed. The second day of the exposure followed the same course as the first up to 4.5 h after starting. The exposure was then halted, because the exhaust system had become plugged and air flow had decreased. The concentration at which the animals had been exposed was not determined, but certainly had risen somewhat. After removal from the chamber, one dog developed severe bilateral corneal ulcers, which had re-epithelialized after a month. Within a few days, all the animals were essentially normal, except for the presence of corneal ulcers in one dog.

Horn and Weir (1955) also exposed two dogs and 20 rats to chlorine trifluoride at an average concentration of 5.15 ppm for 6 h/d, 5 d/wk, for 6 wk (31 exposures). The same signs developed over the first several days as had after acute exposure, but they were less severe. By the midpoint of the experiment, some respiratory distress developed; one dog died after 17 d, and another on the twenty-sixth day. Both apparently died of pneumonia, although penicillin therapy was given to the second. Only one rat died during the experiment; its death was preceded by a convulsion. All others appeared to be in poor health. All the animals that died had bronchopneumonia, bronchiectasis, purulent bronchiolitis, and lung abscesses. Those killed at the end of the experiment had lung hyperemia, hemorrhage, and edema. The kidneys and livers showed vascular congestion.

In a chronic exposure study, 20 rats and two dogs were exposed to chlorine trifluoride at an average concentration of 5.15 ppm for 6 h/d, 5 d/wk, for 6 mo (Horn and Weir, 1956). At the start of the experiment, the dogs exhibited the early signs of irritation, but the rats appeared unaffected and quiet. Recovery was complete overnight. By the ninth day, the rats started preening immediately after exposure began; they them became “depressed” and remained so for the rest of the exposure period. One-fourth of the rats died during the experiment. Autopsy of these rats showed pulmonary edema and bronchopneumonia. The animals that survived showed essentially the same signs as were seen in the subacute exposures. On autopsy, pulmonary irritation was observed. One dog died on day 115 of the experiment of purulent bronchitis and pulmonary abscesses. The other had alveolar hemorrhage, interstitial edema, and pulmonary irritation on autopsy.

INHALATION EXPOSURE LIMITS

The ACGIH has established a ceiling limit for chlorine trifluoride of 0.1 ppm approximately 0.4 mg/m^3) (ACGIH, 1980, 1983). Its recommendation noted that this limit is probably low enough to prevent development of serious injury, but the suitability of the limit requires further evaluation in controlled worker exposure.

COMMITTEE RECOMMENDATIONS

The toxicology of chlorine trifluoride was reviewed originally by the Committee on Toxicology in 1962 and updated in 1968.

The only new information that was not available to the Committee at the previous updating deals with the acute toxicity of the compound by inhalation. The determined values are consistent with previous data. Therefore, there appears to be no reason to change the previously established exposure limits. However, as stated by ACGIH, data are still needed on controlled exposure of workers in occupational settings.

The present Committee's recommended EELs for chlorine trifluoride and the limits proposed in 1968 are shown below.

	1968	1984
10-min EEL	7 ppm	7 ppm
30-min EEL	3 ppm	3 ppm
60-min EEL	1 ppm	1 ppm

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ETHANOLAMINE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	C_2H_7NO
Molecular weight:	61.08
Chemical Names:	2-Aminoethanol, ethylolamine, ß-aminoethyl alcohol, glycinol, 2-hydroxyethylamine, ß-hydroxyethylamine, monoethylamine
Synonyms:	Olamine, colamine
CAS number:	141-43-5
Melting point:	10.5°C
Boiling point:	170.5°C (760 mm Hg)
Flash point (open cup):	200°F
Specific gravity:	1.0179
Vapor pressure:	0.4 mm Hg (20°C)
Vapor density:	2.1 (air = 1)
Solubility in water:	Complete
Odor threshold (sensation):	2.6 ppm (Weeks et al., 1960)
Odor threshold (describable):	25 ppm (Weeks et al., 1960)
General characteristics:	Colorless liquid with mildly ammoniacal odor and relatively strong base
Conversion factors:	1 ppm = 2.5 mg/m^3 1 mg/m^3 = 0.4 ppm

OCCURRENCE AND USE

Ethanolamine is used to remove carbon dioxide from submarines. It is also used to scrub natural gas; as a dispersant for agricultural products; as a softening agent for hides; as an accelerator (after reaction with other substances) in the production of antibiotics, polishes, and waving solutions for hair; as a corrosion inhibitor; as a rubber accelerator; an intermediate in the production of emulsifiers, soaps, and detergents; and in some hair-care products. Dow, Olin, Texaco, and Union Carbide are the primary producers in the United States. Ethanolamine may contain isopropylamine, diethanolamine, triethanolamine, water, and ammonia.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

The I.G. Elberfeld Toxicology Index of 1931, as quoted by Browning (1953), stated that pure ethanolamine produced marked redness and infiltration when it was applied to human skin on gauze and allowed to

remain for 1.5 h. There is little other information on the effects of ethanolamine in man. An anonymous report in Bioenvironmental Safety News Letter (1972) described a case in which "a drop of amine fell" into the right eye of a sailor aboard a submarine. Within a minute, he was able to get to an eye bath, and he flushed his eye for 30 min. He had prompt medical attention, but vision in his right eye deteriorated from 20/20 to 20/200. The report stated that "he will have partial permanent disability." The same report referred to an earlier, similar incident.

Paustovskaia et al. (1977) stated that "persons working in conditions of increased concentrations of derivatives of cyclo- and dicyclohexylamine and MEA inhibitors of atmospheric corrosion of metals frequently showed changes of the central nervous system, myocardium and hepatobiliary system. Changes in the heart and liver result from the toxic effect of amine derivations on the tissues and also of indirect influence via the central nervous system. Estimation of lactic dehydrogenase isoenzymes is a valuable differential-diagnostic index of myocardial and hepatic pathology due to the effect of amines of the polymethylene series."*

The maximal permissible concentration of ethanolamine suggested by Sidorov and imofeevskaya (1979) was 0.5 mg/m^3 (approximately 0.2 ppm). They stated that workers exposed to ethanolamine at concentrations of greater than 1 mg/m^3 suffer from chronic bronchitis, disorders of the liver, asthenic syndrome, and dystonia.

No controlled-exposure or epidemiologic studies with ethanolamine have been reported.

EFFECTS ON ANIMALS

LD_{50} values are given in Table 4. Grant (1962) referred to Carpenter and Smyth (1946) and stated that a drop of ethanolamine applied to rabbit eyes causes injury similar to that caused by ammonia, but slightly less severe (graded 9 on a scale of 1-10 after 24 h). Union Carbide Corporation (1970) reported that the dermal LD_{50} of ethanolamine in rabbits is 1.00 ml/kg (24-h covered exposure). It was judged a moderate primary skin irritant, on the basis of the response to application of 0.01-ml amounts to uncovered rabbit skin 24 h later. Hinglais (1947) reported that ethanolamine had considerable necrotic action on the skin.

In a study of inhalation toxicity, Sidorov etal. (1968) exposed mice and cats to vapors of ethanolamine (heated to 80°C) for 2 h. The maximal vapor and condensation aerosol concentration achieved was 970 ppm. The cats "displayed vomiting tendencies."* No other signs were noted. A single 8-h exposure to "concentrated vapors" did not kill any of six rats (Union Carbide Corporation, 1970). Guinea pigs survived a 15-min exposure to ethanolamine at 193 ppm, but four of six died after 1-h exposure at 233 ppm (Treon etal., 1957).

* Translation.

Smyth et al. (1951) obtained the following results in a 90-d dietary feeding study in rats in which the minimal daily dose was 160 mg/kg and the maximal, 2,670 mg/kg:

Maximal daily dose with no effect:	320 mg/kg
Minimal daily dose that produced altered liver or kidney weight:	640 mg/kg
Minimal daily dose that produced histopathologic lesions and deaths:	1,280 mg/kg

Investigators at the Kettering Laboratory (Treon et al., 1957) conducted a series of animal inhalation exposures to ethanolamine. The exact amount of free ethanolamine delivered to the animals is unknown, because carbon dioxide in the stream of dried air converted some of the ethanolamine to a carbonate. Dogs and cats survived concentrations of 990 ppm for 7 h on each of four consecutive days. Rats, rabbits, and mice were less susceptible than guinea pigs, but more suspectible than cats or dogs. Of 61 animals, 60 survived exposure at either 104 or 108 ppm for 7 h on each of five consecutive days. All but one of 26 mice survived exposure at 51 ppm for 7 h on each of 25 d over 5 wk. At autopsy, the dogs and cats appeared normal. Animals of the other species that died showed acute pulmonary irritation. The survivors had acute bronchitis and pneumonia superimposed on the pulmonary lesions.

Rats, guinea pigs, and dogs were exposed to ethanolamine for 24 h/d for 1-90 d at mean concentrations of 5-102 ppm (Weeks et al., 1960). High concentrations (66-102 ppm in dogs, 66-75 ppm in rodents) for 30 d caused extensive damage (to skin, liver, and kidney) and some deaths. Dogs exposed at 102 ppm showed some biochemical and hematologic changes; these changes were not seen in the other animals. Intermediate concentrations (12-26 ppm) for 90 d caused no fatalities during the 90-d study. Dogs exposed at 12 or 26 ppm and rodents exposed at 12-15 ppm became lethargic early in the study; the dogs recovered, but the rodents did not. The skin of all animals became irritated. Male dogs and immature rats of both sexes were exposed at 5 or 6 ppm for 40 d (rats) or 60 d (dogs). Some decrease in activity was observed. Skin irritation was also noted, although much less than in the animals exposed at high concentrations.

No data were found on chronic, carcinogenic, teratogenic, or reproductive effects of exposure to ethanolamine. This compound does not appear to be mutagenic in the Salmonella typhimurium reverse-mutation bioassay with and without S-9 using strains TA 1535 and TA 100 (Hedenstedt, 1978). Inoue et al. (1982) reported that ethanolamine was very toxic at 500 μg/ml in a cell-transformation assay; it did not produce any morphologic transformation at 25-500 μg/L.

PHARMACOKINETICS

Ethanolamine is a normal constituent of mammalian urine (Table 5), and 6-48% of ethanolamine given to rats orally is recovered in the urine

(Luck and Wilcox, 1953). In rats, 8 h after an intraperitoneal injection of ^{14}C-labeled ethanolamine, 54% of the ^{14}C was found in the liver, spleen, kidneys, brain, and diaphragm, and 11.5% was accounted for as expired $^{14}CO_2$. The liver contained approximately 50% of the ^{14}C, nearly all in the lipid fraction. The main metabolic pathway is incorporation into the phospholipid fraction. The maximal rate of respiratory excretion of $^{14}CO_2$ was observed between 1 and 2 h after administration; that indicates rapid oxidation of ethanolamine. The rate of excretion then dropped rapidly, and that suggests either dilution of the compound by endogenous ethanolamine or conversion of ethanolamine into compounds not readily catabolized (Taylor and Richardson, 1967).

Weeks et al. (1960) cited unpublished data from the Mellon Institute that showed that, in dogs treated with Nembutal (sodium pentobarbital), ethanolamine either stimulated (at low doses) or depressed (at lethal doses) the central nervous system.

INHALATION EXPOSURE LIMITS

The ACGIH (1983) recommended an 8-h TLV-TWA of 3 ppm and a 15-min TLV-STEL of 6 ppm. The OSHA (1983) standard is an 8-h PEL (permissible exposure limit) of 3 ppm. Sidorov and Timofeevskaya (1979) suggested an occupational exposure limit of 0.2 ppm.

COMMITTEE RECOMMENDATIONS

The toxicity of ethanolamine was studied by the Committee on Toxicology in 1967. The study of Weeks et al. (1960) indicated that skin and eye irritation and immediate signs of irritability and restlessness followed by central nervous system depression are the major adverse effects seen in unanesthetized experimental animals exposed to ethanolamine at 12-26 ppm for 24 h. Continuous exposure at 5-6 ppm produced some behavioral changes in animals, but only after 2-3 wk of exposure. On the basis of these data, the commitee believes that the previous recommendations are adequate. However, we note that additional data could help to refine these exposure limits. For example, reports concerning dose- and time-dependent central nervous system changes after ethanolamine exposure need to be confirmed and elaborated. It would be desirable to have better quantitative data on these changes. Although behavioral-toxicology studies are relatively new and their results are difficult to interpret, some of them might be incorporated into the studies suggested above or run separately. It would be most useful if more data on accidental exposure to humans or 40-h/wk occupational exposure could be gathered, including estimated concentrations, symptoms (if any), clinical findings, and sequelae.

The present Committee's recommended EELs and CEL for ethanolamine and the limits proposed in 1967 are shown below.

	1967	1984
60-min EEL	50 ppm	50 ppm
24-h EEL	3 ppm	3 ppm
90-d CEL	0.5 ppm	0.5 ppm

TABLE 4 LD50 Values of Ethanolamine

Species (Sex)[a]	Route	LD_{50}, mg/kg[b]	Reference
Rat (male)	Oral	1,970 (1,430-1,710)	Vernot et al., 1977
Rat (female)	Oral	1,720 (1,160-2,540)	Vernot et al., 1977
Rat (male)	Oral	3,320 (1,710-4,070)	Hartung and Cornish, 1968
Rat (male)[c]	Oral	2,740 (2,390-3,150)	Smyth et al., 1951
Rat	Oral	2,050	Sidorov et al., 1968
Mouse	Oral	1,475	Sidorov et al., 1968
Rabbit	Oral	1,000	Sidorov et al., 1968
Guinea pig	Oral	620	Sidorov et al., 1968
Rat	Subcutaneous	1,500	Sidorov et al., 1968
Rat	Intramuscular	1,750	Sidorov et al., 1968
Rat	Intravenous	225	Sidorov et al., 1968
Rat	Intraperitoneal	67	Sidorov et al., 1968

[a] If specified. [b] Ranges in parentheses. [c] Animals not fasted.

TABLE 5 Urinary Excretion of Ethanolamine[a]

		Excretion rate[b]	
Species	N	mg/d	mg/d-kg b.w.
Human:			
Males	8	12.2 (4.8-22.9)	0.162 (0.071-0.293)
Females	11	29.9 (12.9-49.8)	0.491 (0.291-0.930)
Rat:			
Males	12	0.41 (0.33-0.52)	1.46 (1.21-1.89)
Females	11	0.40 (0.36-0.45)	1.26 (0.81-1.62)
Cat	2	(1.53-1.91)	(0.443-0.465)
Rabbit	2	(3.02-3.10)	(0.80-1.01)
Dog	1	3.10	0.80

[a] Data from Luck and Wilcox, 1953.
[b] Ranges in parentheses.

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FLUOROCARBON 11

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	CCl_3F
Molecular weight:	137.38
Chemical names:	Trichlorofluoromethane, fluorotrichloromethane
Synonyms:	FC-11, Freon 11
CAS number:	75-69-4
Freezing point:	−111°C
Physical state:	Liquid below 23.7°C
Specific gravity:	1.494 (17.2°C)
Vapor density:	5.04 (air = 1)
Vapor pressure:	792 torr (25°C)
Solubility:	Insoluble in water; soluble in ethanol or alcohol
General characteristics:	At ordinary ambient temperatures, a colorless, nonflammable liquid or gas
Conversion factors:	1 ppm = 5.6 mg/m^3 1 mg/m^3 = 0.18 ppm

OCCURRENCE AND USE

Fluorocarbon 11 (FC-11) has been used primarily as an aerosol propellant, refrigerant, and blowing agent for polymeric foams. Its use is now banned because of its potential effects on the ozone layer.

It is prepared from carbon tetrachloride and antimony trifluoride (Stecher et al., 1968; ACGIH, 1980). FC-11 may be a contaminant of submarine atmospheres.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Inhalation of fluorocarbons during the years 1960-1970 was a prominent cause of abusive death among teen-agers. Severe cardiac arrhythmia--resulting from light plane anesthesia and intensified by hypercapnia, stress, or activity--was suggested as an explanation for 110 cases of sudden sniffing death (Bass, 1970). Typically, a person would spray the Freon into a paper bag from a commercial aerosol product and inhale it; after a few breaths and a short excitement period, death might occur. Fluorocarbons are thought to sensitize the heart to asphyxia-induced sinus bradycardia, atrioventricular block, and ventricular T-wave depression (Haj et al., 1980).

Accidental ingestion of FC-11 occurred when a healthy man mistook a bottle in a refrigerator for a bottle of plain water. This resulted in freezing, tissue necrosis, and multiple perforations of the

stomach. The patient recovered after surgery to remove the damaged tissue (Haj et al., 1980).

Labeled FC-11 administered to four healthy males by inhalation of a single breath held for 5 s was eliminated from the body rapidly. Results in humans appeared to parallel those in rats in more detailed studies (Williams et al., 1974). The investigators found rapid transfer of FC-11 to blood followed by distribution to fat, from which release was slow. Mergner et al. (1975) exposed a male and a female volunteer to radiolabeled FC-11 at 1,000 ppm for 7-17 min. Recovery of administered radioactivity in exhaled air was essentially complete (99% and 79%). Errors in collection of rapidly eliminated gases account for the differences from 100%. Only a very small fraction of the administered radioactivity (less than 0.2%) was exhaled as $^{14}CO_2$ or excreted as nonvolatile urinary activity. The impurities in FC-11--namely, chloroform and carbon tetrachloride--known to be metabolized could account for all the radioactivity found in urine and exhaled CO_2 after exposure to FC-11.

Cardiac effects have been studied in healthy subjects and patients with bronchopulmonary disease. None of the subjects exhibited cardiotoxic effects (Fabel etal., 1972).

Human volunteers were exposed to FC-113 (similar to FC-11) at 500 or 1,000 ppm for 6 h/d, 5 d/wk during a 2-wk period. No adverse changes were seen in performance of complex mental tasks, clinical status, or results of biochemical tests. Breath analysis did not reveal a significant buildup of FC-113 (Reinhardt etal., 1971).

EFFECTS ON ANIMALS

FC-11 has not shown appreciable oral toxicity in rats and dogs in either acute or chronic studies (Haskell Laboratory, 1970; NCI, 1978). The chronic investigations include 1-mo, 90-d, and 2-yr studies. FC-11 was tested on the intact skin of mice. It was well tolerated by the skin, but retarded the recovery of wounds and burns and regrowth of hair (Quevauviller, 1960; Quevauviller et al., 1963). Dermal application of FC-11 to rabbit skin did not produce any lesions (Scholz, 1962). Transient conjunctival irritation was observed after application of FC-11 solution to the rabbit eye. No irreversible eye damage was seen (Haskell Laboratory, 1970; Kudo et al., 1971).

The LC_{50} of FC-11 for rats in a 4-h exposure is 26,200 ppm (Haskell Laboratory, 1970). A 30-min exposure of rats at 50,000 ppm caused no signs of intoxication. Similar exposure at higher concentrations caused clinical signs of central nervous system depression. Concentrations of 100,000 ppm or more were fatal after less than 30 min (Lester and Greenberg, 1950). Acute exposure of other species of laboratory animals produced similar effects (Caujolle, 1964; Haskell Laboratory, 1970; Nuckolls, 1933; Scholz, 1962).

Rats, guinea pigs, monkeys, and dogs were continuously (24 h/d) exposed to FC-11 at approximately 1,000 ppm for 90 d. One monkey died on day 78, but its death was not definitely linked to exposure to FC-11. No other animals were affected. No compound-related pathologic changes were observed. Another group of animals was

exposed at 10,250 ppm, 8 h/d, 5 d/wk for 6 wk without adverse effects (Jenkins etal., 1970). In another study, dogs, cats, guinea pigs, and rats were exposed to FC-11 for 3.5 h/d, 5 d/wk for 4 wk; the dogs were exposed at 12,500 ppm, and the other animals at 25,000 ppm. No microscopic evidence of damage to the lungs, heart, spleen, liver, or kidneys was seen (Scholz, 1962).

Rats and mice exposed to FC-11 at 1,000 or 5,000 ppm for lifetime showed no evidence of carcinogenicity or other adverse health effects (C. Maltoni, unpublished).

FC-11, like other chlorofluorocarbons and hydrocarbons, was capable of sensitizing the beagle heart to exogenous epinephrine in standard 5-min cardiac-sensitization screening studies. A 5-min cardiac-sensitization screening test consists of a control intravenous injection of epinephrine at 8 μg/kg, followed later by a 5-min exposure to fluorocarbon and then a challenge with 8 μg/kg intravenously. Manifestation of arrhythmia (multiple consecutive ventricular beats), which is considered to pose a serious threat to life, or cardiac arrest (ventricular fibrillation) constitutes a positive test. The lowest concentration that elicited a marked response in exposed dogs was 5,000 ppm. A concentration of 1,000 ppm was ineffective. Dogs exposed while running on a treadmill (to increase their circulating epinephrine) were not sensitized at concentrations up to 10,000 ppm (Mullin et al., 1972).

Azar etal. (1973) studied nonanesthetized dogs and reported that the average blood concentrations of FC-11 associated with cardiac sensitization were 28.6 μg/L in arterial and 19.7 μg/L in venous blood.

Belej and Aviado (1975) studied cardiopulmonary toxicity of propellants in anesthetized dogs. They concluded that FC-11, unlike eight other halocarbon propellants studied, produced bronchodilation, rather than bronchoconstriction. It also reduced pulmonary compliance and respiratory minute volume. FC-11 had the greatest tachycardiac effect of all compounds studied. Effects of FC-11 on the circulatory system were summarized by Aviado (1975, 1978).

In a bioassay supported by the National Cancer Institute (1978), oral FC-11 was not carcinogenic in rats or mice. No significant increase in tumor formation was seen in a study that used subcutaneous injection (Epstein et al., 1967). Additionally, FC-11 has not been shown to be mutagenic in the Salmonella typhimurium reverse-mutation bioassay (C.F. Reinhardt, Haskell Laboratory, personal communication). No embryotoxic, fetotoxic, or teratogenic effect of FC-11 was shown in a study with pregnant rats and rabbits; the animals were exposed for 2 h/d to a 200,000 ppm of a FC-11/FC-12 (1:9) mixture from day 4 to 16 of gestation for rats and from day 5 to 20 for rabbits (Paulet, 1976). Blake and Mergner (1974) studied the biotransformation of ^{14}C-labelled FC-11 (8,000-12,000 ppm) in male and female beagles after a short (6-20 min) inhalation. Essentially all the inhaled fluorocarbon was recovered in the exhaled air within 1 h. Only traces of radioactivity were found in urine or exhaled CO_2. The investigators concluded that FC-11 is relatively refractory to biotransformation after a short inhalation exposure and that it is rapidly exhaled chemically unaltered.

INHALATION EXPOSURE LIMITS

The American Conference of Governmental Industrial Hygienists (1980, 1983) recommended a ceiling of 1,000 ppm. The Occupational Safety and Health Administration's (1983) permissible exposure limit currently in effect for FC-11 is a ceiling of 1,000 ppm.

COMMITTEE RECOMMENDATIONS

The previous EELs and CEL were established by the Committee on Toxicology in 1966. No adverse effects have been observed in dogs, monkeys, guinea pigs, or rats continuously exposed to FC-11 at 1,000 ppm for 90 d or in a similar group repeatedly exposed at 10,250 ppm, 8 h/d, 5 d/wk for 6 wk (Jenkins et al., 1970). Dogs exposed at 12,500 ppm and cats, guinea pigs, and rats at 25,000 ppm for 4 wk were not affected (Scholz, 1962). Human exposure to FC-113 (a compound similar to FC-11) at 1,500 ppm produced no adverse effects after 2.75 h. Signs of central nervous system involvement were seen after exposure to FC-113 at 2,500 ppm for 30 min. These effects were reversible, and the volunteers appeared normal 15 min after cessation of the experiment (C.F. Reinhardt, Haskell Laboratory, personal communication). FC-11 can sensitize the mammalian heart to epinephrine and result in serious cardiac arrhythmia. However, the possible combined effects of excitement-stimulated epinephrine release and FC-11 on the heart are not easy to predict. It would therefore be prudent to take a more cautious approach to EEL recommendations than was taken by the Committee in 1966, when it was not aware of the sudden-sniffing-death syndrome. The previous 60-min and 24-h EELs are too high, on the basis of experimental cardiac sensitization of dogs, which occurred when they were exposed at 5,000 ppm and given a large challenge injection of epinephrine. However, no sensitization occurred in resting dogs exposed at 1,000 ppm and given epinephrine or in exercising dogs exposed at 10,000 ppm (Mullin etal., 1972).

Based on the no-observed-adverse-effect concentration of FC-113 in humans (1,500 ppm for 2.5 h), the 10,000-ppm concentration (which did not cause cardiac arrhythmia in exercising dogs), and the results in standard 5-min cardiac-sensitization screening tests in dogs, the Committee recommends a 60-min EEL of 1,500 ppm. It bases its 24-h EEL on the finding in humans that repeated exposure to FC-113 at 500 or 1,000 ppm for 2 wk did not result in adverse effects. Finally, using the no-observed-effect concentration of 1,000 ppm in a continuous-exposure animal study and applying an uncertainty factor of 10, the Committee arrives at a recommended CEL of 100 ppm.

The present Committee's recommended EELs and CEL for FC-11 and the limits proposed in 1966 are shown below.

	1966	1984
60-min EEL	30,000	1,500 ppm
24-hr EEL	20,000	500 ppm
90-d CEL	1,000	100 ppm

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FLUOROCARBON 12

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	CCL_2F_2
Molecular weight:	120.92
Chemical name:	Dichlorodifluoromethane
Synonyms:	FC-12, Freon 12
CAS number:	75-71-8
Melting point:	−158°C
Boiling point:	−29.8°C
Specific gravity:	1.1834 (57°C)
Vapor pressure:	5.7 atm (20°C)
Solubility:	Soluble in alcohol and ether; insoluble in water
General characteristics:	Nonflammable, colorless gas
Conversion factors:	1 ppm = 4.94 mg/m^3 1 mg/m^3 = 0.2 ppm

OCCURRENCE AND USE

Fluorocarbon 12 (FC-12) has been used primarily as an aerosol propellant, refrigerant, and blowing agent for polymeric foams. Air conditioning is the suspected source of FC-12 contamination in submarines.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Of 34 cases of sudden death reported by the medical examiner of Dallas, Texas, to be due to abusive, deliberate use of products that can be inhaled, 16 involved fluorocarbons (Garriott and Petty, 1980). The victims were mainly white males aged 13-30 (mean, 18.4). FC-11 and FC-114 were used in addition to FC-12, and many products contained mixtures of FC-11 and FC-12. The sequence of events has been summarized by Aviado (1978) and others as follows: sensitization of the heart to prearrhythmic effects of epinephrine, depression of myocardial contractility, reduction in cardiac output, and irritation of mucosa in upper and lower respiratory tract that causes an increase in sympathetic and vagal impulses to the heart.

Azar etal. (1972) exposed two human volunteers to FC-12 at 1,000 and 10,000 ppm for 2.5 h. Each volunteer was exposed twice at each concentration. Electrocardiographic monitoring and psychomotor performance tests revealed no adverse effects of exposure at 1,000 ppm. At 10,000 ppm, there was only a 7% reduction in psychomotor-test score. Rapid elimination from the lungs occurred when exposure stopped. The investigators concluded that a single brief exposure

(up to 2.5 h) to FC-12 at 10,000 ppm could be tolerated without adverse health effects.

Kehoe (1943) reported that exposure to FC-12 at up to 60,000 ppm was tolerated for 80 min by one human subject. When exposed at 40,000 ppm for 14 min and then at 20,000 ppm for 66 min, a second subject developed EEG changes and had slurred speech and decreased scores in psychologic tests. At 110,000 ppm, amnesia and cardiac arrhythmia occurred within about 10 min.

Mergner etal. (1975) exposed a male and a female volunteer to radiolabeled FC-12 at 1,000 ppm for 7-17 min. Recovery of administered radioactivity in exhaled air was essentially complete. Radioactivity in urine and exhaled CO2 together amounted to less than 0.2% of administered radioactivity.

EFFECTS ON ANIMALS

FC-12 has not shown appreciable oral toxicity in laboratory animals in either acute or chronic exposures. These included 18-wk rat and dog feeding studies (fed at 160-379 mg/kg per day) and 2-yr rat feeding studies (up to 150 mg/kg per day) (Haskell Laboratory, 1955a; Hood, 1956; Sherman, 1974; Sherman and Barnes, 1966).

No skin irritation was observed after contact of the gas with the skin of rats, rabbits, or guinea pigs. Transient eye irritation followed application of a 50% solution to rabbit eyes. Treated eyes were normal 24 h later. No eye irritation was seen after an aerosol mixture containing FC-12 was sprayed into the eyes of rabbits (Haskell Laboratory, 1955b; Hood, 1956).

The lethal concentration of FC-12 for rats in a 3-h exposure was 620,000 ppm (Shugaev, 1963). Two-hour exposure at 600,000 ppm was lethal to rats, but not to guinea pigs (Scholz, 1962). Central nervous system effects were observed in all exposed species. In rats exposed for 30 min, there were no reactions at 200,000 ppm (Lester and Greenberg, 1950). At higher concentrations, the following effects were observed: muscular twitching and tremors at 300,000-400,000 ppm, loss of postural reflex at 500,000 ppm, and loss of righting reflex at 600,000 ppm. Guinea pigs were similarly affected at 200,000-300,000 ppm (Nuckolls, 1933). Mice survived a 24-h exposure at 10,000 ppm, but microscopic examination revealed nonspecific lung changes (Quevauviller et al., 1963).

Rats, guinea pigs, monkeys, rabbits, and dogs were exposed to FC-12 continuously at 810 ppm for 90 d (Prendergast et al., 1967). Although 2 of 15 rats and 1 of 15 guinea pigs died during exposure, there were no visible signs of toxicity. During the course of the experiment--which involved tests of several other chemicals, such as trichloroethylene, carbon tetrachloride, and other fluorocarbons--7 of 304 control rats and 2 of 34 control guinea pigs died. Pathologic examination revealed focal necrosis in the livers of the guinea pigs. This change was thought to be due to the continuous nature of the exposure or the high degree of susceptibility of the guinea pig. No pathologic changes were seen in the tissues of the other four species. In another experiment, test animals were exposed at 840 ppm for 8 h/d, 5 d/wk, for 6 wk (Nuckolls, 1933). No signs of toxicity were seen,

and pathologic examination revealed changes similar to those seen in the continuous study (Nuckolls, 1933). At higher concentrations, toxic signs indicative of CNS effects were observed on repeated exposure (Sayers etal., 1930; Scholz, 1962; Watanabe and Aviado, 1975). In addition, rats and mice exposed to FC-12 at 1,000 and 5,000 ppm for 104 wk showed no evidence of carcinogenicity (C. Maltoni, unpublished).

FC-12, like other chlorofluorocarbons and hydrocarbons, is capable of sensitizing the beagle heart to exogenous epinephrine in standard 5-min cardiac-sensitization screening studies. The concentration needed to elicit marked responses in 50% of exposed dogs is 80,000 ppm (Clark and Tinston, 1973). Dogs exposed to FC-12 while running on a treadmill to increase their own epinephrine concentration were sensitized at concentrations over 100,000 ppm (Mullin, 1970; Mullin et al., 1972).

Lessard et al. (1978) reported that epinephrine perfusion induced cardiac arrhythmia in rabbits and dogs breathing gas mixtures of 79% FC-12 and 21% 02. After 5 min of inhalation, arterial blood contained FC-12 at 0.8 mg/L in rabbits and 0.7 mg/L in dogs.

Blake and Mergner (1974) studied the biotransformation and elimination of FC-12 in beagles after exposure to radiolabeled FC-12 (8,000-12,000 ppm, v/v). Essentially all the inhaled air was recovered in the exhaled air within 1 h. Only traces of radioactivity were found in urine or exhaled CO_2. All tissues contained measurable concentrations of nonvolatile radioactivity 24 h after exposure, but together represented less than 1% of the administered dose. It was not possible to determine whether this radioactivity was associated with metabolites of FC-12 or with unavoidable radiolabeled impurities present in the administered gas mixture. The investigators concluded that FC-12 is relatively refractory to biotransformation after a short inhalation exposure and that it is rapidly exhaled in its unaltered form.

INHALATION EXPOSURE LIMITS

The ACGIH TLV-TWA (1983) and the OSHA federal standard (1983) for FC-12 are both 1,000 ppm; ACGIH recommended a TLV-STEL for 15-min excursions of 1,250 ppm.

COMMITTEE RECOMMENDATIONS

The previous EELs and CEL were established by the Committee in 1966. On the basis of a small decrement in human psychomotor performance at 10,000 ppm and none at 1,000 ppm for 2.5 h and positive findings in dogs in the 5-min cardiac-sensitization screening test at 80,000 ppm and in exercising dogs at 100,000 ppm, the Committee recommends a 60-min EEL of 10,000 ppm for FC-12. Because FC-12 is rapidly eliminated in expired air, the Committee recommends a 24-h EEL of 1,000 ppm and a CEL of 100 ppm.

The present Committee's recommended EELs and CEL for FC-12 and the limits proposed in 1966 are shown below.

	1966	1984
60-min EEL	30,000 ppm	10,000 ppm
24-hr EEL	20,000 ppm	1,000 ppm
90-d CEL	1,000 ppm	100 ppm

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FLUOROCARBON 21

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	$CHCl_2F$
Molecular weight:	102.92
Chemical name:	Dichlorofluoromethane
Synonyms:	FC-21, fluorocarbon 21, Freon 21
CAS number:	75-43-4
Melting point:	−135°C
Boiling point:	8.9°C
Specific gravity:	1.405 (9°C)
Solubility:	Insoluble in water; soluble in alcohol and ether
General characteristics:	Colorless, nearly odorless, nonflammable, heavy gas
Conversion factors:	1 ppm = 4.2 mg/m^3 1 mg/m^3 = 0.24 ppm

OCCURRENCE AND USE

Dichlorofluoromethane (FC-21) is used primarily as a solvent, as a refrigerant, in aerosol propellants, and in fire extinguishers. Recently, it has found use as a heat-transfer liquid in the space-shuttle program.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

The Committee is aware of no data on human exposure to FC-21.

EFFECTS ON ANIMALS

The lethal concentration of FC-21 for rats in a 4-h exposure was 49,900 ppm (Tappan and Waritz, 1964). A 2-h exposure of guinea pigs at 50,000-52,000 ppm was not fatal, but exposure produced loss of coordination in 3 min and unconsciousness within 30 min (Nuckolls, 1935). Exposure at 100,000 ppm killed rats and guinea pigs within 1 h (Weigand, 1971). Central nervous system effects (loss of coordination, tremors, and narcosis) were observed in both exposed species.

Contact of propylene glycol solutions of FC-21 with the skin of guinea pigs produced mild irritation at FC-21 concentrations of 25-40% (Goodman, 1976; Hood, 1964a). No irritation was seen at 2.5%. No evidence of sensitization potential was observed.

Transient eye irritation was seen after instillation of liquid FC-21 chilled to the temperature of dry ice or of a 40% solution in propylene glycol into the eyes of rabbits (Brittelli, 1976; Hood, 1964b). Mild lacrimation, but no corneal or iritic effect, was seen after FC-21 was sprayed directly into the eyes of rabbits (Hood, 1964b).

A group of 10 rats exposed at 10,000 ppm, 6 h/d, 5 d/wk, for 2 wk all survived, but pathologic examination revealed liver damage (Trochimowicz et al., 1977b). In a later 90-d study, groups of 54 rats and 4 dogs were similarly exposed at 1,000 and 5,000 ppm (Trochimowicz et al., 1977a). Excessive mortality and bilateral hair loss were seen in both groups of rats. The dogs lost weight at both concentrations. Histopathologic examination revealed cirrhosis in all rats, but only minimal changes in the livers of dogs exposed at 5,000 ppm. No compound-related effects were seen in dogs exposed at 1,000 ppm. Another incomplete 90-d study reported gross pathologic changes in the livers of rats exposed at 500 ppm, probable changes at 200 ppm, but no gross effects at 50 ppm (Allied Chemical, unpublished report to TLV Committee, 1978).

FC-21, like other chlorofluorocarbons and hydrocarbons, is capable of sensitizing the beagle heart to exogenous epinephrine in 5-min cardiac-sensitization screening studies (Mullin, 1975). A concentration of 10,000 ppm produced a marked response in 2 of 12 exposed dogs. No response was seen at 5,000 ppm; at this concentration, FC-21 is considered slightly less cardiotoxic than FC-11, which produced sensitization at 5,000 ppm. In the monkey, respiratory depression and tachycardia were seen after 5 min at 25,000 ppm (Aviado and Smith, 1975).

Kelly et al. (1978) exposed 25 pregnant rats to FC-21 at 10,000 ppm 6 h/d on days 6-15 of gestation. There was an unspecified adverse effect on maternal weight and a preimplantation loss of fertilized ova in 15 of the 25 rats. No teratogenic effects were observed.

INHALATION EXPOSURE LIMITS

The ACGIH (1980, 1983) established a TLV-TWA for FC-21 of 10 ppm (40 mg/m^3). This represented a downward revision from the previous TLV-TWA of 1,000 ppm and was recommended because data had suggested that FC-21 was considerably more hepatotoxic than closely related fluorinated compounds and was similar in that respect to chloroform (ACGIH, 1980). OSHA (1983) recommended a permissible exposure level (PEL) of 1,000 ppm.

COMMITTEE RECOMMENDATIONS

On the basis of 5-min cardiac-sensitization screening findings in dogs, which were positive at 10,000 ppm and negative at 5,000 ppm; hepatotoxic effects in rats exposed at 10,000 ppm over a 2-wk period; and reproductive changes with exposure at 10,000 ppm at a critical period in gestation, the Committee recommends a 60-min EEL of 100 ppm.

For 24-h and 90-d exposures, the most relevant data are those from the two 90-d studies in rats and dogs. In rats, 50 ppm was a no-observed-adverse-effect concentration; 1,000 ppm was the minimal-effect concentration in dogs, causing weight loss. On the basis of the subchronic data in animals, which suggest that the toxicity of FC-21 is greater than that of other fluorocarbons and similar to that of chloroform, the Committee has applied an uncertainty factor of 1,000 to the minimal-effect concentration in dogs and recommends a 90-d CEL of 1 ppm. For a single 24-h exposure, a somewhat higher concentration would be expected not to have adverse effects, and a 24-h EEL of 3 ppm is recommended.

The Committee's recommended EELs and CEL for FC-21 are shown below.

		1984
60-min	EEL	100 ppm
24-h	EEL	3 ppm
90-d	CEL	1 ppm

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FLUOROCARBON 113

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	CF_3CCl_3
Molecular weight:	197.5
Chemical name:	1,1,2-trichloro-1,2,2-trifluoroethane
Synonyms:	FC-113, fluorocarbon 113, Freon 113
CAS number:	76-13-1
Melting point:	−35°C
Boiling point:	47.6°C
Specific gravity:	1.5635 (25°C)
Vapor pressure:	284 mm Hg (20°C)
Solubility:	Insoluble in water; soluble in alcohol, ether, and benzene
General characteristics:	Colorless, nonflammable liquid
Conversion factors:	1 ppm = 8.0 mg/m^3 1 mg/m^3 = 0.12 ppm

OCCURRENCE AND USE

Fluorocarbon 113 (FC-113) has been used principally as a dry-cleaning solvent, refrigerant, and blowing agent. It is also used as a cleaning solvent for sensitive electronic parts and in the maintenance of hydraulic piping systems in submarines.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Exposure of the skin of human subjects to FC-113 resulted in localized numbness followed by transient erythema after exposure stopped (Reinhardt and Schultze, 1968). End-tidal air samples demonstrated that some solvent had been absorbed through the skin.

Human exposure at 1,500 ppm produced no effects after 2.75 h (Stopps and McLaughlin, 1967). Signs indicative of CNS involvement were seen after 30 min of exposure at 2,500 ppm. These slight decreases in psychomotor performance were reversible and disappeared by 15 min after exposure stopped.

Human volunteers were exposed at 500 or 1,000 ppm for 6 h/d, 5 d/wk, during a 2-wk period. No adverse changes were seen in performance of complex mental tasks, clinical status, or results of biochemical tests. Breath analysis did not reveal a significant buildup of FC-113 (Reinhardt et al., 1971).

EFFECTS ON ANIMALS

FC-113 has very low acute oral toxicity, with an LD_{50} in rats of 43 g/kg (Michaelson and Huntsman, 1964). Its lethal dose after application to the skin of rabbits is greater than 11 g/kg, the largest feasible dose. Mild irritation results from contact with the skin and eyes (Haskell Laboratory, 1963; Reinke, 1962).

Exposure to FC-113 at 50,000-60,000 ppm has proved lethal to rats after 4 h. Signs of toxicity indicative of CNS involvement were incoordination, tremors, irregular respiration, and convulsions (Bodganowicz, 1973; Dashiell, 1971; Sarver, 1971).

Rats were exposed at an average concentration of 2,520 ppm, 7 h/d, 5 d/wk, for 6 wk (Limperos, 1954). No signs of toxicity were seen throughout the experiment.

Other groups of laboratory animals were similarly exposed at up to 5,100 ppm without effect (Carter et al., 1970; Philadelphia Naval Shipyard, 1952; Steinberg et al., 1969). In a limited study involving six rats exposed at 12,000 ppm for up to 24 mo, a slight sleepiness was observed and disappeared immediately after daily exposure stopped (Desoille et al., 1968). Rats were exposed by inhalation for 6 hr a day, 5 d/wk, for 104 wk. Exposures were at 0, 2,000, 10,000, and 20,000 ppm (v/v). No significant toxic effects were observed, and no evidence of carcinogenicity was seen (C. F. Reinhardt, personal communication).

FC-113, like other chlorofluorocarbons and hydrocarbons, is capable of sensitizing the beagle heart to exogenous epinephrine in standard 5-min cardiac-sensitization screening studies. A concentration of 5,000 ppm can sensitize 25-35% of exposed dogs; 2,500 ppm is ineffective (Clark and Tinston, 1973; Reinhardt et al., 1973). However, dogs exposed while running on a treadmill (to increase their own epinephrine concentration) were not sensitized at concentrations up to 20,000 ppm (Mullin et al., 1971; Trochimowicz et al., 1974).

FC-113 is analogous to FC-11 with regard to its pharmacokinetics and metabolism. It has a short half-life in the body, is not metabolized to any significant extent, and is rapidly expelled through the lungs upon removal from exposure (C. F. Reinhardt, personal communication).

INHALATION EXPOSURE LIMITS

The ACGIH TLV-TWA and the OSHA federal standard (ACGIH, 1983; OSHA, 1983) for FC-113 are both 1,000 ppm. ACGIH recommended a TLV-STEL for 15-min excursions of 1,250 ppm (ACGIH, 1980). The TLV-TWA was recommended on the basis of a belief that it would provide a margin of safety for systemic effects and an adequate margin against cardiac sensitization.

COMMITTEE RECOMMENDATIONS

The previous EELs and CEL were established by the Committee in 1969. On the basis of 5-min cardiac-sensitization screening tests with dogs (which showed no effects at 2,500 ppm and positive findings at 5,000 ppm), an absence of effects in unexcited humans exposed at 1,500 ppm for 1.5 h, but changes in manual dexterity at 2,500 ppm for 1.5 h, the

Committee suggests a 60-min EEL of 1,500 ppm. The Committee recommends a 24-h EEL of 500 ppm on the basis of an absence of adverse health effects in unexcitead humans exposed at 500 ppm or 1,0 h/d, 5 d/wk, for 2 wk. In view of absence of adverse effects in rats exposed to 20,000 ppm (v/v) for two years, its short half-life, little metabolism, and rapid removal from the body, the Committee recommends a 90-day CEL of 100 ppm.

The present Committee's recommended EELs and CEL for FC-113 and the limits proposed in 1969 are shown below.

	1969	1984
60-min EEL	1,500 ppm	1,500 ppm
24-h EEL	200 ppm	500 ppm
90-d CEL	100 ppm	100 ppm

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FLUOROCARBON 114

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	CF_4CCl_2
Molecular weight:	170.93
Chemical name:	1,2-Dichloro-1,1,2,2-tetrafluoroethane
Synonyms:	FC-114, cryofluorane, Freon 114
CAS number:	76-14-2
Melting point:	−94°C
Boiling point:	3.8°C
Specific gravity of liquid:	1.5312 (0°C)
Vapor pressure:	1444 mm Hg (20°C)
Solubility:	Soluble in alcohol, ether, and water (0.01%)
General characteristics:	Colorless, noncorrosive, nonflammable gas
Conversion factors:	1 ppm = 7 mg/m^3 1 mg/m^3 = 0.14 ppm

OCCURRENCE AND USE

1,2-Dichloro-1,1,2,2-tetrafluoroethane (FC-114) has been used primarily as an aerosol propellant and refrigerant. Air conditioning is a suspected source of FC-114 contamination in submarines.

SUMMARY OF TOXICITY DATA

EFFECTS ON HUMANS

Human exposures to FC-114 at up to 20,000 ppm have shown it to be poorly absorbed and rapidly excreted. Warning signs of overexposure are dizziness, headache, and a tingling sensation (Dollery et al., 1970; Morgan et al., 1972a,b; Paulet, 1970; Paulet and Desbrousses, 1969; Paulet et al., 1969).

EFFECTS ON ANIMALS

FC-114 has not shown appreciable oral toxicity in laboratory animals in either acute or subchronic studies (Griffith and Sherman, 1969; Haskell Laboratory, 1955a; Quevauviller, 1965; Sherman, 1972). Administration of a foam propelled by FC-114 or of the gas itself to the skin or eyes of guinea pigs and rabbits has resulted in only mild transient irritation (Haskell Laboratory, 1955b; Hood, 1967; Quevauviller et al., 1964).

Underwriters' Laboratories, Inc., (1933) has placed FC-114 in Category 6 of its classification of life hazards. This category contains the least toxic gases and vapors; i.e., they do not appear to produce injury or death in test animals as a result of exposures at 200,000 ppm for about 2 h.

The lethal concentration of FC-114 for rats in a 2-h exposure is greater than 600,000 ppm, and for guinea pigs, greater than 500,000 ppm (Scholz, 1962). The LC_{50} in mice exposed for 30 min is 700,000 ppm (Paulet and Desbrousses, 1969). A dog survived an 8-h exposure at 200,000 ppm, but a 16-h exposure was lethal to another dog (Yant et al., 1932). Exposure of dogs at 150,000 ppm for 24 h was not lethal and resulted only in a loss of appetite (Yant et al., 1932). Exposure at 200,000 ppm caused pupillary dilation, convulsions, opisthotonus, and unconsciousness in dogs. However, exposure at 400,000-600,000 ppm was necessary to cause mild CNS effects in rats and guinea pigs. Recovery was rapid and complete in all species.

FC-114, like other chlorofluorocarbons and hydrocarbons, is capable of sensitizing the beagle heart to exogenous epinephrine in standard 5-min cardiac-sensitization screening studies. The concentration needed to elicit marked responses in 50% of a group of beagles is 45,000 ppm (Reinhardt et al., 1971). However, dogs exposed to FC-114 while running on a treadmill to increase their own epinephrine concentration were not sensitized until exposures reached 50,000-100,000 ppm. In another endogenous-epinephrine study, a concentration of 800,000 ppm (80% FC-113:20% oxygen) was shown to sensitize the beagle heart after its epinephrine concentration was increased by fright (Mullin et al., 1972).

Rats and mice were exposed at 200,000 ppm for 2.5 h/d, 5 d/wk, for 2 wk (Paulet and Desbrousses, 1969). Slight blood and body-weight changes were seen, as well as slight evidence of lung irritation. Exposure at 100,000 ppm had no effect, even after 2 mo of exposure (Paulet and Desbrousses, 1969). Dogs and guinea pigs were exposed at 141,600 ppm for 8 h/d for 21 d (Yant, 1933). The severity of the clinical signs attributable to CNS effects decreased during the 21 d of exposure. In the dogs, slight hematologic changes were observed, but the measures in question returned to normal 15-17 d after exposure; no gross pathologic changes were seen.

No effects were seen in dogs, cats, guinea pigs, or rats exposed at 100,000 ppm for 3.5 h per exposure for 20 exposures (Scholz, 1962). No effects were seen in rats and rabbits exposed at 10,000 ppm for 2 h/d, 5 d/wk, during 8-9 mo (Desoille et al., 1973).

INHALATION EXPOSURE LIMITS

The ACGIH TLV-TWA (ACGIH, 1980, 1983) and the OSHA Federal Standard (OSHA, 1983) for FC-114 are both 1,000 ppm. ACGIH recommended a TLV-STEL for 15-min excursions of 1,250 ppm (ACGIH, 1983). The TLV-TWA was “recommended as exposure level which should provide a margin of safety in preventing systemic toxicity and an adequate margin in preventing cardiac sensitization” (ACGIH, 1980).

COMMITTEE RECOMMENDATIONS

The Committee on Toxicology previously established EELs and CEL for FC-114 in 1966.

On the basis of positive 5-min cardiac-sensitization studies in dogs at 45,000 ppm and the absence of effects in dogs, cats, guinea pigs, or rats exposed to FC-114 at 10,000 ppm 3.5 h/day for 20 d, the Committee recommends a 60-min EEL of 10,000 ppm and a 24-h EEL of 1,000 ppm. In the absence of long-term exposure data, it appears appropriate to recommend a CEL of 100 ppm for 90 d.

The present Committee's recommended EELs and CEL for FC-114 and the limits proposed in 1966 are shown below.

	1966	1984
60-min EEL	30,000 ppm	10,000 ppm
24-h EEL	20,000 ppm	1,000 ppm
90-d CEL	1,000 ppm	100 ppm

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American Conference of Governmental Industrial Hygienists. 1980. Dichlorotetrafluoroethane. Documentation of the Threshold Limit Values. 4th ed. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists. p. 135.

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ISOPROPYL ALCOHOL

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	C_3H_8O
Molecular weight:	60.09
Chemical names:	2-Propanol, isopropanol, propan-2-ol
Synonyms:	Secondary propyl alcohol, alcosolve 2
CAS number:	67-63-0
Freezing point:	−89.5°C
Boiling point:	82.4°C
Specific gravity:	0.786
Vapor pressure:	33 mm Hg (20°C)
Flash point:	53°F
Auto ignition temperature:	455.6°C
Solubility:	Miscible with water, alcohol, ether, and chloroform
General characteristics:	Colorless liquid with slight odor resembling that of rubbing alcohol
Conversion factors:	1 ppm = 2.45 mg/m^3 1 mg/m^3 = 0.41 ppm

OCCURRENCE AND USE

Isopropyl alcohol is manufactured in the United States by an indirect hydration technique in which a fraction containing 40-60% propylene that is isolated from refinery exhaust gases reacts with sulfuric acid (Lowenheim and Moran, 1975). In an older (strong-acid) process, 88-93% sulfuric acid reacted with propylene gas at 25-60°C for a long time. In a newer (weak-acid) process, which has replaced the strong-acid process, propylene gas is absorbed in 60% sulfuric acid at 85°C for a short reaction time (NIOSH, 1976). Estimated annual production capacity for 1981 was 2.8 million pounds (SRI, International, 1982).

Isopropyl alcohol was used primarily in the production of acetone, by dehydrogenating catalytically at 400°C to give acetone and hydrogen (major process) or oxidizing at high pressure to give acetone and hydrogen peroxide. However, the use of isopropyl alcohol in acetone manufacture has been decreasing in recent years. Its second main use is as a solvent: to extract or purify numerous natural products, such as oils, gums, shellacs, waxes, kelp, and pectin; in the manufacture of fish-protein concentrate; as a solvent for synthetic resins, e.g., such coatings as phenolic varnishes and nitrocellulose lacquers; and as a solvent in drug and cosmetic formulations (it is the major component of rubbing compounds used as solvents and rubefacients) (Lowenheim and Moran, 1975; Wickson, 1968; National Formulary Board, 1975). Its use in cosmetics has generally been limited to highly scented or

relatively inexpensive products. The third principal use is in the manufacture of other chemicals, such as isopropyl acetate, isopropylamine, diisopropylamine, herbicidal ester, isopropyl xanthate, isopropyl myristate, isopropyl palmitate, isopropyl oleate, aluminum isopropoxide, and isopropyl ether (Wickson, 1968).

Isopropyl alcohol toxicity is of interest to the Navy, because of its presence as an atmospheric contaminant in nuclear submarines.

SUMMARY OF TOXICITY INFORMATION

Table 6 summarizes some data on toxic doses of isopropyl alcohol in animals and man. The International Agency for Research on Cancer has also reviewed toxicity data (IARC, 1977).

EFFECTS ON HUMANS

The documented toxicity of isopropyl alcohol in man is confined for the most part to accidental ingestion (not inhalation), with a few cases reported in association with rectal and topical application.

Several deaths have reportedly resulted from ingestion of about 1 pint of 70% isopropyl alcohol (Adelson, 1962). Other persons have survived after ingesting similar amounts (Chapin, 1949; Freireich et al., 1967; Juncos and Taguchi, 1968; King et al., 1970). The lethal dose of isopropyl alcohol is estimated as 160-240 ml (Ashkar and Miller, 1971) and 250 ml (McBay, 1973).

In 1978, 372 Melanesian men consumed a solution of 82% methyl alcohol and 18% isopropyl alcohol in the mistaken belief that the solution was methylated spirits; 18 of them died. A disparity was noted in the amount of solution consumed and the sequelae; for example, 100 ml produced blindness and death in one case, but 500 ml seemed to cause no disability in two other men who claimed to have drunk this high quantity (Scrimgeour, 1980). The rates of ingestion were not specified.

Ballard et al. (1975) reported that 15 of 41 persons working in a drug company became ill and had nausea, vomiting, weakness, and abdominal pain. Their illness was attributed to their exposure to carbon tetrachloride and isopropyl alcohol, inasmuch as 13 of the 15 had been within 25 ft of these chemicals when they were spilled.

In two factories manufacturing isopropyl alcohol by the strong-acid process (involving the formation of isopropyl oils as byproducts), an excess risk of cancers of the paranasal sinuses was found (Eckhardt, 1974; Hueper, 1966; Weil et al., 1952). An excess risk of laryngeal cancer may also have been present. However, diisopropyl sulfate, an intermediate substance in the preparation of isopropyl alcohol suspected of being an animal carcinogen, is formed in the strong-acid process.

Zakhari et al. (1977) quoted several studies (Garrison, 1953; Vermeulen, 1966; McFadden and Haddow, 1969; Moss, 1970; Wise, 1969) of coma produced in hospital patients by topical application of isopropyl alcohol during sponge baths intended to reduce fever. Blood isopropyl alcohol concentrations ranged from 10 to 220 mg/100 ml; recovery in all cases was complete in 24-36 h.

Ten volunteers exposed for 3-5 min to isopropyl alcohol vapor at concentrations of 200, 400, and 800 ppm reported mild to moderate irritation of the eyes, nose, and throat at the two higher concentrations (Nelson et al., 1943).

Daily oral intake of low doses of isopropyl alcohol (2.6 or 6.4 mg/kg of body weight) by groups of eight men for 6 wk had no effect on blood cells, serum, or urine and produced no subjective symptoms (Wills et al., 1969).

Fuller and Hunter (1927) reported that dizziness occurred within a short time of oral exposure of seven human subjects to 20-30 cm^3 of 50% solution of isopropyl alcohol. They also experienced moderate to severe headache lasting one to three h. The odor threshold for isopropyl alcohol ranges from 40 ppm (May, 1966) to 200 ppm (Scherberger et al., 1958).

Isopropyl alcohol is not a cutaneous irritant (Nixon et al., 1975), although several cases of allergic contact dermatitis have been reported (Fregert et al., 1971; McInnes, 1973; Richardson et al., 1969; Wasilewski, 1968).

EFFECTS ON ANIMALS

The oral LD_{50} of isopropyl alcohol in rats, rabbits, and dogs is about 5 g/kg (Lehman and Chase, 1944). The dermal LD_{50} in rabbits is about 13 g/kg, and inhalation at 16,000 ppm for 8 h was lethal to four of six rats (Smyth and Carpenter, 1948). The intravenous lethal dose in cats is 2.5 ml/kg (Macht, 1922). Isopropyl alcohol vapor at maximal saturation in air (i.e., 5.8% at 25°C) is not lethal to mice exposed for less than 1 h. The LC_{50} administered for 120 min to mice is 10.39 ± 3.68 mg/L (49,120 ppm). The oral and intraperitoneal LD_{50}s are approximately equal in mice and rats. LC^{50}s measured in rats exposed to isopropyl alcohol for 8 h were 19,000 ppm for females and 22,500 ppm for males.

The signs of intoxication after application of isopropyl alcohol are similar to those with ethyl alcohol, although it is 1.5-2 times more toxic than ethyl alcohol (International Agency for Research on Cancer, 1977). Death is usually preceded by dizziness, narcosis, deep coma, and shock (Lehman et al., 1945; Morris and Lightbody, 1938). An orally administered dose of 2 g/kg produced narcotic effects in rabbits for about 8 h (Morris and Lightbody, 1938). Augmented hepatotoxicity of various chlorinated hydrocarbons was noted in mice administered isopropyl alcohol at 2.5 ml/kg 18 h before hydrocarbon exposure (Traiger and Plaa, 1974). Lehman and Chase (1944) demonstrated the doses of isopropyl alcohol that produced anesthesia and death in rabbits and dogs:

	Anesthetic Dose	Lethal Dose
Rabbits	3.23 ml/kg	8.23 ml/kg
Dogs	3.35 ml/kg	5.12 ml/kg

The respiratory system may be paralyzed by isopropyl alcohol; this is usually the cause of death after isopropyl alcohol ingestion (Zakhari et al., 1977). A concentration of isopropyl alcohol in air of 97.5 mg/L caused respiratory minute-volume depression, broncho-constriction, hypotension, and bradycardia in rats. Single exposure to atmospheric isopropyl alcohol results in an increase in pulmonary resistance and a decrease in pulmonary compliance. These effects are more pronounced if more than six daily exposures are administered (Zakhari etal., 1977).

In anesthetized dogs, isopropyl alcohol inhalation caused various effects: depression of myocardial contractility at 1.0% (2.45 mg/L), reduction in cardiac output at 2.5% (6.12 mg/L), and systemic hypotension at 7.5% (18.37 mg/L) (Zakhari etal., 1977). Histopathologic examination of rats exposed at 21,000 ppm for 8 h showed typical lesions of chemical pneumonitis and pulmonary edema accompanied by foamy vacuolization of liver cells and severe focal cytoplasmic degradation (Laham etal., 1980).

Baikov etal. (1974) investigated the effects of chronic inhalation of isopropyl alcohol by rats. Groups of 15 animals were exposed to isopropyl alcohol continuously for 24 h/d for 86 d at concentrations of 20, 2.5, and 0.6 mg/m^3 (approximately 8.14, 1.02, and 0.24 ppm). The animals inhaling isopropyl alcohol at 20 mg/m^3 (8.14 ppm) showed changes in reflex behavior, increases in the retention of BSP, the total leukocyte count, and the number of abnormal fluorescent leukocytes. They also showed a decrease in the blood nucleic acid content, the blood oxidase and catalase activities, and the amount of coproporphyrin in blood. Animals inhaling isopropyl alcohol at 2.5 mg/m^3 (1.02 ppm) demonstrated some of the same effects, but none were statistically significant. In animals inhaling isopropyl alcohol at 20 mg/m^3 (8.14 ppm), postmortem findings included hyperplasia of the spleen with the development of hemorrhages of the sinuses and erosion of follicular cells, some evidence of liver parenchymal cell dystrophy, hyperplastic ependymal cells, and degenerative changes in the cerebral motor cortex. None of these effects were observed in animals inhaling isopropyl alcohol at 0.6 mg/m^3 (0.24 ppm). On the basis of this continuous exposure study, the authors suggested that 0.6 mg/m^3 (0.24 ppm) be adopted as the maximal daily average concentration. Some of the physiological responses reported in this study, such as the increase in abnormal fluorescent leukocytes, are obscure and are therefore difficult to interpret. Furthermore, they suffer from a lack of experimental details.

Isopropyl alcohol (10%) in the diet of young rats for 30 d had no effect on growth, liver weight, or lipid content (Miyazaki, 1955). Dogs given daily doses of 1.3 g/kg in the drinking water had the appearance of drunkenness 3-5 h after intake, but no consistent pathologic changes over a 6-mo period (Lehman et al., 1945).

No evidence of carcinogenicity was found when several strains of mice were exposed to isopropyl alcohol in air at 7,700 mg/m^3 3-7 h/d, 5 d/wk, for 5-8 mo. However, the animals were not observed over a normal lifetime and were killed at 8-12 mo of age (Weil et al., 1952). The authors reported no increases in the incidence of lung tumors in mice given subcutaneous injections of 0.025 ml of isopropyl

alcohol once a week for 20-40 wk. However, in mice sacrificed at 40 wk, effects of lifetime exposure were not assessed. No skin tumors were detected (NIOSH, 1976) in a group of 30 Rockland mice that received skin applications of isopropyl alcohol twice a week for a year. Because of methodologic limitations in the preceding studies, it is difficult to draw a conclusion regarding the carcinogenicity of isopropyl alcohol (IARC, 1977).

Lehman et al. (1945) reported that growth, reproductive function, and embryonic and postnatal development of rats were not affected, except for some retardation of growth early in the life of first-generation offspring when parents and two successive generations of rats were given isopropyl alcohol continuously in the drinking water at 1.5, 1.4, and 1.3 g/kg per day, respectively.

Solvent controls of isopropyl alcohol in an assay of the mutagenicity of Fusarium moniliforme were negative when tested in the S. typhimurium reverse-mutation bioassay with strains TA 98 and TA 100 (Bjeldanes and Thomson, 1979).

PHARMACOKINETICS

After oral intake of 0.1-20 g of isopropyl alcohol, none was excreted in the urine of volunteers during the next 48 h, and no formic acid was detected (Kemal, 1927).

Isopropyl alcohol is absorbed from all segments of the gastro-intestinal tract, most rapidly in the small intestine and least rapidly in the stomach. Wax et al. (1949) reported that absorption from isolated canine loops of intestine and stomach was 99% complete at the end of 2 h, 82% being absorbed during the first 30 min. Intravenous injections of ethyl alcohol (0.8 cc/kg) significantly reduced the absorption of isopropyl alcohol from the digestive tract.

Before 1940, the toxicity of isopropyl alcohol was compared with that of methyl alcohol, in which the long and cumulative action was attributed to low rates of metabolism and excretion. But most data now point to a fairly rapid disposal of isopropyl alcohol, which is eliminated from the bloodstream of dogs within 24 h after administration.

The elimination of isopropyl alcohol in rats is decreased by simultaneous ingestion of ethyl alcohol or 1-propanol, but not methyl alcohol or tertiary butyl alcohol. These results suggest that isopropyl alcohol is oxidized by alcohol dehydrogenase (Abshagen and Rietbrock, 1970).

Determination of blood isopropyl alcohol and its metabolite, acetone, was carried out during and after a single 4-h exposure (concentration, 500-8,000 ppm) in Sprague-Dawley rats. The amounts of acetone and isopropyl alcohol were directly related to the air concentrations of alcohol inhaled. Increase in exposure time to 8 h considerably increased the amount of blood acetone that could be determined even 20 h after exposure. These findings indicate a slow conversion of this alcohol to acetone, which can be used as a biochemical indicator of exposure, but it is a nonspecific indication and may be produced by other compounds (Laham et al., 1980).

Exposure of male Wistar rats to isopropyl alcohol vapor at 12.3 mol/L (300 ppm) for 6 h/d, 5 d/wk, for 5-21 wk with simultaneous ethyl

alcohol administration in drinking water (5% v/v) caused a significant increase in isopropyl alcohol removal as assessed by blood isopropyl alcohol and acetone determinations (Savolainen et al., 1979). This study confirmed the production of acetone from isopropyl alcohol. The novel aspect of this study is the more rapid metabolism of acetone induced by ethyl alcohol. This effect might be attributable to synergistic effects of ethyl alcohol and isopropyl alcohol on aldehyde and ketone dehydrogenation. Neurochemical studies revealed decreased superoxide dismutase and azoreductase activities in cerebellar homogenate at the end of the exposure, whereas increased protein degradation was found in glial cells isolated from rats fed ethyl alcohol. Analyses of spinal cord axon lipid composition showed increases in cholesterol content in relation to lipid phosphorus in animals exposed to isopropyl alcohol or to the combination of isopropyl and ethyl alcohol. Spontaneous behavioral tests indicated minor effects on reactivity from the tenth week on with isopropyl alcohol exposure. Coexposure to isopropyl alcohol vapor and ethyl alcohol abolished the increased excitability. Savolainen et al. concluded that isopropyl alcohol vapor causes significant metabolic and functional chages in rats at relatively low doses--300 ppm.

Another synergistic effect has been an increase in the toxicity of carbon tetrachloride caused by pretreatment with isopropyl alcohol (Plaa and Traiger, 1973; Traiger and Plaa, 1973; Traiger and Plaa, 1974). The concentration of isopropyl alcohol in rat saliva 15 and 60 min after exposure was proportional to the exposure concentration and the duration of exposure and was closely correlated with the blood concentration (Tomita, 1980).

Liver alcohol dehydrogenase is the principal enzyme involved in the oxidation of isopropyl alcohol. The acetone produced by action of the enzyme on isopropyl alcohol is eliminated from the human body in expired air and urine (Zakhari et al., 1977).

Rat liver microsomes are capable of oxidizing branched-chain alcohols, and hydroxyl radicals generated from microsomal electron transfer may have a role in isopropyl alcohol oxidation (Cederbaum et al., 1981).

INHALATION EXPOSURE LIMITS

The OSHA health standards for exposure to air contaminants require that an employee's exposure to isopropyl alcohol not exceed an 8-h TWA of 400 ppm in the working atmosphere in any 8-h shift of a 40-h workweek (OSHA, 1982); a ceiling of 800 ppm was determined during a sampling time of 15 min (NIOSH, 1976). An estimated 141,000 employees may be exposed occupationally to isopropyl alcohol in the United States (NIOSH, 1976).

The American Conference of Governmental Industrial Hygienists established the value of 400 ppm as the TLV for isopropyl alcohol; as described above, this is the TLV currently recommended in the United States (American Conference of Governmental Industrial Hygienists, 1980, 1983). The permissible concentration of isopropyl alcohol was established by the Japan Association of Industrial Health in 1966 at 400 ppm (Japan Association of Industrial Health, 1971). In the

U.S.S.R., the maximal permissible concentration of isopropyl alcohol in a single dose or as a daily average is 0.6 mg/m^3(U.S.S.R. Ministry of Public Health Individual Reports, 1971).

COMMITTEE RECOMMENDATIONS

The National Research Council's Committee on Toxicology (1960) recommended, as a part of the submarine toxicology program, the EELs and CEL for isopropyl alcohol. The basis for these limits was primarily the ACGIH TLV of 400 ppm, which was recommended by the Committee as the 60-min EEL. The Committee stated: "From the data available it would appear that isopropyl alcohol is not an industrial health hazard. The threshold limit value of 400 ppm set by the ACGIH may cause mild irritation of the eyes, nose and throat, especially in those not regularly exposed." The 24-h EEL and 90-d CEL were apparently recommended by the Committee on the basis of its judgment concerning tolerable doses for these periods and extrapolations from the 400-ppm 60-min EEL. No new information has become available to suggest changes in previously proposed EELs for 1 and 24 h. However, data from long-term, low-dose, continuous-exposure studies show adverse effects on behavior, liver, and spleen in rats (Baikov et al., 1974). Although these data are not conclusive, prudence dictates that previously recommended long-term exposure limit (CEL) of 50 ppm be lowered to 1 ppm.

The present Committee's recommended EELs and CEL for isopropyl alcohol and the limits proposed in 1960 and 1966 are shown below:

	1960/1966	1984
60-min EEL	400 ppm	400 ppm
24-h EEL	200 ppm	200 ppm
90-d CEL	50 ppm	1 ppm

TABLE 6 Acute Toxicity of Isopropyl Alcohol[a]

Species	Route	Measure	Value
Human	Eye	Irritation	20 ppm
Human	Oral	TD_{Lo}	15,710 mg/kg
Human	Oral	LD_{Lo}	8,600 mg/kg
Human	Inhalation	TC_{10}	400 ppm
Human	Subcutaneous	LD_{Lo}	6 mg/kg
Human	Unknown	LD_{Lo}	2,770 mg/kg
Rat	Oral	LD_{50}	5,840 mg/kg
Rat	Inhalation	LC_{50}	16,000 ppm, 8 h
Mouse	Oral	LC_{Lo}	192 mg/kg
Mouse	Intraperitoneal	LD_{50}	933 mg/kg
Mouse	Subcutaneous	LD_{Lo}	6,000 mg/kg
Dog	Oral	LD_{50}	6,150 mg/kg
Dog	Intravenous	LD_{Lo}	5,120 mg/kg
Cat	Intravenous	LD_{Lo}	1,963 mg/kg
Rabbit	Eye	Irritation	16 mg
Rabbit	Oral	LD_{Lo}	5,000 mg/kg
Rabbit	Skin	LD_{50}	13 g/kg
Rabbit	Intravenous	LD_{Lo}	8,230 mg/kg

[a] Data from NIOSH Registry of Toxic Effects of Chemical Substances, 1982.

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PHOSGENE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	$COCl_2$
Molecular weight:	98.9
Chemical name:	Carbonyl chloride, carbon oxychloride, chloroformyl chloride
CAS number:	75-44-5
Freezing point:	−127.8°C
Boiling point:	7.5°C
Density, liquid:	1.4187 (20°C)
Density gas:	4.39 (20°C)
Specific gravity, gas:	3.4 (2°C) (air = 1)
pecific gravity, liquid:	1.392 (19°C/4°C)
Solubility:	Slightly soluble in water (hydrolyzes to HCl and CO_2); soluble in carbon tetrachloride, chloroform, acetic acid, and toluene
General characteristics:	Easily liquified, colorless, nonflammable gas; odor, sweet at low concentrations and pungent at higher concentrations
Conversion factors:	1 ppm = 4 mg/m^3 1 mg/m^3 = 0.25 ppm

OCCURRENCE AND USE

Phosgene was first prepared in 1812 by the photochemical reaction of carbon monoxide and chlorine; it is now commercially prepared by passing chlorine and excess carbon monoxide over activated carbon. Depending on the quantity required and the availability of the raw material, numerous variations of the basic synthetic process are used. Continuous processing and a high degree of automation are required for phosgene purification, condensation, and storage.

In its first application, phosgene was the most heavily used chemical-warfare agent during World War I (Moore and Gates, 1946; Stavrakis, 1971). Its utility as a reactive chemical intermediate is of relatively recent origin (Chadwick and Hardy, 1967; Chadwick and Cleveland, 1981; Hardy, 1982; NIOSH, 1976). It is now an important and widely used intermediate; the majority of its production is captive, e.g., in the manufacture of other chemicals within the same plant. The principal use of phosgene is in the polyurethane industry, which consumes over 85% of the world's phosgene output. It is also used in polycarbonate resins, dyes, and pharmaceutical intermediary products (Chadwick and Cleveland, 1981; Hardy, 1982; NIOSH, 1976).

In 1978, demand for phosgene was an estimated 1,630 million pounds. The growth in U.S. demand for phosgene from 1970 to 1979 was 9.2%/yr; future growth in demand is forecast at 7.0%/yr through 1984 (Anonymous, 1980). The capacity for the production of phosgene in the United States (12 producers at 15 sites) in 1983 was estimated to be < 2,101 million pounds (SRI International, 1983).

In 1973, the pattern of phosgene use was as follows: production of toluene diisocyanate (TDI), 61.7%; production of polymethylene polyphenylisocyanate (PMPPI), 23.6%; production of polycarbonate resins, 3.9%; and other uses (including production of acyl chlorides, chloroformate esters, diethylcarbonate, dimethylcarbamylchloride, isocyanates other than TDI and PMPPI, dyes, biocides and pharmaceuticals and use as a chlorinating agent), 10.7% (SRI International, not dated).

In 1977, the polycarbonate industry consumed approximately 6% of the phosgene produced and herbicide manufacture and processing used 9% (Hardy, 1982).

World production of isocyanates in 1978 has been estimated as 635,000 metric tons of TDI and 454,000 metric tons of diphenyl methane-4,4'-diisocyanate (MDI) products. The estimated 1981 capacities of U.S. manufacturers of isocyanates amounted to 318,000 and 444,000 metric tons for TDI and polymeric isocyanates, respectively (Chadwick and Cleveland, 1981).

TDI is a precursor of polyurethane resins, which are widely used to make foams, elastomers, and coatings. Polycarbonate resins based on phosgene find use in appliance and electric-tool housings, electronic parts, and break-resistant glazing. A rapidly growing use of phosgene is in the preparation of PMPPI for the production of rigid polyurethane foams (SRI International, not dated). The reaction of phosgene with primary alkyl and aryl amines, referred to as phosgenation, yields carbamoyl chlorides, which can be dehydrohalogenated readily to isocyanates:

$RNH_2 + COC1_2$ #8594; $RNHCOCl \rightarrow RN=C=O + HCl$.

This procedure is used almost exclusively for the production of isocyanates (Chadwick and Cleveland, 1981). All commercial manufacturing processes for aromatic isocyanates currently in use appear to have the following steps:

- A solution of an amine in an aromatic solvent--such as xylene, monochlorobenzene, or o-dichlorobenzene--is mixed with a solution of phosgene in the same solvent at a temperature below 60°C.
- The resulting mixture slurry is digested in one to three stages for several hours at progressively increasing temperatures up to 200°C; digestion is accompanied by the injection of additional phosgene.
- The final solution of reaction products is fractionated to recover hydrogen chloride, unreacted phosgene, and solvent for recycling, isocyanate product, and distillation residue.

In addition to commercial production, phosgene can be produced by the thermal decomposition of chlorinated hydrocarbons (Spolyar etal., 1951) and by the photooxidation of chlorinated hydrocarbons in the atmosphere (NIOSH, 1976; Singh, 1976). For example, Singh (1976) demonstrated by field monitoring at four California sites (urban and nonurban) that chloroethylenes (primarily C_2Cl_4 and C_2HCl_3), which are emitted worldwide in extremely large quantities (1.5 million metric tons in 1975), photodecompose to form highly toxic species, such as phosgene and chloroacetylchlorides. On the basis of estimates from recent laboratory studies, present C_2Cl_4 and C_2HCl_3 emission could result in the formation of about 0.3 million metric tons of phosgene per year (Gay etal., 1976). Because these solvents are typically emitted in urban areas and are relatively reactive (the tropospheric half-lives of C_2HCl_3 and C_2Cl_4 are 2 and 4 days, respectively), high concentrations of phosgene could be encountered during adverse meteorologic conditions in and around urban centers. The atmospheric sinks of phosgene have not been fully delineated. Simulated tropospheric irradiation in the presence of water vapor suggests negligible tropospheric loss through photolysis and gas-phase hydrolysis. The two important sinks of phosgene appear to be heterogeneous decomposition and slow liquid-phase hydrolysis (Singh, 1976).

NIOSH estimated that about 10,000 workers have potential occupational exposure to phosgene during its manufacture and use (NIOSH, 1976). Their occupations include those involved in the production of phosgene itself, chlorinated compounds, dyes, glass, herbicides, insecticides, isocyanates, organic chemicals, and resins and firefighting, welding, and brazing (Gafafer, 1966; NIOSH, 1976). Long-term exposure at low concentrations may occur in submarines. The potential source of phosgene in submarines could be leaked Freon undergoing thermal decomposition.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Three sources of exposure to phosgene in air are readily identifiable: direct emission of phosgene during manufacture, handling, and use (ACGIH, 1980; Polednak, 1980); thermal decomposition of polyvinylchloride (PVC) (Brown and Birky, 1980) and chlorinated hydrocarbons (Cucinell, 1974; NIOSH, 1976), such as chloroform, carbon tetrachloride, and trichloroethylene--solvents, paint removers, and nonflammable dry-cleaning fluids containing chlorinated hydrocarbons may decompose to phosgene in the presence of fire or heat (Diller, 1978); and photooxidation of chloroethylenes in air (Gross etal., 1965). The first two sources might result in serious indoor hazard (Diller, 1978; NIOSH, 1976; Spolyar etal., 1951), but their contribution to the total ambient phosgene content is minimal (Spolyar etal., 1951), whereas segments of the general population could be exposed at higher concentrations from atmospheric pollution, e.g., from fuel emission of municipal incinerators (Carotti and Kaiser, 1972).

Human exposure to gaseous phosgene reported in the literature is generally limited to episodes of acute exposure (Diller, 1978). The acute toxicity of phosgene is both dose- and time-dependent. Phosgene at concentrations of 3-5 ppm causes irritation of the eyes and throat with coughing; exposure at 25 ppm for 30-60 min is dangerous; and brief exposure at 50 ppm may be rapidly fatal (Henderson and Haggard, 1943; Hygienic Guide Series, 1968; Patty, 1963; Sax, 1968).

The symptoms of moderate exposure to phosgene are often dryness or a burning sensation in the throat, vomiting, pain in the chest, and dyspnea (Patty, 1963). Phosgene poisoning is characterized by a symptom-free latent period of 2-24 h followed by chest pain, shortness of breath, and increasing difficulty in breathing. Severe respiratory distress may be delayed for up to 72 h; the latent interval depends on the concentration and duration of exposure (Hygienic Guide Series, 1968). The distress is caused by pulmonary edema and is characterized by cough, production of foamy sputum, progressive dyspnea, and severe cyanosis (Patty, 1963). Pulmonary edema may progress to pneumonia, and cardiac failure may intervene. In nonfatal cases, no permanent residual damage is believed to occur (Patty, 1963; Sax, 1968).

The mortality among two groups of workers exposed to phosgene gas at the same uranium-processing plant in 1943-1945 has been described by Polednak (1980). One group consisted of 699 white men with daily exposure at low concentrations or at concentrations above 1 ppm; the second group consisted of 106 men with definite acute exposures and symptoms at exposures equal to or greater than 50 ppm/min. A control group included 9,352 white men who worked at the same plant. Of the group of 106 men, 25 had x-ray evidence of acute pneumonitis, and one death from pulmonary edema due to phosgene occurred less than 24 h after exposure. A total of 30 deaths had occurred in this group as of 1974 (SMR = 113); there were no deaths from lung cancer, but three deaths (vs. 1.37 expected) were due to respiratory disease. Mortality ratios (SMRs) for most causes of death among the 699 chemical workers were similar to those among 9,352 controls employed at the same plant but not exposed to phosgene (or uranium dust).

Table 7 lists a number of cases of human phosgene inhalation exposure (NIOSH, 1976). Splashes of liquid phosgene into the eye may produce severe irritation, and skin contact may cause severe burns (Hygienic Guide Series, 1968).

Fatal exposure to phosgene has resulted in extensive degenerative changes in the epithelium of the trachea, bronchi, and bronchioli and hemorrhagic edematous focal pneumonia (Gerritsen and Buschmann, 1960). Most fatalities due to acute phosgene exposure occur during the first 24-48 h (Chadwick and Hardy, 1967). Most patients who died within the first 72 h died of pulmonary edema or cardiac problems; those who died later had such complications as pulmonary infection, thrombosis, and embolism. The clinical course has also been described by NIOSH (1976), Boyd and Perry (1960), Delephine (1923), Gerritsen and Buschmann (1960), Glass etal. (1971), Long and Hatch (1961), Spolyar etal. (1951), Stavrakis (1971), and Underhill (1920).

No effects other than odor detection were reported (NIOSH, 1976) in 56 military personnel (without upper respiratory problems) who were exposed to phosgene at increasing concentrations until they could all smell it. Of “technically trained” personnel, 50% detected phosgene

at 1.5 ppm, 39% detected it at 1.2 ppm, and none below 0.4 ppm (Wills etal., 1938).

EFFECTS ON ANIMALS

Acute overexposure to phosgene for short periods has generally produced the same symptoms in all animal species tested (NIOSH, 1976). The lungs appear to be the principal target organ for phosgene, and the characteristic pathologic feature is the development of pulmonary edema of unknown pathogenesis. Survivors of an acute episode exhibit various degrees of bronchopneumonia, benign pneumonia, bronchial plugging, lung collapse, pulmonary consolidation, pneumonia, and emphysema; animals that die after exposure show severe pulmonary edema. For example, Cameron etal. (1942a) exposed mice, rats, guinea pigs, rabbits, cats, monkeys, and goats to phosgene at 0.86 ppm for 5 h. Within 24 h, 10% of the rats and 60% of the mice died. Microscopic examination of the lungs showed severe effects in 39% of the animals, mild effects in 31%, and slight effects in 30%; pulmonary edema was the most common finding. Cameron etal. (1942b) also exposed mice, rats, guinea pigs, rabbits, cats, and goats to phosgene at 0.2 ppm, 5 h/d for 5 d. No deaths occurred from the acute exposure, and few animals showed any evidence of distress. Necropsy disclosed pulmonary lesions in 67% of the animals; an estimated 4-11% displayed moderate to severe lesions. Pulmonary edema was noted in 41% of the animals; but was usually slight. It was concluded that repeated exposure to phosgene at low concentrations induced lung damage, although rarely to a severe degree. However, Cucinell (1974), in reviewing the latter study, stressed the extensive lung lesions present in 4% of the animals. Exposure of the same species at 1 ppm, 5 h/d for 5 d caused pulmonary lesions that were considered “likely to give rise in man to serious clinical symptoms” (Cameron and Foss, 1941). Exposure of cats at the same concentration caused hemoconcentration and leukocytosis (Cucinell, 1974).

Gross etal. (1965) demonstrated chronic pneumonitis in rats as early as 4 h after exposure to phosgene. The sensitivity of the alveolar epithelium to phosgene is such that the pulmonary reaction can be identified after exposures at concentrations as low as 0.5 ppm for 120 min. The lowest exposure that produced a recognizable typical pulmonary lesion had a Ct value (concentration of the gas, in parts per million, multiplied by the time of exposure, in minutes) of 15 (e.g., 3 ppm for 5 min). Ct values producing pneumonitis are summarized in Table 8. The chronic pneumonitis is initially centered in the respiratory bronchiole and its evaginating alveoli. There is cellular thickening of these structures with the elaboration of new reticulin fibers. In addition to having thickened walls, the alveoli are often filled with desquamated cells (Gross etal., 1965).

Table 9 lists a number of additional phosgene inhalation studies conducted in animals (NIOSH, 1976).

Phosgene is reportedly responsible for the development of long-term lung disease in man, as well as emphysema and obliterative bronchiolitis in dogs (Cucinell, 1974; Galdston etal., 1947; Rossing, 1964). Although no quantitative data are available on the dosage that

might cause permanent lung damage in man, it has been shown experimentally that exposure of dogs at 80-160 mg/m^3 for 30 min every other day for a week causes interferences in lower airway resistance and, with continued exposure, permanent pathophysiologic changes within the lung (Rossing, 1964). According to Cucinell (1974), these concentrations are toxic and are 10-20 times greater than the dosage needed to produce pneumonitis (Table 8). The exact relation of phosgene exposure at these concentrations to human disease is unknown. Histopathologic examination of rats exposed at 0.2 and 1.0 ppm, 4 h/d, 5 d/wk for 2 wk at Haskell Laboratory (1976) showed no effects.

The Committee is unaware of any data on the carcinogenic effects of phosgene. However, exposure at high concentrations could conceivably lead to neoplasia related to scarring or regeneration of damaged lung tissue (NIOSH, 1976).

Cucinell (1974) reviewed aspects of the development of tolerance to phosgene in several species. For example, guinea pigs treated with low doses of phosgene--1.5 ppm (6 mg/m$^{3)}$ for 10 min--for 7 d became relatively resistant to toxic concentrations--35 ppm for 10 min (Cordier and Cordier, 1953b). Repeated exposure of cats to phosgene at 1.5-3.8 ppm or 5-6 ppm for 10 min every day had caused no greater lung damage after 40 d than after 2 d (Cordier and Cordier, 1953a). These animals were able to tolerate a total Ct of 9,000 mg. min/m^3 (total time, 400 min), even though the LCt_{50} for cats is about 2,000 mg min/m^3 for 1 min (Cucinell, 1974). Tolerance to high doses of phosgene is believed by some to represent a manifestation of pathologic changes in the lungs (Cucinell, 1974). The Committee is unaware of any data on the development of tolerance to phosgene in man.

PHARMACOKINETICS

When phosgene (which is only slightly soluble in water) is inhaled at a moderate concentration, it does not react noticeably with the aqueous mucous film of the upper respiratory tract. Without decomposition, phosgene then reaches the alveolar region and interacts there with components of the blood-air barrier.

Immediate and irreversible damage occurs (Potts etal., 1949)--e.g., the membrane function breaks down, and fluid leaks from the capillaries into the interstitial space and then into the alveolar space, finally spreading to the trachea. The duration of this process--the developmental phase or clinical latent period (Diller, 1978)--depends on the inhaled dosage; the higher the dosage, the shorter the latent period. After moderate dosage, the clinical latent period may be about 6-15 h (Diller, 1978). Much of the current information on the metabolism of phosgene has been gained indirectly through recent studies of the in vitro metabolism of chloroform (Cresteil etal., 1979; Mansuy etal., 1977; Pohl etal., 1977) and carbon tetrachloride (Shah etal., 1979); that shows the intermediary formation of phosgene from both chlorinated hydrocarbons. For example, cysteine can form a stable adduct with chloroform metabolites when added to the incubation mixture (Mansuy etal., 1977; Pohl etal., 1977) and carbon tetrachloride (Shah etal., 1979);that shows

the intermediary formation of phosgene from both chlorinated hydrocarbons. For example, cysteine can form a stable adduct with chloroform metabolites when added to the incubation mixture (Mansuy etal, 1977; Pohl etal., 1977); this adduct is 4-carboxythiazolidine-2-one, the reaction product of cysteine with phosgene. The reactions of phosgene as a chloroform metabolite depend on which nucleophiles are present in the incubation medium (Cresteil etal., 1979; see Figure 3). Direct reaction with water leads to CO_2, which is the final chloroform metabolite (Lavigne and Marchand, 1974; Paul and Rubinstein, 1963). Nucleophilic groups of microsomal macromolecules or free amino acids could react with phosgene and generate unstable acyl chlorides--e.g., carbamyl chlorides, chloroformates, or thiochloroformates, depending on whether the reacting group is amine, hydroxyl, or thiol (Cresteil etal., 1979). The reaction of these electrophilic intermediate acyl chlorides with water yields CO_2 and regenerates the starting amino acid (or nucleophilic group of macromolecules). Finally, in this pathway, the nucleophilic group of amino acids catalyzes the hydrolysis of phosgene to CO_2.

With the evidence that phosgene is the precursor of CO_2 from carbon tetrachloride (Shah etal., 1979), it was suggested that it might also be one of the reactive species that bind to lipids and proteins. Reynolds (1967) reported that $^{14}COCl_2$ given to rats was found in liver protein and to a smaller extent in lipids, but the pattern was quite different from that of $^{14}CCl_4$. Cessi etal., (1966) also reported that [^{14}C]phosgene administered to rats labeled the liver proteins.

INHALATION EXPOSURE LIMITS

In 1980, ACGIH recommended a TLV for phosgene of 0.1 ppm for an 8-h working day (ACGIH, 1980). This figure is based on data obtained by the Chemical Warfare Service before 1921 that indicated that at 1 ppm phosgene may be safe for prolonged exposure (Cucinell, 1974). It is also based on the studies of Gross etal. (1965) that showed that exposure to phosgene at concentrations as low as 0.5 ppm for 2 h caused definitive pathologic changes in the lungs of rats killed 96 h after exposure. (Some abnormalities were considered to be present 3 mo after rats had been exposed at 2 ppm for 80 min.)

A safe concentration zone of 0.1-0.125 ppm was recommended for international adoption in 1968 by the Joint ILO/WHO Committee on Occupational Health (ILO/WHO, 1968). In 1980, ACGIH recommended a TLV of 0.1 ppm, on the basis of its irritating effects on the respiratory tract at slightly above 0.1 ppm, to which tolerance develops (ACGIH, 1980). Table 10 lists additional maximal allowable concentrations (MACs) for 15 countries (ACGIH, 1983, International Labour Office, 1970; Jpn. Assoc. Ind. Health, 1971; OSHA, 1983; Soc. Ital. Med. Lav., 1975; Winell, 1975). NIOSH recommended in 1976 that occupational exposure to phosgene not exceed 0.1 ppm, determined as a TWA concentration for up to a 10-h workday in a 40-h workweek, or 0.2 ppm, as a ceiling concentration for any 15-min period (NIOSH, 1976).

Cucinell (1974) suggested that the current standard of 0.1 ppm may be too high for 8 h/d, 5 d/wk at room temperature. It is also

believed that ambient concentrations of phosgene in industrial situations in the United States are considerably below the TLV. Industrial intoxication by phosgene has been due primarily to accidental exposure at high concentration. Cucinell (1974) further suggested that some adjustments in the acceptable concentration for the general population must be made for a continuous 24-h/d exposure, as opposed to single or intermittent exposure; as noted previously, animals tolerate intermittent exposures to phosgene better than continuous exposure. It was further noted that, although high doses of phosgene can cause chronic lung disease in man and animals, it is not certain whether low doses can aggravate pre-existing conditions or cause lung disease (Cucinell, 1974). Because the lowest experimental values available for long-term exposure suggest that 0.2 ppm for 5 h/d for 5 d may cause slight changes in the lung (Cameron etal., 1942b), Cucinell (1974) suggests that a value of 0.1 ppm would not be safe enough. If a safety margin of a factor of 10 is used, the environmental concentration should be 0.02 ppm, and that should not be exceeded by working personnel during an 8-h/d, 5-d/wk exposure. In support of the suggested ceiling concentration of phosgene, it was suggested that a Ct of 10 ppm. min is safe and that this applicaton of Haber's law--constant toxic effect = (concentration) (duration of exposure)--is valid. For an 8-h workday, the ceiling would be 0.02 ppm. Cucinell (1974) further proposed that, for a 24-h/d exposure, the ceiling should be lowered by about one-third to 0.006 ppm and an additional safety factor of 10 was recommended for situations in which the general population may be exposed (0.0006 ppm).

Tentative EELs for phosgene were reviewed by Zielhuis (1970), who suggested that the most relevant animal exposures to consider were those of Rinehart and Hatch (1964) and Gross etal. (1955). For example, when rats were exposed at 0.5-4 ppm for 5-480 min, death occurred when the Ct exceeded 180; at a Ct of 300, the mortality was 60%. There were no respiratory-function effects or observable pathologic changes at autopsy at a Ct of 15 (3 ppm for 5 min). Accordingly, the above information suggests that the Ct for man should remain below 15 when t is less than 60 min. Zielhuis (1970) proposed the following exposure limits:

Duration, min	EEL, ppm	EEL/TLV ratio
5	2.0	20
15	0.8	8
30	0.4	4
60	0.2	2

COMMITTEE RECOMMENDATIONS

In 1966, the Committee on Toxicology recommended EELs and CEL for phosgene.

On the basis of what appear to be the most relevant animal-exposure studies (Gross etal., 1965; Cameron etal., 1942a,b; Cameron and Foss, 1941; Rinehart and Hatch, 1964) and the rationale for lowered concentrations of phosgene as described by Cucinell (1974) and Zielhuis (1970), it appears prudent to propose lower EELs than the Committee recommended in 1966. The Committee has based its recommendations on studies done by Cameron and Foss (1941) and Cameron etal. (1942a,b) that show that animals do not tolerate phosgene at 0.2 ppm administered 5 h/d for 5 d (they developed slight pulmonary edema).

The present Committee's recommended EELs and CEL for phosgene and the limits proposed in 1966 are shown below.

	1966	1984
60-min EEL	1.0 ppm	0.2 ppm
24-h EEL	0.1 ppm	0.02 ppm
90-d CEL	0.05 ppm	0.01 ppm

TABLE 7 Phosgene Inhalation Exposure Effects on Humansa

No. Cases[a]	Exposure Variables	Duration of Exposure	Effects	Reference
109	Unknown 1 mol of phosgene Unknown[b]	Brief Brief 30 min	Pulmonary edema Pulmonary edema Pulmonary edema, death	Thiess and Goldmann, 1968
2	Unknown[b] Unknown[b]	Indefinite 3 h	Pulmonary edema Pulmonary edema	Gerritsen and Buschmann, 1960
1	Unknown (15 ppm)[b,c]	3.5 h	Pulmonary edema, death	Spolyar etal., 1951
1	Unknown[b]	4.5 h	Acute bronchitis	Glass etal., 1971
2	Unknown Unknown	Brief Brief	Bronchial irritation, death	Delephine, 1923
1	Unknown[b]	Brief	Pulmonary edema	Seidelin, 1961
7	Unknown	Brief	Acute bronchitis, delirium, pulmonary edema	Steel, 1942

[a] Data from NIOSH, 1976. [b] Simultaneous exposure to chlorinated hydrocarbons. [c] Recreated exposure and simulating accident.

TABLE 8 Pneumonitis Caused by Phosgene in Ratsa

Ct, ppm-min	Conc., ppm	Time, min	Chronic Pneumonitis[b]
13	1.3	10	0
15	1.5	10	0
24	0.8	30	+
27	0.9	30	+
33	1.1	30	−
36	1.2	30	+
40	1.0	40	+
48	0.8	60	++
48	0.8	60	+,P
54	0.9	60	++,P
60	0.5	120	+
84	1.4	60	+++,P
88	1.1	80	+
90	0. 5	180	+
90	0.5	180	++
90	0.5	180	+
90	1.5	60	+++
96	0.8	120	+++
108	0.9	120	0,P
120	1.0	120	++,P
120	1.0	120	+
120	1.5	80	+
180	0.5	360	+
180	0.5	360	+
180	1.0	180	+
180	1.5	120	+++,P
192	1.2	160	++
198	1.1	180	+++
210	1.0	210	++
228	1.9	120	++
240	0.5	480	++,P
240	0.5	480	++
240	0.5	480	+++,P
240	1.0	240	++,P
342	1.9	180	++,P
360	1.0	360	+,F

[a] Data from Gross etal., 1965.
[b] 0 = no chronic pneumonitis; + = slight chronic pneumonitis; ++ = moderate chronic pneumonitis; +++ = severe chronic pneumonitis; P = acute pneumonia; and F = fibrinous pneumonia.

TABLE 9 Phosgene Inahalation Exposures and Effects in Animalsa

Species	Concentration, ppm	Duration of Exposure	Duration of Effects	Reference
Rat	55-100	10 min	Reduction in death rate from 74% to 33% by previous challenge	Box and Cullumbine, 1947
Rabbit	50-200	14-25 min	Decrease in sympathetic tone	Ivanhoe and Meyers, 1964
Rabbit	67	30 min	Pulmonary edema	Boyd and Perry, 1960
Dog	44-120	30 min	Pulmonary edema, pneumonia, emphysema, death	Underhill, 1920
Dog	72	30 min	Pulmonary consolidation, death	Durlacher and Bunting, 1947
Dog	24-40	30 min, 1 or 2 exposures, 1-3/ week	Acute bronchiolitis	Clay and Rossing, 1964
Dog	24-40	30 min, 4-10 exposures, 1-3/ week	Chronic bronchiolitis	Clay and Rossing, 1964
Dog	24-40	30 min, 30-40 exposures, 1-3/ week	Emphysema	Clay and Rossing, 1964
Cat and guinea pig	2.5-6.25	10 min/d, 2-41 d	Pulmonary edema, bronchitis, bronchopneumonia, death	Cordier and Cordier, 1953[b]

[a] Data from NIOSH, 1976.
[b] Animals were pregassed at 20 ppm for 10 min to determine effect of pregassing on response to later challenge.

TABLE 10

Country	Year[a]	MAC, mg/m^3	Reference
United States	1974	0.4	ACGIH, 1983
United States (OSHA)	1974	0.4	OSHA, 1983
West Germany	1974	0.4	Winell, 1975
East Germany	1973	0.5	Winell, 1975
Sweden	1975	0.3 (ceiling)	Winell, 1975
CSSR (Czechoslovakia)	1969	0.4	Winell, 1975
USSR	1972	0.5 (ceiling)	Winell, 1975
Italy	1975	0.4	Soc. Ital. Med. Lav., 1975
Japan	1969	0.4	Jpn. Assoc. Ind. Hlth., 1971
Bulgaria	NG	0.5	Inter. Lab. Off., 1970
Finland	NG	4	Inter. Lab. Off., 1970
Hungary	NG	0.5	Inter. Lab. Off., 1970
Poland	NG	0.5	Inter. Lab. Off., 1970
Rumania	NG	0.5	Inter. Lab. Off., 1970
United Arab Republic	NG	4	Inter. Lab. Off., 1970
Yugoslavia	NG	0.4	Inter. Lab. Off., 1970

[a] NG = Not given.

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SODIUM HYDROXIDE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	NaOH
Molecular weight:	40.01
Synonyms:	White caustic, caustic soda, soda lye, lye
CAS number:	1310-73-2
Melting point:	318.4°C
Boiling point:	1390°C
Specific gravity:	2.13
Solubility:	Soluble in water, ethanol and glycerol; insoluble in acetone and ether
General characteristics:	White deliquescent solid

OCCURRENCE AND USE

Sodium hydroxide is widely used in the manufacture of soaps, paper, rayon, cellophane, mercerized cotton, aluminum, and many chemicals. It is also used in petroleum refining, degreasing, etching, zinc extraction, tin plating, oxide coating, and food processing (for peeling fruits and vegetables). In concentrated form, it is used as a drain cleaner. Sodium hydroxide has been used in the management of pleural effusions.

SUMMARY OF TOXICITY INFORMATION

Sodium hydroxide toxicity depends on the concentration of the sodium hydroxide solution and the duration of its contact with tissue. The chemical acts locally, exerting a strong corrosive action whose mechanism is not known, and causes almost immediate degeneration of the tissue, which can result in rapid absorption of sodium hydroxide into the circulating system and distribution with the body water. It dissociates completely in water, blood, and cytoplasm and is not metabolized.

Because toxicity of sodium hydroxide is determined primarily by concentration of the hydroxyl ion, the total alkalinity is reduced when sodium carbonate (Na_2CO_3) forms. Therefore, measurement of sodium ion concentration is not always an accurate indication of alkalinity and toxic potential (Cooper et al., 1979).

EFFECTS ON HUMANS

Humans can be exposed during the manufacture of sodium hydroxide and in the handling of sodium hydroxide as a solid or concentrated solution.

Sodium hydroxide is corrosive to all body tissues; concentrated vapors cause serious damage to the eyes and respiratory system. Ingestion of sodium hydroxide, which occurs frequently in children, can cause severe necrosis, with stricture of the esophagus and death. Contact with the skin can result in dermatitis, loss of hair, and necrosis due to irritation. Skin types vary in sensitivity to caustic irritation.

Airborne mists of sodium hydroxide around degreasing vats (at 200°F) containing Seco 75 or Tysol 810 (concentrated sodium hydroxide solutions combined with chelating and wetting agents) were associated with irritation of the upper respiratory tract in workers exposed to sodium hydroxide at 0.01-0.7 mg/m^3 (mean, 0.1-0.15 mg/m^3). The work area also contained vapors of Stoddard solvent, ENSIS 254 oil, Zyglo, and Magna-flux solutions (Stoddard solvent air concentrations were 13-780 mg/m^3) and, at vat-cleaning time, sulfuric acid at 0.1-0.6 mg/m^3 (Hervin and Cohen, 1974). The effect of these chelating agents and solvents on sodium hydroxide toxicity is not known.

Ott etal. (1977) assessed mortality rates among chemical-plant employees exposed chronically to caustic dust. Records of acute exposures (unknown concentrations) indicated that the caustic materials in the plant had caused mild to severe responses (irritation, erythema, and "objective damage to organs") in skin, eyes, and the respiratory system. No indication of purity was given, but it was noted that sodium chloride and sodium carbonate were known to be included in the caustic exposures; workers known to be exposed to arsenicals or asbestos, as well as caustic, were excluded from the study. According to the results of a study that measured total alkalinity of air samples in the workplace, sodium hydroxide concentrations of up to 6.7 mg/m^3 in one area of the plant correlated well with subjective response data that indicated increasing respiratory irritation with increasing alkali concentration; in a second area of the plant, where sodium hydroxide content was up to 7.7 mg/m^3, the correlation was poor. No explanation for the poor correlation could be found. Sodium hydroxide estimated to be as high as 2 mg/m^3 (TWA) did appear to cause nasal and skin irritation, especially in plant areas with high temperatures. No correction factor for temperature effects on sodium hydroxide toxicity is available, but it is expected that increased temperatures would increase toxicity.

Controlled exposures to sodium hydroxide solutions have been limited to dermal application, usually to the forearms of volunteers. Malten and Spruit (1966) placed 0.12% (0.03 M) or 0.27% (0.0675 M) solutions of sodium hydroxide in cups fixed to the forearms of human volunteers. Erythema was produced within 0.5 h by the stronger solution and within 1 h by the more dilute preparation (see also Spruit and Malten, 1968). Marzulli and Maibach (1975) applied sodium hydroxide solutions to the backs of human subjects in occluded patches renewed daily for 21 d. The lowest concentration studied (0.05%, 0.0125 M) produced no erythema, a 0.5% (0.125 M) solution was mildly irritating, and solutions of 4% or 5% were severely irritating. Similar results were observed in rabbits.

EFFECTS ON ANIMALS

Many toxicologic evaluations of sodium hydroxide have been carried out in animals; the studies have focused on eyes, skin, and lungs as targets. These investigations are summarized in Table 11.

INHALATION EXPOSURE LIMITS

The current ACGIH (1983) ceiling limit for sodium hydroxide is 2 mg/m^3 (TWA); this concentration is also used by NIOSH. Exposure ceilings in West Germany, Finland and Yugoslavia are 2 mg/m^3. The concentration appears to be based on an undocumented comment by Patty (1949) that 2 mg/m^3 is thought to cause noticeable, but not excessive, respiratory irritation.

COMMITTEE RECOMMENDATIONS

Few inhalation studies to evaluate the toxicity of sodium hydroxide have been reported. The one detailed analysis of workers in a degreasing plant exposed to heated caustic vapor indicated that aerosols containing an average of 0.1 mg/m^3 were reversibly irritating to the upper respiratory tract (Hervin and Cohen, 1974); the workers in that study were also exposed to detergent and organic solvents, so evaluation of the toxicity of sodium hydroxide alone is difficult. Sodium hydroxide at 2 mg/m^3 (TWA) appeared to cause nasal and skin irritation, especially at high temperatures. Because increased temperature increases toxicity, the Committee concludes that a 1-h exposure to sodium hydroxide at 2 mg/m^3 would probably produce no more than a reversible mild irritation of eyes, skin, and respiratory system.

The Committee's previous recommendations for sodium hydroxide exposure limits were made in 1965 on the basis of an undocumented statement that 6.0 mg/m^3 produced intolerable respiratory discomfort; the 1965 recommendation was for 10- and 30-min EELs of 4 mg/m^3 and a 60-min EEL of 2 mg/m^3. Little new information on the toxicity of sodium hydroxide by inhalation is available; experimental-animal studies have concentrated on topical application to eyes and skin, and extrapolation from such studies to human inhalation is difficult. On the basis of the report on workers in a degreasing plant (Hervin and Cohen, 1974), an EEL above 2 mg/m^3 may produce much nasal and skin discomfort, especially at high temperature, but no available inhalation report provides a basis on which to establish an EEL for sodium hydroxide with confidence.

The present Committee's recommended EELs for sodium hydroxide and the limits proposed in 1965 are shown below.

	1965	1984
10-min EEL	4 mg/m^3	2 mg/m^3
30-min EEL	4 mg/m^3	2 mg/m^3
60-min EEL	2 mg/m^3	2 mg/m^3

TABLE 11

Species	Route	Dose	Duration of Exposure	Effects	Reference
Rat	Skin	50%	1 min, no wash 1 min, HA_cwash 1 min, H_2O wash	Edema, sloughing Edema, sloughing Edema, limited sloughing	Davidson, 1927
Mouse	Skin	50%	Immediate rinse 30 min, rinse 1 h, rinse 2 h, rinse No wash	No burn, no dead Burn, 1/5 dead Burn, 2/5 dead Burn, 4/5 dead Burn, 5/7 dead	Bromberg etal., 1965
Rat	Eye	40%	NG[a]	Necrosis, death	Cosgrove and Hubbard, 1928
Rabbit	Eye	20%	10 s	Necrosis	Hubbard, 1937; Hubbard, 1938
Rabbit	Eye	0.2%	3 min	Necrosis	Hughes, 1946
Rabbit	Eye	pH 11 pH 12	15 min 15 min	Slight injury Necrosis	Grant and Kern, 1955
Rabbit	Eye	2%	30 s	Necrosis	Brown, 1971; Brown and Weller, 1970; Brown etal., 1969[a,b,c]; 1970
Rabbit	Eye	0.5%[b] 2.0%[b] 8.0%[b]	Not specified Not specified Not specified	Intraocular pressure up Intraocular pressure up Intraocular pressure up	Chiang etal., 1971

Rabbit	Eye	2%	H_2O rinse,1 min H_2O rinse,4 min	Corneal perforations Corneal perforations	Geeraets etal., 1966
Rabbit	Eye	4%[c]	1 s 2 s	No injury Corneal swelling	Shapiro, 1956
Rat	Inhalation	40% soln.[d]	2.5 mo[e]	Degeneration of pulmonary tissue, **undefined "tumors"**	Dluhos etal., 1969
Rat	Inhalation	40% soln. aerosol[f] 20% soln. aerosol[f] 10% soln. aerosol[f] 5% soln. aerosol[f]	1 mo 1 mo 1 mo 1 mo	Death Degeneration of pulmonary tissue Little change in pulmonary tissue Little change in pulmonary tissue	Vyskocil etal., 1966

[a] 0.5 ml applied.
[b] In impregnated paper.
[c] Aerosol; 80% of particles under 1 μm in diameter.
[d] 30 min twice a day for 2.5 mo with 10-d rest after third week.
[e] Aerosol included quartz dust at 10 g/m^3.
[f] Twice a week.

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SULFUR DIOXIDE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	SO_2
Molecular weight:	64.07
CAS number:	7446-09-5
Specific gravity (liquid):	1.434
Specific gravity (gas):	2.927
Solubility:	Soluble in water, alcohols, acetic acid, and sulfuric acid
General characteristics:	Colorless, nonflammable gas or liquid; strong suffocating odor
Conversion factors:	1 ppm = 2.6 mg/m^3 1 mg/m^3 = 0.38 ppm

OCCURRENCE AND USE

Sulfur dioxide is most noteworthy as an environmental pollutant. It is formed when materials containing sulfur are burned, and is thus an important air pollutant, especially in the vicinity of smelters and plants burning soft coal or high sulfur oil. Others are automobile exhaust, wood-burning stoves, pulp mills, and smelters. Note that, in addition to sulfur dioxide itself, many related compounds and decay products of sulfur dioxide--such as sulfurous and sulfuric acids, sulfates, sulfites, and bisulfites--are present in the ambient air. It is beyond the scope of this brief review to describe all the information on all these substances; only sulfur dioxide will be addressed.

SUMMARY OF TOXICITY INFORMATION

Within the last 8 yr, three reviews of the toxic effects of sulfur dioxide in humans and animals have been published (Greenfield, Attaway and Tyler, 1976; International Electric Research Exchange, 1981; EPA, 1982). These reviews covered epidemiologic reports, health effects of acute and chronic low-dose exposures of humans, health effects of acute and chronic low- and high-dose exposures of animals, projected estimates of pollutant thresholds for adverse effects of short- and long-term exposures, and correlations of sulfur dioxide exposures with asthmatic attacks and effects on children.

EFFECTS ON HUMANS

Few recent reports have described accidental exposure to sulfur dioxide. Of historical interest is the report of a worker exposed directly to liquid sulfur dioxide who suffered effects of acute freezing of the skin and corneas (Kennon, 1927). A more recent report

cited a case of an accidental exposure to sulfur dioxide at a high concentration for 15-20 min that led to the development of a severe, irreversible obstructive syndrome (Woodford etal., 1979). The pulmonary effects of accidental exposure to sulfur dioxide appear to be limited to gaseous sulfur dioxide.

An excellent review of studies involving controlled human exposure is available (Greenfield, Attaway and Tyler, 1976). Briefly, the major health effects of exposure to sulfur dioxide at less than 25 ppm (for various durations) are irritation of mucous membranes, throat, esophagus, and eyes; reflex cough; increase in respiratory rate associated with decrease in depth of respiration; decrease in nasal mucus flow; variable effects on tracheal and bronchial mucus flow; decrease in forced expiratory volume and flow; decrease in airway conductance; and increase in airway resistance.

An estimated 10-20% of the population will respond with hyperreactivity on exposure to sulfur dioxide. Koenig etal. (1980) have shown that asthmatic adolescents are more sensitive than healthy nonsmoking adults to sulfur dioxide at 1 ppm. As demonstrated by Lawther etal. (1975), the changes in airway resistance after exposure to sulfur dioxide at less than 30 ppm are short-lived. Greenfield, Attaway and Tyler, (1976) reviewed similar changes after short-term exposures to sulfur dioxide at concentrations greater than 25 ppm.

Another review (EPA, 1982) indicated that recovery to normal functional values can occur in as little as 5 min after acute exposure of normal resting subjects (Lawther etal., 1975), but may take 30-60 min after exposure during exercise (Bates and Hazucha, 1973), after exposure of exercising asthmatic subjects (Sheppard etal., 1981; Koenig etal., 1981), or after exposure of other sensitive subjects (Gokemeijer etal., 1973; Lawther etal., 1975). Weir and Bromberg (1975) suggested that persons with minimal airway disease are probably not more susceptible than normal persons to the effects of sulfur dioxide. However, this latter conclusion is questionable, in that the presence of pre-existing disease in the subjects interfered with attempts to define threshold concentrations of sulfur dioxide. Asthmatic subjects exposed to sulfur dioxide at 5 ppm for 5 min while exercising have had asthmatic attacks (Sheppard etal., 1980).

Epidemiologic data on sulfur dioxide are characteristically difficult to assess, because of the spectrum of pollutants and particles associated with ambient sulfur dioxide. A number of acute air-pollution episodes in this century have been associated with increased mortality. Incidents in the Meuse Valley, Donora (Pennsylvania), London, and New York City have provided evidence that increased pollution has observable effects on human health (Greenfield, Attaway and Tyler, 1976). Retrospective studies of these events have demonstrated that deaths most often occurred among persons over 45 who were already suffering from chronic heart or lung disease; the effects of sulfur dioxide alone were not assessed. Lung-function measurements made daily on four normal subjects and two with bronchitis in London showed that daily variations in lung function were small and were related to respiratory infections (EPA, 1982). Concentrations of sulfur dioxide correlated with variations in peak flow rates and airway resistance. Increased sulfur dioxide pollution has been related to decreases in lung function (FEV_1) in children. Several

long-term epidemiologic studies of chronic effects have found that populations living in areas characterized by high concentrations of particulate matter and sulfur dioxide tend to have a higher prevalence of respiratory illness and decreased lung function than groups in areas with lower pollution. However, the influence of particles and other factors associated with ambient sulfur dioxide confounds interpretation (EPA, 1982).

In one occupational study, the frequency of chromosomal aberrations was significantly increased among workers at a sulfite pulp factory in Sweden (Nordenson etal., 1980). This increase was found to be associated mainly with exposure to sulfur dioxide (boiling of sulfite pulp and handling of sulfuric acid) and not with chlorine and dust in other workplaces in the factory.

EFFECTS ON ANIMALS

Alarie etal. (1972) reported an accidental exposure of cynomologus monkeys to sulfur dioxide at an estimated 200-1,000 ppm for 1 h. No animals died, but a deterioration in pulmonary function persisted for the following 48 wk of the study. Histopathologic lesions included thickening of alveolar walls, hyperplasia of bronchial epithelium, and bronchiolar plugging with proteinaceous material, macrophages, and leukocytes.

A comprehensive review (Greenfield, Attaway and Tyler, 1976) of published literature on controlled animal exposures to sulfur dioxide may be summarized as follows: Acute exposure of animals results in diminished pulmonary function similar to that seen in man, decreased tracheal mucus clearance, pneumonia, and lesions of the nasomaxillary turbinates. Acute effects generally are transient at lower sulfur dioxide concentrations (20 ppm). In various species, the effects of exposures at over 100 ppm appear to be time-dependent and range from transient physiologic manifestations to death.

Transient adverse effects on pulmonary function have been demonstrated in rabbits exposed to sulfur dioxide at 200 ppm for 3 h (Davies etal., 1978). Rats exposed at 400 ppm died after 22 h of exposure (Asmundsson etal., 1973). Rats exposed at 567 ppm 6 h/d died after 12 d (Laskin etal., 1970). Adaptation apparently occurs if recovery between exposure periods is sufficient.

Subchronic exposure (less than 90 d) of animals to sulfur dioxide has been reviewed (Greenfield, Attaway and Tyler, 1976). Studies in which animals were exposed at concentrations below 10 ppm have demonstrated functional abnormalities that are reversible. Studies with subacute exposures at higher concentrations are lacking.

Chronic exposures (over 90 d) of a variety of species to sulfur dioxide at both low and high concentrations have been reported. The notable effects of exposure of dogs at 500 ppm 2 h/d for 3-5 mo include hypersecretion of mucus, goblet-cell hyperplasia, bronchial-gland hypertrophy, increase in pulmonary resistance, decrease in airway responsiveness to inhaled mediators, and decrease in tracheal mucus clearance (Drazen etal., 1982; Chakrin and Saunders, 1974; Greene etal., 1982; and Islam etal., 1977). Early exposure effects, such as ocular and mucous-membrane irritation, diminished with

repeated exposure; that indicates the existence of an adaptation mechanism.

Sulfur dioxide is not generally considered to be carcinogenic. One study (Laskin etal., 1970) has demonstrated a higher incidence of squamous-cell carcinomas of the lung in rats that inhaled benzo[a]pyrene in combination with sulfur dioxide at 10 ppm than in rats that inhaled only benzo[a]pyrene. This does not show that sulfur dioxide is carcinogenic, but it does suggest that it may increase the carcinogenic activity of known carcinogens.

The embryotoxic and teratogenic potentials of sulfur dioxide have been evaluated in mice and rabbits (Murray etal., 1979). Exposure of mice at 25 ppm and of rabbits at 70 ppm for days 6-15 and days 6-18 of gestation, respectively, yielded no evidence of a teratogenic effect related to sulfur dioxide exposure; however, significant increases in the incidence of minor skeletal variants were observed in both species.

PHARMACOKINETICS

The penetration of sulfur dioxide to the lungs is greater during mouth breathing than during nose breathing. Sulfur dioxide is readily removed during passage through the upper respiratory tract. At concentrations higher than 1 ppm, removal is over 90% (Strandberg, 1964). Sulfur dioxide is converted to bisulfite ion (HSO_3^-) on mixing with water. It has been shown that inhaled sulfuric acid mists with droplets of 0.4-1.1 μm in mass median aerodynamic diameter have deposition patterns similar to those of dry aerosols and that the effect of hygroscopicity is not dominant in determining the site of deposition (Dahl etal., 1983). Studies using [^{35}S] sulfur dioxide have shown that inhaled sulfur dioxide is readily distributed throughout the body. Inhaled sulfur dioxide is only slowly removed from the lower respiratory tract. Radioactivity from inhaled labeled sulfur dioxide can be detected a week or more after inhalation and may be due to ^{35}S binding with protein. Recent work has shown that [^{35}S] sulfuric acid is cleared faster from smaller-diameter than from larger-diameter airways of dogs (A.R. Dahl etal., unpublished manuscript). In addition, species differences have been noted: clearance is slower in guinea pigs than in dogs and slower in dogs than in rats.

ANALYTIC METHODS

Much information is available on ambient sulfur dioxide concentrations, and the assay system is well standardized and reasonably accurate. Among the procedures used are acidimetry, colorimetry, electrochemistry, fluorimetry, flame photometry, and emission and absorption spectroscopy (Cheremisinoff and Morresi, 1981; Perry and Young, 1977). It is important to remember that sulfur dioxide is dynamically related to SO_4^{2-} (sulfate). The rates of oxidation of sulfur dioxide to sulfuric acid and conversion to sulfate are greatly increased in polluted air (Rall, 1974). The atmospheric chemistry of these reactions is complex and not completely understood.

INHALATION EXPOSURE LIMITS

OSHA (1983) recommended a TWA limit of 2 ppm. ACGIH (1980, 1983) recommended a TLV-TWA of 2 ppm for an 8-h period and a STEL of 5 ppm for 15 min. The reduction of the TLV from 5 to 2 ppm was based on available data and, in the opinion of the ACGIH committee, effects reported below 2 ppm were not serious enough to justify a lower limit.

COMMITTEE RECOMMENDATIONS

The Committee on Toxicology previously recommended EELs and CEL in 1966. After reviewing the current literature, the Committee recommended no changes in the EELs and CEL.

The present Committee's recommended EELs and CEL for sulfur dioxide and the limits proposed in 1966 are shown below.

	1966	1984
10-min EEL	30 ppm	30 ppm
30-min EEL	20 ppm	20 ppm
60-min EEL	10 ppm	10 ppm
24-h EEL	5 ppm	5 ppm
90-d CEL	1 ppm	1 ppm

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VINYLIDENE CHLORIDE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	$CH_2=CCl_2$
Molecular weight:	96.96
Chemical names:	1,1-Dichloroethylene, dichloroacetylene, 1,1-dichloroethane
Synonym:	VDC
Boiling point:	37°C
Flash point:	−10°C
Saturated vapor pressure:	591 torr (20°C)
Solubility:	Sparingly soluble in water; soluble in most organic solvents
General characteristics:	Volatile, colorless liquid that polymerizes readily; mild sweet odor
Conversion factors:	1 ppm = 3.97 mg/m^3 1 mg/m^3 = 0.25 ppm

OCCURRENCE AND USE

Vinylidene chloride (VDC) is prepared from ethylene chloride or by passing trichloroethylene over any of several alkaline materials at a temperature above 70°C. It is an intermediate in production of Saran and Velon polymeric plastics for films and coatings. At high concentrations, it may decompose explosively to form CO and phosgene (Stecher etal., 1968). VDC has been reported to be a contaminant of space vehicles and submarines (Saunders, 1967).

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

An uncontrolled 4-d exposure to VDC and many other compounds at a low (but variable and unknown) concentration occurred in a NASA-sponsored Manned Environmental Systems Assessment project involving a five-man crew. Signs and symptoms included loss of appetite, extreme nausea, vomiting, facial-muscle symptoms, and headache. Herpes-like lesions developed on the faces of all participants shortly after the 4-d exposure (Saunders, 1967).

An epidemiologic survey of 138 workers industrially exposed to VDC at 5-70 ppm (TWA) for periods of less than 1 yr and up to over 10 yr revealed no substantial adverse health effects related to exposure (Ott etal., 1976).

EFFECTS ON ANIMALS

LT_{50}s for rats were determined for VDC by Andersen etal. (1979):

Concentration, ppm	Time, h
100	8.0
200	4.1
500	3.0
1,000	2.4
2,000	1.4

Inhalation of VDC by the rat can result in irritation of the eyes and nose, excessive salivation, respiratory distress, tremors, convulsions, incoordination, prostration, narcosis, and death due to vascular collapse and shock (Carpenter etal., 1949; Jaeger etal., 1973). Exposure to VDC at 200 ppm in air for 4 h produced severe liver damage in rats (Carpenter etal., 1949). Mild liver damage resulted from a 23-h exposure at 60 ppm (Short etal., 1977). Mice exposed at 50 ppm showed progressive renal necrosis in the first 24 h (Reitz etal., 1979); severe tubular necrosis has been reported in mice exposed at 15 ppm for 23 h (Short etal., 1977).

Dogs, rats, guinea pigs, rabbits, and monkeys exposed to VDC by inhalation at 99 ppm, 8 h/d, 5 d/wk for 6 wk showed no mortality or evidence of toxicity. However, in continuous exposure at 15 ppm, deaths occurred in 7 of 15 guinea pigs (between days 4 and 9) and 3 of 9 monkeys (days 26, 60, and 64) (Prendergast etal., 1967).

Liver damage and kidney damage were seen in most of the animals exposed continuously at 189 mg/m^3. Nonspecific lung damage was also seen in most animals (Prendergast etal., 1967).

VDC caused epinephrine-induced arrhythmias in rats. Epinephrine in doses as low as 0.5 μg/kg produced a series of premature ventricular contractions in rats exposed to VDC at about 25,000 ppm for 47 min. The cardiac effects were completely reversible on discontinuation of VDC inhalation. Pretreatment of the animals with phenobarbital increased the cardiac effects; that suggests they were due to a metabolite of VDC, in that phenobarbital induces microsomal enzymes (Siletchnik and Carlson, 1974).

Rampy etal. (1977) published an interim report of a 2-yr study on VDC toxicity. Sprague Dawley rats that inhaled VDC at 25 or 75 ppm, 6 h/d, 5 d/wk, for 18 mo failed to develop VDC-related tumors, as judged by gross examination 24 mo after the beginning of exposure.

Maltoni etal. (1977) exposed Sprague Dawley rats to VDC at 10, 25, 50, 100, and 150 ppm, 4 h/d, 4-5 d/wk, for 12 mo and, under a similar protocol, Swiss mice at 10 and 25 ppm. Early results, 30 wk after the last exposure (animal ages, 91-98 wk), showed an increase in the incidence of mammary tumors in treated groups, but the increase was not dose-related; one Zymbal's-gland carcinoma was seen in a rat exposed at 100 ppm. VDC did produce renal adenocarcinomas without metastases in

mice exposed at 25 ppm, but not at 10 ppm. Oral administration of VDC to rats (25 mg/kg) and inhalation exposure of Chinese hamsters (25 ppm, 4 h/d, for 52 wk) did not result in tumor formation (Maltoni etal., 1977). A carcinogenesis bioassay of VDC conducted on rats (1 or 5 mg/kg) and mice (2 or 10 mg/kg) in which the chemical was given by gavage was negative (National Toxicology Program, 1982).

Another carcinogenesis study produced different results (Lee etal., 1978). CD-1 mice were exposed to VDC at 55 ppm, 6 h/d, 5 d/wk, for 12 mo; 3 of 70 mice tested developed hemangiosarcomas of the liver, and 6 of 70 had bronchioalveolar adenomas. Those results are comparable with those of exposure to vinyl chloride. Similar treatment of rats produced a hemangiosarcoma in a lymph node of one animal and another in subcutaneous tissue of a second rat; 71 animals were tested. The VDC was reported to be 99% pure, but analysis was not provided. In the Maltoni etal. study, the material used reportedly contained 99.95% VDC, 0.04% 1,2-dichloroethylene, 0.01% acetone, 0.005% methylene chloride, and 0.002% monochloroacetylene and dichloroacetylene; p-methoxyphenol was added at 200 ppm as a stabilizer. The Lee etal. report commented on gross lesions in several organs in mice, but did not mention any changes in the kidneys; an earlier report from the same laboratory indicated that VDC was renotoxic at 15 ppm in just 23 h.

Hong etal. (1981) conducted a 1-yr followup of neoplastic changes after VDC exposure of rats and mice at 50, 250, and 1,000 ppm as a sequel to the work of Lee etal. (1978). Results showed that cumulative tumor incidence in liver, lung, and mammary gland increased with dose and duration of exposure. Evidence of a VDC exposure threshold was presented. Chu and Milman (1981) reviewed carcinogenesis results on VDC and related compounds.

Reitz etal. (1980) studied the effects of VDC on DNA synthesis and DNA repair in rats and mice. These animals were exposed to VDC at 10 and 50 ppm for 6 h; for comparison purposes, dimethylnitrosamine was also studied in other animals. DNA alkylation was minimal (one or two orders of magnitude lower than dimethylnitrosamine). However, DNA repair in the mouse kidney was much less than in the liver. Tissue damage and increased DNA repair (by a factor of 25) occurred at 50 ppm in the mouse kidney, but not at 10 ppm. This suggests that the tumors observed in mice exposed to VDC arise primarily through effects of the chemical on nongenetic components of the cells.

PHARMACOKINETICS

Exposure of rats to [^{14}C]VDC for several hours has demonstrated that most of the label is excreted in the urine, and the balance is expired as $^{14}CO_2$ and unchanged VDC, excreted in the feces, or retained in the tissues (McKenna etal., 1977). VDC apparently is metabolized to an intermediate that can bind covalently to protein and nucleic acids (McKenna etal., 1977, 1978; Reitz etal., 1979). In a study on the pharmacokinetics of [^{14}C]VDC in rats, McKenna etal. (1978) found that fasting had no effect on its metabolism when rats were exposed to vapor at 10 ppm for 6 h; but fasted rats exposed at 200 ppm for 6 h showed a reduced capacity to metabolize VDC, and liver damage and

kidney damage were also noted. The two major urinary metabolites detected--N-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid--indicate that a major pathway for detoxification of VDC is conjugation with liver glutathione. Reitz etal. (1979) reported that the extent to which DNA alkylation occurs in VDC-treated rats and mice (10-50 ppm) correlates well with the carcinogenicity results of the Maltoni etal. study: alkylation of rat liver and kidney DNA and mouse liver DNA is low, compared with alkylation of DNA in mouse kidney, the target organ for VDC. These investigators suggested that VDC may act as a carcinogen, not only because its administration can lead to alkylation of mouse kidney DNA, but also because of its frank toxicity to mouse kidney, which forces an increase in the rate of DNA replication as regeneration takes place in the kidney. Hence, the toxicity of VDC to the kidney could promote the initiation effect of DNA alkylation. Such a correlation between toxicity and carcinogenicity is well established with a variety of chemical compounds.

The importance of pharmacokinetics needs to be considered. The carcinogenicity of VDC in the mouse kidney can be hypothetically explained by a metabolic transformation of VDC to an alkylating agent that initiates the carcinogenic process by covalent binding to DNA and promotes the process by stimulating cellular regeneration. If such initiation and promotion can occur only when VDC exposures are high enough to deplete tissue stores of glutathione (which detoxifies activated VDC), then it can be argued that there is some degree of exposure to VDC that would result in a low probability of tumor formation. Although not yet substantiated, this is a plausible hypothesis. Therefore, it seems reasonable that, in the case of VDC, EELs can be set if sufficient data are available to permit the Committee to judge what might be an exposure unlikely to result in a toxic effect in humans.

INHALATION EXPOSURE LIMITS

The ACGIH has recommended a TLV-TWA for VDC of 5 ppm and a 15-min TLV-STEL of 20 ppm (ACGIH, 1983). The TLV-TWA of 5 ppm was considered “low enough to prevent overt toxicity in exposed workers” (ACGIH, 1982). OSHA adopted 10 ppm as the federal workplace standard for VDC (OSHA, 1983).

COMMITTEE RECOMMENDATIONS

In 1966, the Committee recommended a 24-h EEL and a 90-d CEL for VDC; however, considerable data have since accumulated (Table 12) that indicate that VDC is a potent hepatotoxin and is also a hepatocarcinogen.

The data most helpful in recommending an EEL for VDC come from the study of Ott etal. (1976), who examined the mortality and health-examination findings of 138 company employees exposed to VDC at measured concentrations in the absence of vinyl chloride. No occupation-related disorders could be detected among workers exposed to VDC at estimated concentrations of 5-70 ppm (TWA) over several years.

The Committee notes that, although the effects of single short-term exposures to carcinogens cannot be predicted, the probability of tumor formation under these conditions would be low--and less than that associated with repeated exposures. Because of the possibility of liver and kidney damage from acute exposure, the Committee recommends a lowering of the 24-h EEL to 10 ppm. The Committee notes that this concentration is approximately 20 times greater than that suggested by the Committee for short-term exposures to VDC as a drinking-water contaminant. However, as pointed out in the introduction to this report, the EELs given here are for a narrowly defined, healthy, adult working population, whereas drinking water containing VDC could be consumed for up to a week by a more heterogeneous population, including young children and other persons with increased sensitivity to the effects of this chemical.

The Committee's recommendation for the 90-d CEL is based on animal studies (continuous and repeated exposure of rats, rabbits, guinea pigs, dogs, and monkeys) and the previously cited (8 h/d) occupational exposure of humans. Continuous exposure at 15 ppm produced mortality among some guinea pigs and monkeys, but surviving animals displayed no organ toxicity. Applying a 100-fold uncertainty factor to the concentration fatal to these species, i.e., guinea pigs and monkeys, the Committee recommends a CEL of 0.15 ppm.

The present Committee's recommended EEL and CEL for VDC and the limits proposed in 1966 are shown below.

1966	1984	
24-h EEL	25 ppm	10 ppm
90-d CEL	2 ppm	0.15 ppm

TABLE 12

Species	Concentration, ppm	Duration of Exposure	Toxic Effects	Reference
Human	5-70	Several years	No clinical signs	Ott etal., 1976
Monkey	25, 47	24 h/d, 90 d	Death	Prendergast etal., 1967
Guinea pig	15, 25, 47	24 h/d, 90 d	Death	Prendergast etal., 1967
Rat	500	6 h/d, 20 d	Decreased body weight, liver toxicity	Gage, 1970
Rat	150	4 h	Increased serum alanine-α-keto-glutarate transaminase 24 h later	Jaeger etal., 1975
Rat	100	4 h	None	Jaeger etal., 1975
Rat	75, 100	4 h/d, 5 d/wk, 12 mo	No dose-related tumors	Viola and Caputo, 1977
Rat	25, 75	6 h/d, 5 d/wk, 18 mo	Cytoplasmic vacuolization in hepatocytes after 1 mo, no gross tumors at 24 mo	Rampy etal., 1977
Rat	60	22-23 h/d, 2 d	Increased serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase	Short etal., 1977
Rat	55	6 h/d, 5 d/wk, 12 mo	Hemangiosarcoma in lymph nodes and subcutaneous tissue	Lee etal., 1978
Rat	47	24 h/d, 90 d	Kidney injury	Prendergast etal., 1967
Rat	10, 40	6 h/d, 5 d/wk, 4 wk	No vacuolization	Rampy etal., 1977

Mouse	100	4 h/d, 2 d	Death	Maltoni etal., 1977
Mouse	60	22-23 h/d, 2 d	Death	Short etal., 1977
Mouse	55	6 /d, 5 d/wk, 12 mo	Liver hemangiosarcoma and bronchioalveolar adenoma	Lee etal., 1978
Mouse	50	4 h/d, 4 d	Death	Maltoni etal., 1977
Mouse	15	1 d	Increased serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase	Short etal., 1977
Dog, rat, monkey	47	24 h/d, 90 d	Liver injury	Prendergast etal., 1967
Not stated	50, 100	8 h/d, 5 d/wk, several months	Liver and kidney injury	Torkelson and Rowe, 1981
Not stated	25	8 h/d, 5 wk, several months	“Minimal” liver and kidney injury	Torkelson and Rowe, 1981

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XYLENE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES*

	o-Xylene	m-Xylene	p-Xylene
CAS number:	1330-20-7	1330-20-7	1330-20-7
Chemical formula:	$C_6H_4(CH_3)_2$	$C_6H_4(CH_3)_2$	$C_6H_4(CH_3)_2$
Molecular weight:	106.16	106.16	106.16
Boiling point (760 mm Hg):	144.411°C	139.103°C	138.351°C
Freezing point:	−25.182°C	−47.872°C	13.263°C
Density (25°C):	0.87596 g/ml	0.85990 g/ml	0.85669 g/ml
Vapor density (air = 1):	3.7	3.7	3.7
Flash point (closed cup):	17.2°C	25°C	25°C
Vapor pressure (25°C,760 mm Hg):	6.6	8.39	8.87
Conversion factors for three isomeric xylenes:	1 ppm= 4.34 mg/m^3 1mg/m^3 = 0.23 ppm		
General characteristics:	Clear flammable liquid; aromatic hydrocarbon odor; commercial form is mixture of three isomers, with meta form usually principal component; insoluble in water; miscible with organic solvents		

OCCURRENCE AND USE

The xylenes are major commodity chemicals in this country and around the world. The National Research Council report The Alkyl Benzenes (1981) showed that in the United States the annual production of xylenes over the last decade averaged approximately 2.7 million metric tons; about 15.3 million metric tons has been used per year by the chemical industries. Because of the impetus to remove lead from gasoline and the excellent antiknock properties of these compounds, they are found in increasing concentrations in gasoline. In a gasoline sample reported in the NRC document, m- and p-xylenes constituted 6.73% and o-xylene 2.86% by weight. Reports on the use of these compounds in solvents have suggested that as much as 500,000 metric tons of xylenes is used for this purpose per year. Because of their high volatility and ubiquitous use, these compounds pervade the environment; one result is extensive human exposure. Xylenes are monitored as possible contaminants of submarine atmosphere.

* Adapted from NRC, 1980.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Evidence of brain hemorrhages and axonic anoxia was observed in a person who died as a result of exposure to xylene at approximately 10,000 ppm over an 18-h period (Morley etal., 1970). In another case, a man was exposed at 60-350 ppm to mixed solvents containing 75% xylene and experienced giddiness, anorexia, and vomiting (Glass, 1961). In a similar report of exposure to a mixed solvent containing 80% xylene, a person who apparently suffered from latent epilepsy displayed seizures; that suggested that xylene might exacerbate seizures in susceptible people (Goldie, 1960). In each of these instances, either mixtures were involved or the extent of exposure was not well documented.

Neither flicker fusion* nor reaction time was affected in 23 volunteers exposed at 100 or 200 ppm for 3-7 h (Ogata etal.,1970). In a similar study, Gusev (1968) reported changes in brain electric activity at 0.07 ppm, but not at 0.05 ppm. Fifteen male subjects were exposed to xylene vapor at approximately 100 or 300 ppm for 70 min (Gamberale etal., 1978). No noticeable change in test performance (numerical ability, reaction time, short-term memory, and critical flicker fusion) was seen. However, subjects exposed to xylene at 300 ppm for 70 min when the exposure period began with 30 min of exercise on a bicycle showed significant impairment of performance in tests for numerical ability, short-term memory, and choice reaction time. The difference was apparently due to an increase in the uptake of xylene in subjects that exercised during the first part of the exposure period.

Savolainen etal. (1979b), Riihimaki and Savolainen (1980), and Savolainen etal.(1980) exposed six volunteers to m-xylene at 100 or 200 ppm, 6 h/d, 3 d/wk for 2 wk. In one part of the experiment, constant exposure concentrations were used; in another, the concentration was varied so that peak concentrations of 400 ppm were obtained. During the first week, significant increases in reaction time and some impairment of equilibrium were observed at 100 ppm, but these effects were transient, perhaps because tolerance developed. The effects reappeared during the second week at the higher concentration. No changes in manual dexterity or visual functions were observed. The authors suggested that light exercise reverses the effects of xylene. At 200-400 ppm, the report suggested, the subjects displayed decreased vigilance, as indicated by EEG changes.

Carpenter etal. (1975) studied the odor threshold for mixed xylenes. They estimated it to be about 1 ppm. They suggested that discomfort and dizziness would ensue at 460 ppm and concluded that 110 ppm would be tolerable for working.

* Flicker fusion refers to the frequency at which a flickering light no longer appears to flicker.

EFFECTS ON ANIMALS

Cameron etal. (1938) reported that, in rats and mice, the lethal doses by subcutaneous injection were 5-10 ml/kg for p- and m-xylenes and 2.5-5.0 ml/kg for o-xylene. The lethal doses by intraperitoneal injection were 2-2.5 ml/kg for p- and m-xylenes and 1.5-2 ml/kg for o-xylene. The acute LD_{50} in male rats receiving a single peroral administration of 95% pure xylene (19% o-, 52% m-, and 24% p-) was 4.3 g/kg (Wolf etal., 1956). The impurities were not identified. Repeated skin contact with the undiluted xylene solution led to erythema and slight necrosis in rabbits. Instillation into the rabbit eye led to conjunctival irritation and very slight, transient corneal injury.

Exposure of rats and mice to o- and m-xylenes (separately) by inhalation at 2,000-3,000 ppm (8.7-13.0 g/m^3) for 24 h resulted in deaths, and mice were reportedly more sensitive than rats to m-xylene (Cameron etal., 1938). Deaths were not observed in either rats or mice that had been exposed to o-xylene at 4,912 ppm (21.3 g/m^3) for 24-28 h, but they did occur after exposure at 19,650 ppm (85.3 g/m^3) for 12 h. Exposure of rats to the various pure isomers of xylene separately at 1,000-1,500 ppm (4.3-6.5 g/m^3) 8 h/d for 14 d produced no deaths, and no specific organ changes were observed on autopsy. It should be noted that, generally, only small groups of animals were studied in this relatively early report, and the source and purity of the compounds used were not specified.

In a later study (Carpenter etal., 1975), the LC_{50} in male rats for a 4-h inhalation exposure to a mixture of xylenes was 29 (22-37) g/m^3. Pathologic findings in the 16 rats that died after exposure at 43 g/m^3 included atelectasis, hemorrhage, and interlobular edema of the lung (two cases each). At concentrations as low as 5.8 g/m^3, the investigators observed transient irritation, protraction of the eyes, and lack of coordination of the extremities. Rats exposed at 4 g/m^3 displayed a slight loss of coordination by the second hour of exposure. No unusual effects were observed after exposures at approximately 2 g/m^3. Respiratory-tract irritation, as evidenced by a decrease of 50% or more in respiratory rate, was observed in mice exposed at 5.6 g/m^3 or more for 1 min. This did not occur at 2 g/m^3 or during the 15-min period after exposure.

Exposure of cats at 41 g/m^3 for 2 h resulted in a classic nervous-system effect: the sequential development of salivation, ataxia, tonic and clonic spasms, anesthesia, and death. Pathologic examination revealed no lesions that were obviously related to the exposure. Dogs exposed at approximately 4 g/m^3 experienced an increase in lacrimation that began after 1 h and persisted throughout the 4-h exposure period.

LC_{50}s of 5,267 ppm (22.8 g/m^3) for m-xylene, 4,595 ppm (19.9 g/m^3) for o-xylene, and 3,907 ppm (17 g/m^3) for p-xylene were reported in mice (Bonnet etal., 1979).

Carpenter etal. (1975) exposed 4 male beagles and 25 male rats at 3.5, 2.0, or 0.77 g/m^3 or to control air 6 h/d, 5 d/wk, for up to 66 d. There was no evidence of toxicity of xylene.

Jenkins etal. (1970) exposed rats, guinea pigs, monkeys, and dogs to o-xylene at either 780 ppm (3358 mg/m^3) for 8 h/d, 5 d/wk for 30 exposures or 78 ppm (389 mg/m^3) continuously for 90 d. Mortality was 3 of 15 rats, none of 15 guinea pigs, none of 2 dogs, and 1 of 4 monkeys. One dog was tremulous and one rat died during the continuous exposure. Hematologic studies and evaluation of necropsy material did not show any effect of o-xylene.

Male guinea pigs were given intraperitoneal injections of American Chemical Society reagent-grade xylene (isomer not specified) at 1,000 mg/kg (DiVincenzo and Krasavage, 1974). The investigators observed an increase in serum ornithine carbamoyl transferase, which is said to be an indicator of hepatocellular damage. Histologic examination revealed a moderate degree of hepatic lipid accumulation, but no tissue necrosis. After intraperitoneal injections at 2,000 mg/kg, three of four guinea pigs died.

In behavioral studies, Battig and Grand Jean (1964) failed to detect alterations in a conditioned-avoidance protocol with rats exposed to xylene by inhalation at 800 ppm initially and then 550-750 ppm for the balance of the 2.5-h exposure. Desi etal. (1967) injected xylene into rats at 0.02, 0.05, or 0.1 ml/100 g of body weight subcutaneously and compared them with control animals for ability to run a maze. Treatment continued for 28 d, after which the rats given the highest dose died. Other treated animals lost weight. The authors concluded that xylene prevents the acquisition of learned behavior, but does not facilitate loss of acquired behavior. The authors' conclusions require substantiation.

Carpenter etal. (1975) exposed rats to mixed xylenes at 2,800 ppm (12.2 g/m^3 and reported irritation and prostration within 2-3 h. Exposure at 1,300 ppm (5.6 g/m^3) led to ataxia. Exposure of dogs and rats at 580 ppm did not produce these effects. Batchelor (1927) had previously reported that exposure at 980 and 620 ppm (4.3 and 2.7 g/m^3) caused no central effects. Lazarev (1929) reported that the production of narcosis in mice by o-, m-, and p-xylenes required 3,846, 1,923, and 7,885 ppm, (16.7, 8.3, and 34.2 g/m^3), respectively.

Intravenous infusion of a 10% solution of m-xylene (commercial-grade) as a lipid emulsion into rabbits produced a concentration of 30 ppm (0.130 g/m^3) in blood and caused positional nystagmus, but no vestibular effects, at a steady-state blood content of 10 ppm (Aschan etal., 1977).

Savolainen etal.(1979a) studied behavioral and neurochemical changes in young rats exposed to xylene at 300 ppm (1.3 g/m^3) 6 h/d, 5 d/wk, for 5-18 wk with and without simultaneous ingestion of ethanol. Although the xylene alone had no behavioral effects, the mixed exposure resulted in increases in preening and ambulation, which suggested a synergistic effect; when ethanol was given alone, there was a transient decrease in preening. Minor changes in brain enzymes were observed, including an increase in superoxide dismutase activity after 14 wk of exposure to xylene alone and an increase in brain proteolytic activity in animals given both ethanol and xylene at 9-14 wk. There was no indication of a cause-effect relation between the enzyme changes and changes in preening and ambulation, nor was there evidence that these minor changes in enzyme activity constituted serious toxic impairment.

Savolainen and Pfaffli (1980) studied neurochemical changes in rat brain after inhalation of m-xylene at 48.8, 393, and 739 ppm (0.21, 1.7, and 3.2 g/m^3) 6 h/d, 5 d/wk, for 2 wk. Xylene in brain and peripheral fat increased from the first to the second week. Brain content of NADPH diaphorase increased, whereas brain superoxide dismutase decreased. Biochemical analyses on rats withdrawn from exposure for 2 wk indicated that the biochemical effects were largely abolished within that time, although cerebral RNA was above the control value at the two higher exposures. The latter data disagree with the results of the earlier study, however, and the difference in duration of exposure may account for the discrepancy. The most important finding was the increase in brain RNA, which persisted after the termination of the treatment period.

Andersson etal. (1981) exposed rats to commercial xylene and to its component o-, m-, and p-xylenes and ethylbenzene at 2,000 ppm (8.7 g/m^3) 6 h/d for 3 d. Within 16-18 h after exposure stopped, they found increases in norepinephrine turnover in the hypothalamus caused by all the compounds and increases in dopamine in the median eminence of the forebrain caused by all but ethylbenzene and o-xylene. Ethylbenzene selectively reduced norepinephrine in the paraventricular region of the hypothalamus. Prolactin secretion was reduced by p- and o-xylenes. Although no overt behavioral signs were found in these experiments, the authors suggested that xylene (by disturbing dopamine neurotransmission) can produce motor disturbances and motivational deficits.

A connection between the occurrence of sacral aplasia and occupational exposure to organic solvents has been demonstrated by Kucera (1968), who also observed a developmental malformation analogous to sacral aplasia in chick embryos treated with an unspecified concentration of xylene, which was positively correlated with time of exposure and negatively correlated with embryonic age. Krotov and Chebotar (1972) did not find any developmental defects in fetuses of rats that had inhaled xylene. Hudak and Ungvary (1978) evaluated the embryotoxic effects of xylene (a mixture of 10% o-xylene, 50% m-xylene, 20% p-xylene, and 20% ethylbenzene) at 230 ppm (1 g/m^3) given by inhalation to rats for 24 h/d on days 1-21 of pregnancy. Untreated groups of animals that inhaled pure air served as controls. No evidence of teratogenicity was found, but skeletal anomalies (extra ribs and fused sternebrae) increased, although they were not significant ($p < 0.05$ for both). Mirkova etal. (1983) studied the effect of daily exposure (6 h/d, 5 d/wk) to xylene at 10, 50, and 500 mg/m^3 on pregnant white Wistar rats during days 1 through 21 of gestation. The authors observed that concentrations of 50 and 500 mg/m^3 exerted pronounced embryotoxic and teratogenic effects. Xylene increased the incidence of anomolies of internal organs (hydroephalus, microphthalmia, intracerebral hematomas and hemorrhages in the liver). It impaired the processes of ossification of sternum and skull. At concentrations of 50 and 500 mg/m^3 , xylene causes disturbances in postnatal development of the F_1 generation.

Xylene was not mutagenic in a battery of short-term tests: a test for mitotic gene conversion in yeast Saccharomycescerevisiae D4, gene-mutation tests in bacteria (with Salmonellatyphimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538) with and without activation,

and specific-locus forward-mutation induction in the L5178Y thymidine kinase Fischer mouse lymphoma cell assay. Xylene did not produce significant increases in chromosomal aberrations in rat bone marrow cells at 0.044, 0.157, and 0.441 ml/kg (Litton Bionetics, 1978).

PHARMACOKINETICS

All the xylene isomers enter the body rapidly by inhalation and less rapidly by absorption from the gastrointestinal tract (Gerarde, 1960) or through the skin (Dutkiewicz and Tyras, 1968). The blood-to-gas partition ratio for xylene has been calculated to be 29:1 (Astrand, 1975) and 42:1 (Sherwood, 1976). The rate at which xylene is absorbed through human skin that is immersed in liquid xylene has been estimated to be 4.5-9.6 mg/cm^2 per hour (Dutkiewicz and Tyras, 1968).

Xylene is distributed rapidly into all tissues of the body, especially into the adrenals, bone marrow, brain, spleen, and adipose tissue (Fabre etal., 1960). The pharmacokinetics of m-xylene in rats and mice fit a three-compartment model (Bergman, 1979) and more than 90% of an administered dose should be eliminated within 24 h (NRC, 1981). Comparable studies have not been conducted in humans, but Sedivec and Flek (1976) reported that only 5% of a dose of a mixture of xylenes was exhaled. Their finding that 95% of the urinary metabolites was excreted within 10 h indicates that the total body clearances of the xylenes are rather high.

The xylenes undergo side-chain oxidation to methylbenzoic acids, which in turn are conjugated with glycine and excreted into urine as toluic acids in all mammals studied, including dogs, humans, rabbits, rats, and guinea pigs. In addition to side-chain oxidation, the xylenes undergo ring hydroxylation, but only to a minor extent (Bakke and Scheline, 1970). In rats, approximately 1% of a dose (100 mg/kg) of p-xylene was converted to 2,5-xylenol, 0.9% of m-xylene was converted to 2,4-xylenol, and 0.1% of o-xylenol was converted to 3,4-xylenol. Pretreatment of rats with phenobarbital or 3-methylcholanthrene markedly increased the activity of the hepatic enzyme that converts p-xylene to p-methylbenzyl alcohol, but did not alter the activity of the enzyme in the lungs (Harper etal., 1977). Patel etal. (1978, 1979) reported that pretreatment of mice with individual xylene isomers did not alter the activity of cytochrome P-450 in the liver. However, the administration of p-xylene to rabbits inactivated cytochrome P-450 in the lung.

INHALATION EXPOSURE LIMITS

The American Conference of Governmental Industrial Hygienists (1980, 1983) recommended a TLV-TWA of 100 ppm and a 15-min TLV-STEL of 150 ppm. It believed that irritant effects will be minimal, and that no substantial degree of narcosis or chronic injuries will result from continued occupational exposure at 100 ppm. OSHA (1983) recommended a PEL of 100 ppm. Other recommendations were as follows: ANSI (1970), 100 ppm; West Germany (1974), 200 ppm; Sweden (1975), 100 ppm; Czechoslavakia (1969) and East Germany (1973), 45 ppm; and USSR (1972), 11 ppm (ACGIH, 1980).

COMMITTEE RECOMMENDATIONS

The Committee on Toxicology suggested limits for exposure to xylene in 1966: a 60-min EEL of 200 ppm, a 24-h EEL of 100 ppm, and a 90-d CEL of 50 ppm.

The Committee on Alkyl Benzene Derivatives (NRC, 1981) reviewed the toxicologic data on xylene and included the following statement in its report:

> The acute toxicity of the xylenes predominantly reflects effects on the central nervous system similar to those produced by other alkyl benzenes and related compounds. Irritant effects on mucous membranes have been reported, particularly upon direct contact. There is negligible evidence of acute or chronic effects in organ systems other than the central nervous system.

Xylene is a major commodity solvent and component of gasoline, and the potential for human exposure is large. The major effects are on the central nervous system and appear to be reversible. There is no indication of genetic toxicity or carcinogenesis.

The lowest doses at which any biologic effects have been observed in humans were reported by Ogata etal. (1970) and Gusev (1968), who detected changes in electric activity of brain in humans exposed at 0.05-0.07 ppm. These changes were not related to any functional impairment. Although Savolainen etal. (1979b), Riihimaki and Savolainen (1980), and Savolainen etal. (1980) described changes in psychophysiologic functions, such as reaction time and body balance, that were also accompanied by EEG changes in humans exposed to xylene at 90-200 ppm, one of the authors (Seppolainen, personal communication) has questioned the wisdom of using these results to set exposure limits. Chronic exposure does not seem to increase sensitivity to these effects. The available evidence does not warrant revision of the exposure limits recommended in 1966.

The present Committee's recommended EELs and CEL for xylene and the limits proposed in 1966 are shown below.

	1966	1984
60 min EEL	200 ppm	200 ppm
24-h EEL	100 ppm	100 ppm
90-d CEL	50 ppm	50 ppm

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