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W. R. F. Notten R. F. M. Herber W. J. Hunter
A. C. Monster R. L. Zielhuis (Eds.)

Health Surveillance of Individual Workers Exposed to Chemical Agents

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Wilfried R. F. Notten
Medisch Biologisch Laboratorium TNO
Postbus 45, NL-2280 AA Rijswijk

William J. Hunter
Division Industrial Medicine and Hygiene
CEC Health and Safety Directorate, Bâtiment Jean Monnet
L-2920 Luxembourg

Rob F. M. Herber
Aart C. Monster
Reinier L. Zielhuis
Coronel Laboratorium, Universiteit van Amsterdam
Meibergdreef 15, NL-1105 AZ Amsterdam

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Preface

Early in 1985, a meeting was held to discuss the organization of a workshop in honour of Professor Reinier L. Zielhuis on the occasion of his retirement on November 30, 1986. Various themes for such a workshop were considered, but it was Zielhuis himself, who ultimately selected "Health surveillance of individual workers exposed to chemical agents" as the theme of the workshop. Although this topic is of the utmost importance for occupational health practice, it is also a very difficult one, given our currently limited knowledge on the subject.

The choice of this topic is characteristic of Reinier Zielhuis, a scientist and scholar who throughout his career has been deeply concerned with the health and health risks of workers. Because he regards occupational and environmental exposure – including life style – as two aspects of the total exposure to chemical and physical factors, he emphasizes the need to assess the impact of this total exposure on workers' health. The impact of total exposure probably determines to a large extent the individual variability in response. This was the main reason why he selected the above-mentioned topic for the workshop.

Reinier's interest in preventive medicine was awakened when he was working as a physician in Indonesia from 1948 to 1954; his career in occupational toxicology began in the mid-1950s with research on the health risks associated with occupational exposure to lead. After his appointment in 1964 as professor and director of the Coronel Laboratory at the University of Amsterdam, his research activities extended to many other topics, including asbestos, heavy metals and organic solvents. Reinier was one of the first to recognize the importance of biological monitoring as an instrument for the health surveillance of workers exposed to chemical compounds. Without his persistent efforts and those of his co-workers, biological monitoring would not have reached the level of acceptance and application it has today, nationally and internationally. The results of these investigations are the basis of many biological limit values, for instance those of the American Conference of Governmental and Industrial Hygienists in the United States.

Reinier's contributions to the assessment of occupational exposure limits are also worth mentioning. His ongoing crusade for a clear and distinct approach to the assessment of health-based versus policy-based occupational exposure limits has resulted at a national level in the es-

tablishment of a well-designed advisory structure for the setting of both types of limits according to a two-step procedure that is still almost unique. For the purpose of assessing health-based exposure limits, Reinier and his co-workers have prepared numerous criteria documents. These documents have been utilized both in the Netherlands and abroad.

More than anyone else, Reinier is keenly aware that exposure limits may not prevent health impairments in all workers. For several years now, he has paid special attention in this regard to the impact of toxic compounds on pregnancy and offspring. He has constantly stressed the need for more knowledge regarding the adverse effects on reproduction of occupational exposure to chemical compounds. The growing interest in reproduction toxicology can, to a certain extent, be attributed to his efforts in this field of occupational toxicology.

Reinier has participated in many national and international advisory committees, including those from the World Health Organization and the European Communities. With his creative mind and ability to combine insight and knowledge, together with enormous productivity, Reinier Zielhuis has provided important stimuli to both occupational toxicology and occupational health practice.

Despite the challenging theme of the workshop, all the participants invited to prepare a working document were willing to do so. Their contributions , together with the conclusions and recommendations of the workshop, are found in this report. The organizers and participants of the workshop hope that the present publication will stimulate research in this almost unknown area of individual variability, and that, ultimately, it will further the prevention of health impairment in workers.

Wilfried R. F. Notten

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Organizing Committee

Dr. Wilfried R. F. Notten, Chairman, Medical Biological Laboratory TNO, Rijswijk

Dr. Rob F. M. Herber, Coronel Laboratory, Amsterdam

Dr. William J. Hunter, Commission of the European Communities, Luxembourg

Dr. Aart C. Monster, Coronel Laboratory, Amsterdam

Prof. Dr. Reinier L. Zielhuis, Coronel Laboratory, Amsterdam

Committee for Summary Report, Conclusions and Recommendations

Dr. R. Murray (Chairman), Dr. V. J. Feron, Dr. R. F. M. Herber, Dr. W. J. Hunter, Dr. A. C. Monster, Dr. W. R. F. Notten, Prof. Dr. R. L. Zielhuis

Contents

List of Contributors

H. M. Bolt
Institut für Arbeitsphysiologie, Universität Dortmund
Ardeystraße 67, D-4600 Dortmund

P. C. Bragt
Medisch Biologisch Laboratorium TNO
Postbus 45, NL-2280 AA Rijswijk

F. J. H. van Dijk
Coronel Laboratorium, Universiteit van Amsterdam
Meibergdreef 15, NL-1105 AZ Amsterdam

V. J. Feron
CIVO-TNO, Postbus 360, NL-3700 AJ Zeist

E. Fournier
Hôpital Fernand-Widal, 200 Rue de Faubourg, Saint-Denis
F-75010 Paris

F. van Geen
BGD Hoogovens, Postbus 10000, NL-1970 CA IJmuiden

J. J. van Hemmen
Medisch Biologisch Laboratorium TNO
Postbus 45, NL-2280 AA Rijswijk

P. Th. Henderson
Vakgroep Toxicologie, Katholieke Universiteit Nijmegen
Postbus 9101, NL-6500 HB Nijmegen

R. F. M. Herber
Coronel Laboratorium, Universiteit van Amsterdam
Meibergdreef 15, NL-1105 AZ Amsterdam

S. Hernberg
Institute of Occupational Health
Haartmaninkatu 1, SF-00290 Helsinki-29

W. J. Hunter
Division Industrial Medicine and Hygiene
CEC Health and Safety Directorate, Bâtiment Jean Monnet
L-2920 Luxembourg

W. H. C. Kerkhoff
Vakgroep Sociale Arbeids- en Organisatiepsychologie
Universiteit van Amsterdam
Weesperplein 8, NL-1018 XA Amsterdam

B. Kolmodin-Hedman
National Board of Occupational Safety and Health
Box 6104, S-90006 Umeå

D. Lahaye
Afd. Arbeids- en Verzekeringsgeneeskunde, Provisorium 1
Minnebroederstraat 17, B-3000 Leuven

R. R. Lauwerys
Unité de Toxicologie Industrielle et Médicale
Université Catholique de Louvain
30 Clos Chapelle-aux-Champs, B-1200 Brussels

T. F. Meijman
Coronel Laboratorium, Universiteit van Amsterdam
Meibergdreef 15, NL-1105 AZ Amsterdam

G. de Mik
Medisch Biologisch Laboratorium TNO
Postbus 45, NL-2280 AA Rijswijk

A. C. Monster
Coronel Laboratorium, Universiteit van Amsterdam
Meibergdreef 15, NL-1105 AZ Amsterdam

R. Murray
London School of Hygiene, Keppel Street-Gower Street
GB-London WC1E 7HT

T. Norseth
Institute of Occupational Health, Postboks 8149 Dep
N-Oslo1

W. R. F. Notten
Medisch Biologisch Laboratorium TNO
Postbus 45, NL-2280 AA Rijswijk

J. J. G. Opdam
Coronel Laboratorium, Universiteit van Amsterdam
Meibergdreef 15, NL-1105 AZ Amsterdam

M. Piscator
The Karolinska Institute
P. O. Box 60400, S-10401 Stockholm 60

J. Rutenfranz
Institut für Arbeitsphysiologie, Universität Dortmund
Ardeystraße 67, D-4600 Dortmund

K.-H. Schaller
Institut für Arbeits-und Sozial Medizin der Universität Erlangen-Nürnberg
Schillerstraße 25/29, D-8520 Erlangen

A. M. Seppäläinen
Department of Neurology, University of Helsinki
Haartmaninkatu 1, SF-0029 Helsinki 29

G. Thomas
Hôpital Fernand-Widal, 200 Rue de Faubourg, Saint Denis
F-75010 Paris

P. Ulenbelt
Coronel Laboratorium, Universiteit van Amsterdam
Meibergdreef 15, NL-1105 AZ Amsterdam

J. H. B. M. Willems
Directoraat-Generaal van de Arbeid, Ministerie van Sociale Zaken en
Werkgelegenheid, Postbus 69, NL-2270 MA Voorburg

R. L. Zielhuis
Coronel Laboratorium, Universiteit van Amsterdam
Meibergdreef 15, NL-1105 AZ Amsterdam

Summary Report, Conclusions and Recommendations*

General Scope

The aim of occupational health practice is to prevent adverse health effects of exposure at work. Such exposure arises from inhalation of dusts, fumes and gases, from ingestion or by dermal absorption. The respiratory tract is the main portal of entry, and this is reflected in the occupational exposure limits (OELs) adopted in a number of countries. These are usually expressed as time-weighted averages on the basis of an 8-h day over a 40-h week. Because of the wide variations in industrial practices from industry to industry and from individual to individual, the measurement of atmospheric concentrations (environmental monitoring, EM), using a personal sampler, does not necessarily give a correct assessment of the intake of any given systemic chemical. In these circumstances, biological monitoring (BM) is in many cases preferable, as it provides an integrated measurement of absorption from all routes of entry. Moreover, it makes is possible in principle to estimate the concentration in the critical organ. In addition, BM takes into account intra- and interindividual variation in biotransformation and elimination processes.

Occupational health research usually arrives at conclusions by studying groups of workers and/or animals. The assumption is made that the effect/response relationships and no-adverse-effect/response levels can be applied to men/animals in general, even though the group under consideration may not, in fact, be representative of the distribution of individual variabilities in exposure and coping capacity among the general population of workers. Consequently, the same is largely true for health-based recommended OELs, e.g. threshold limit values (TLVs) and maximal acceptable concentrations (MACs), biological exposure limits and reference levels. OELs aim at prevention of early health impairment, but only "in general". The percentage of workers and their offspring not protected is usually not known.

However, in the occupational setting, one has to consider both groups and individual workers who are in fact members of these groups. Occupational hygienists and engineers base their work mainly on "standard" workers and on exposure, whereas occupational physicians and nurses are confronted with the variability of coping capacity around the standard.

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* The Organizing Committee of the Workshop delegated the writing of this report to: R. Murray (Chairman-rapporteur), V. J. Feron, R. F. M. Herber, W. J. Hunter, A. C. Monster, W. R. F. Notten and R. L. Zielhuis.

To date, research has paid little attention to this variability, and even less to the factors which may determine it. Why has this worker a problem today and why not in the past? What is the impact of pregnancy? Why should this worker be affected and not that fellow worker with apparently similar exposure?

This workshop was convented to discuss the present knowledge of (a) the intra- and interindividual variability of external and internal exposure and of capacities to cope with such exposure and (b) the factors which may determine this variability. The ultimate aim is the greatest possible protection of those workers who fall in the lower ranges of coping capacities. In the ideal situation, each worker should remain within his or her own coping limits. If occupational health research and practice can establish the impact of the contributing factors, prevention of early health impairment for almost all active workers will be achieved.

The Organizing Committee was well aware that the writers had to tackle an almost unknown area. The objective was not to explore the present state of the art, but first of all to locate the bottle-necks and to recommend topics for future research and preventive measures in occupational health practice.

The flow chart presented by van Dijk et al. provides a framework for an overall approach. It gives a concept of the dynamics of determinants of intra- and interindividual variability in exposure and in coping capacity. The research projects which may ultimately lead to preventive measures will have to be based upon interdisciplinary cooperation. One should take into account that at the start of exposure, intra- and interindividual variability in response may already exist. Preventive measures should at least prevent an increase of the deviation and should preferably reduce this insofar as it is dependent on work-related and host-related factors.

It should be emphasized that variability should not only be studied in relation to personal traits and inborn or acquired biological susceptibilities: studies should also take into account the results of specific interactions between workers and their total environment at and off work. The results of such interactions may modify every phase of the dynamic flow and, therefore, may explain at least a part of the intra- and interindividual variability.

Within the programme of the workshop, three themes were discussed:

1. Intra- and interindividual variability in external and internal exposure to chemicals
2. Intra- and interindividual variability in response
3. The impact of other conditions at and off work on exposure and response

A total of about 60 invited experts from the Netherlands and various other European countries attended the workshop. Twenty-four of them were invited to prepare 19 working documents on different subtopics. These were circulated to all participants before the workshop started. During the workshop, the participants were split up into small discussion groups, each group discussing a working document in depth. For each theme, the opinions, conclusions and recommendations of the discussion groups were presented and discussed in plenary sessions. This summary report reflects the results of all the discussions at various levels. The definitions of the most important terms used in this report are presented at the end of this chapter.

Theme I: Intra- and Interindividual Variability in External and Internal Exposure to Chemicals

There are a number of problems in respect of the measurement of both external (EM) and internal exposure (BM). In the case of EM, the 8-h time-weighted average does not take into account peak concentrations. Such short-term overexposure may be of great significance in the case of substances such as isocyanates and benzene and may affect the immunological processes. Therefore, the frequency and duration of sampling should take into account the toxicokinetics and -dynamics of the agent under consideration. It is also necessary to identify correctly the nature of the atmospheric contaminant. It is, for example, not sufficient to measure the total amount of a metallic component in the environment; the effects of different compounds (metal speciation), possibly with different physical properties, may be crucial.

Many personal work-related and host-related factors may affect both intake and uptake. Having entered the body, the substance is transported, metabolized and excreted; these processes can also be modified by such factors. Knowledge of the impact of these factors will help in the prevention of overexposure, at least when workers and management are well informed and educated.

Age appears to be a minor interacting factor in metal toxicokinetics, although an increased susceptibility has been alleged in the case of fetuses, young children and the elderly. Prenatal and neonatal exposure may be related significantly to the occupation of the parents; chemicals excreted with breast milk lead to postnatal exposure. In some cases, the effect of exposure may be delayed until later years. Few data exist on the impact of impaired organ functions on the toxicokinetics of metals, but kidney dysfunction and gastrointestinal disorders, for example, are likely to affect the mobilization and distribution of toxic substances. The impact of physical workload on respiratory intake is considered unter Theme III.

With regard to absorbed contaminants related to life style, it was recognized that there is no good classification of life style and social class. Little investigation has been made in this area.

The toxicokinetics of particular substances may be difficult to elucidate. A number of models have been proposed to deal with this topic. It was agreed that the physiological simulation models may oversimplify intersubject variation. Volunteer exposure experiments may yield valid data for the assessment of intra- and interindividual kinetics. The data should be analyzed by means of compartment models or transfer functions; the latter are based on individual kinetic characteristics. Model compounds may be used for specified groups of chemicals, e.g. tetrachloroethene as a model compound for fat-soluble, hardly metabolized solvents.

Screening models have been discussed in relation to single-substance exposure and multiple exposure. As far as single-substance exposure is concerned, an adequate knowledge of toxicokinetics is a prerequisite for BM strategies. This is generally more easily attained for organic solvents than for several metal compounds. The actual nonconjugated toxic agent measured in blood or exhaled air should preferably be used for BM. In principle, it appears to be possible – at least for some agents – to develop BM methods which elucidate individual factors.

Studies on multiple exposure should include interaction not only between various chemicals but also with nonchemical factors, e.g. physical, biological and psychosocial determinants. Interaction with nonchemical factors is also relevant for single-substance exposure. Mixtures of chemicals should be tested in animals, preferably using the formulation in which they are found at the workplace. OELs should be established not only for the pure compound but also for inherent mixtures and mixtures which are widely used in industry.

The workshop considered BM to be a useful tool for estimating total exposure when workers are exposed to the same agent at and off work. Moreover, BM of specific chemicals offers better possibilities than EM for assessing the relationship with work because it permits one to establish individual internal exposure. BM is considered to be particularly important in assessing exposure in those jobs for which EM hardly offers a solution, e.g. maintenance jobs. BM does not elucidate health effects; however, for exposure to several widely used compounds, it should facilitate measurement of the variability in internal exposure and consequently in health risks. It is necessary to collect data on unexposed workers to ascertain the pre-exposure interindividual variability in internal exposure, especially in relation to personal characteristics.

Theme II: Intra- and Interindividual Variability in Capacity to Cope with Chemicals

Knowledge of individual coping capacity is a prerequisite for assessment of individual health risks. Periodical biological effect monitoring (BEM) and health surveillance (HS) programmes are inadequate if only mean group levels are assessed, without taking into account the variation around the mean. For periodical health monitoring, both group- and subject-based reference values are needed. A method of assessing intra- and interindividual variabilities of some biochemical and haematological parameters was illustrated . Assessment of individual variation is essential before one can assess the health significance of environmental factors for individual workers.

The topic of enzyme induction has been discussed at length. It has been shown that the antipyrine metabolism, for example, can be increased by some chemicals. The relevance to health of a long-lasting inductive effect is not known. It may lead to a higher degree of either detoxification or toxification of chemicals; moreover, it may have an impact on the metabolism of nonwork-related, biologically essential chemicals, e.g. hormones. A majority of the participants agreed that enzyme induction as such is not a toxic effect, but that it should be considered to have at least a warning function. Therefore, it might be wise to keep exposure well below the level at which enzymatic changes occur. Various other, nonwork-related factors besides workplace chemicals may also lead to enzyme induction, e.g. prescribed drugs, contraceptives, smoking and alcohol; age and sex also determine the induction potential. Moreover, the possibility of enzyme inhibition should not be neglected.

Interference with the reproductive system may involve a direct action on the sex organs or the fetus, but an indirect deregulation of the endocrine balance, for example, may also be important. It was mentioned that metallothionein is not influenced by sex hormones, but by steroid hormones of another origin.

In studying the relationship between exposure to chemicals in the workplace and health effects, several difficulties arise. Most chronic effects are the result of longterm exposure (several years), but exposure levels from previous periods are hardly known. Therefore, it is difficult to establish whether interindividual variability is due to variation of exposure or of individual response. The importance of these variation depends on the severity of the response; establishment of both variations is important.

Knowledge of the impact of acquired or genetic predisposition on the toxic response to industrial chemicals is still very limited. So far, only suggestive evidence of possible interactions between genetic factors and toxicity of industrial chemicals has been offered. For instance, genetic differences in the metabolism of carcinogenic chemicals (e.g. polycyclic hydrocarbons, debrisoquine and aromatic amines) may increase or decrease the risk of cancer. Subjects with partial genetic deficiency in α_1- antitrypsin are more prone to develop emphysema or chronic obstructive pulmonary disease when exposed to irritant gases, dusts and mists. Atopic subjects are more likely to develop allergic reactions.

Pathological conditions may affect the response to toxic chemicals by increasing the susceptibility of the target organs. It has been suggested that subjects with myocardial conduction defects may be more susceptible to the arrythmogenic activity of trichloroethene. Clinical studies have suggested that asthmatic patients are more responsive to various lung irritants. Kidney, liver and skin diseases may also influence responses to chemicals.

It was proposed that one could test early changes of the function of various organ systems: one could study the relationship with, for example, potential hepato-, nephro-, neuro-, pulmo- and haematotoxic agents present in the workplace. However, the early BEM parameters are usually nonspecific in respect of causal factors: many nonwork-related causes exist. Therefore, this would not be very helpful in assessing the causal relationship in an individual worker. In practice, the assessment of a predisposition for the most frequent occupational diseases might too easily lead to exclusion of a subject from employment; in particular, too much emphasis might be put upon "inborn errors of metabolism".

Good laboratory practice is important for BM, BEM and HS parameters. There is a need for quality control programmes not only for BM parameters but also for those of BEM and HS. The preanalytical phase, i.e. the phase before the real determination, is the most critical step from the point of view of deterioration of the sample (enzymes, protein), sample contamination and loss of volatile compounds. Good communications between the analytical chemist and the physician or occupational hygienist is essential. In the analysis of parameters, the requirements for precision, accuracy and sensitivity depend on the aim of the investigation; analytical data should not be regarded as an end in itself.

Theme III: The Impact of Other Conditions at and off Work on Exposure and Response

There is a need to take into account and recognize social problems which may be part of social policy, differing from country to country. In industry, economic considerations are significant. These may have an impact on the intra- and interindividual vari-

ability of exposure and on standard setting, and they may hamper employment of those with increased susceptibility.

This aspect led to sometimes hectic disussions on what was "science" and what "policy". There were different opinions on where science ends and politics begins. Even scientific evaluation of the state of the art in order to underpin OELs, for example, requires choices: which effects on health are relevant and what intensity of a chosen effect, how often and for how long is irritation of mucosae acceptable during a work shift, what percentage of workers will not be affected, which method of extrapolation from animal to man and/or from high to low exposure levels is chosen, what is health, what is adverse? Policy determines the impact of socioeconomic and technological constraints.

With different work schedules, no problems are to be expected in the case of local irritants or substances having intensive odours where OELs are set with the intention of avoiding irritation or intensive odour, respectively. For cumulating compounds with a long half-life, such as some heavy metals, polychlorinated biphenyls (PCBs) and chlorinated organic insecticides, the OELs also seems independent of the exposure pattern. However, for compounds with a shorter but still relatively long half-life, extending the work shift to 12 h, for example, may mean an increase of internal peak loads of solvents or metabolites by 50% or even more in the case of nonlinear kinetic towards the end of the work shift. For such compounds, the OELs should be adapted to extended work schedules. This seems not to be necessary for very short-lived compounds which are rapidly eliminated. In general, toxicokinetics should be considered in setting OELs.

BM can and should be used to find out which workplace chemicals are affected by novel work schedules or shift work, and also to establish the appropriate time of sampling. In most cases, samples should be taken around the last hour of the shift.

It is well documented that changes in physical workload may alter the intake and the toxicokinetics of workplace chemicals. Workload effects are of special importance for interpretation of the differences in toxicokinetics between laboratory experiments on volunteers and field studies of workers. This should be taken into account in setting biological exposure limits and in developing BM strategies.

Diurnal rhythms and variations in time of food intake have been shown to influence the hepatic metabolism and toxicity of drugs and other chemicals. The extent to which such phenomena modify the toxic effects of chemicals in man at the workplace is difficult to evaluate and has hardly been studied (chronotoxicology).

The ideal way to prevent adverse health effects at work is by ensuring that no exposure takes place. This strategy cannot be followed in the majority of cases because of socioeconomic constraints, but also in some cases because the presence of agents in workroom air is generally accepted, e.g. in laboratories and research institutes.

One should be aware that – at least on a group basis – with decreasing socioeconomic status (SES), conditions both at work (e.g. exposure levels, combined exposure also to physical conditions, pressure of time and degree of freedom to organize one's own work) and off work (e.g. life style, crowding at home, ambient pollution and level of education) tend to be less favourable than for workers of higher SES. This again emphasizes the need to take into account the relevance to health of total exposure at and off work.

To ensure that exposure is kept as low as is reasonably practicable, standards have been developed and established. Such standards are usually the outcome of political negotiations, both on the national level and also in everyday practice on the shop floor. Worldwide, there are no more than 1000 OELs, mostly for single agents, yet there are some 95000 compounds to which workers may be exposed. The development of workplace standards is usually a long-drawn-out process, which requires well-described exposure-effect/response relationships on which a decision can be based.

Nevertheless, there is reason to fear that to date, relatively speaking, too much research has been carried out on a limited number of industrial chemicals, whereas too little research has dealt with the large majority of chemicals. There is an urgent need to provide at least basic toxicity data. Moreover, more attention should be paid to research on general principles of working mechanisms for groups of chemicals. Redistribution of manpower and budget could lead to a more rapid increase in the number of at least tentative OELs.

It is necessary to set priorities, both for research and for carrying out screening programmes in occupational health practice. Preconditions for screening activities are the existing legislation, the identification of an industrial chemical as hazardous and the potential value of such programmes. In order to make this possible and to fill the enormous gap in toxity data for the large majority of industrial chemicals, one has not only to know the seriousness of the hazard but also to take into account the number of workers exposed, increasing use in industry and the actual exposures (frequency, duration). Additional reasons for priority are the presence of confounding factors, the number of cases of disease partly attributable to occupational exposure, exposure to the same agent off work and the availability of well-validated methods of analysis; moreover, agents for which programmes for analysis of the results are available should receive a higher priority.

When data on combined exposure are lacking and are unlikely to become available in the near future, especially for mixed exposures, the workshop considered additional types of standards worth investigating such as a "profile" description of a process or a job, which also take into account other chemical and nonchemical working conditions. These standards could also serve as a primary preventive measure aiming at reduction of exposure when used in the early construction stage of plant and equipment.

OELs tend to decrease in the course of time; consequently, actual exposure and work-related health risks will also decrease. Therefore, one can expect the relative impact of nonwork-related factors on internal exposure and on the capacity to cope with chemical, physical and social working conditions to become greater. Because of this, one has to rely more on BM and BEM programmes, on process- and job-dependent standards and on treating workers as members of the team that determines the overall working conditions.

The present OELs are based on animal studies and on epidemiological studies on workers from industrialized countries, if, that is, they are reliably underpinned at all. In developing countries, one may expect less favourable conditions at and off work and, therefore, larger intra- and interindividual variabilities in exposure and particularly in coping capacities than in industrialized countries.

Epidemiological research on exposure-response relationships will probably only elucidate evidence of interaction between exposure and coping capacity when each study

is limited in scope to a few-work- and nonwork-related factors and is carried out under determinate conditions of exposure and on well-defined workers. Therefore, the impact of epidemiological research will be limited.

Occupational health services are in a *unique* position to gather information on intra- and interindividual variablity because of the possibility to conduct periodical follow-up programmes. This can hardly be done in curative practice; moreover, knowledge of work- and nonwork-related factors is generally poor among curative physicians. Because of this unique position, occupational health also has the duty to try to assess the impact of such factors.

During the workshop, the facts and fallacies of the common reference values of biochemical and haematological parameters were clearly shown. Occupational health, therefore, can contribute to knowledge of the impact of host-related factors at and off work on variability, which will also have a favourable influence on curative medicine.

The workshop concluded that personal behaviour of workers and, at a personal and structural level, of management has a large impact on working conditions. In order to change this behaviour, dissemination of information will not suffice. Education of workers by educated workers will probably be more effective. The essential role to be played by each individual worker in this respect as a member of his or her group should be better appreciated than is often the case. Management should also be educated so that it becomes committed to the control of exposure at work.

Recommendations for Future Research and Occupational Health Practice

As stated before, knowledge on the intra- and interindividual variation of both exposure and response and on the determining factors of this variation is largely lacking at present. Nevertheless, this knowledge is essential for providing optimal occupational health care. Therefore, there is a need for research to tackle this unknown area. Moreover, occupational health practice also has to consider the impact of this variability on periodical follow-up programmes, the preventive measures to be taken, the interpretation of OELs and information and education programmes for workers and management. Both occupational health research and practice have to set priorities to tackle this large unknown area.

The discussions during the workshop and the conclusions arrived at led to the following sets of recommendations:

1. Future research

a) To study the toxicokinetics of the actual toxic compound (agents or nonconjugated metabolites) in blood or – if possible – in exhaled air (e.g. trichloroethanol in exposure to trichloroethene). Moreover, the relationship between internal exposure to toxic chemicals (BM) and effects (BEM, HS) should be studied.

b) To refine the methods for assessment of external exposure (EM), internal exposure (BM) and of early effects (BEM), and to develop measurement strategies adapted to the toxicokinetics and -dynamics of each agent. This also applies to exposure to common mixtures.

c) To develop sensitive BEM programmes for early detection of susceptible workers, and to assess the relevance to health of these parameters. Tests should be developed for specific organ systems, e.g. kidney, liver, nervous system, respiratory tract, reproductive system and haematopoiesis.
d) To develop animal models (in animals with specified organ dysfunction) to study the interaction between preexistent health impairment and the toxicokinetics and -dynamics of specified chemicals. Moreover, this should also be studied in individual workers with predisposition or clinical diseases (follow-up of cases).
e) To develop knowledge on the interaction of multiple chemical exposure at work and other workplace and nonworkplace factors.
f) To study the impact of circadian rhythms, novel work schedules and shift work on the toxicokinetics and -dynamics of workplace chemicals.
g) To direct manpower and budget more according to the set of priorities discussed under Theme III, paying particular attention to the very large number of chemicals for which basic toxicity data are lacking and to the study of basic working mechanisms for specified groups of chemicals.
h) To develop process- and job-dependent standards, taking into account both chemical and nonchemical workplace factors.
i) To develop OELs based upon the distribution of data on exposure and effects, also taking into account the frequency and duration of exposure in order to permit the tolerance limit to be set.

2. Future occupational health practice
a) To carry out EM, BM, BEM and HS programmes geared to specified objectives (e.g. compliance to accepted limits, assessment of health risks in groups and individual workers), taking into account as far as possible specified (combinations of) chemical exposures, nonchemical workplace factors and nonwork-related factors. The monitoring strategies should take into account the toxicokinetic and -dynamic properties of each chemical. The data should not be presented as average group data, but as frequency distributions. The data on exposure and response of each worker should be registered in personal files, if possible with graphic presentation over the course of time.
b) To carry out BM and BEM studies at preemployment examinations in order to gain information on the individual exposure and coping capacity (before exposure at work).
c) To inform and educate workers, management, occupational physicians, hygienists and curative physicians about the interaction between exposure to workplace and/or nonworkplace chemicals and coping capacity. Moreover, to inform and educate workers and management on the impact of personal hygiene, hygienic working methods and host factors on internal exposure and coping capacity.
d) To discuss with employers' and workers' representatives the ethical and social aspects of BM, BEM and HS programmes for the establishment of baseline data at preemployment examinations, and to formulate specific guidelines agreed upon by all parties.
e) To ensure close cooperation between occupational physicians, hygienists and engineers in the evaluation of actual exposure levels and health risks and of the preventive measures to be taken. In proposing preventive measures, the occupational physician

should pay particular attention to the impact of intra- and interindividual variability on the assessment of exposure and of health risks.

f) To set up a toxicovigilance system for collection of case reports on suspected health hazards and potential evidence of interaction within large chemical industries and/or at the national level.

Some Definitions

In this summary report, terms have been used which may have different meanings in the literature. Therefore, the terms as used in this report are defined as follows.

Health

The WHO defines health as "optimal physical, mental and social wellbeing". This definition points to a goal to be achieved. In the occupational setting, no worker is fit to carry out all types of job. The following definition appears to be more appropriate for occupational health practice: health may be definded as "a nonstable condition of the human organism, of which the functional capacities leave nothing to be desired in the workers' own opinion and/or according to health experts. Preexisting physical and mental capacities, depending on age and sex, for example, have to be taken into account. The functional conditions should be comparable to those in nonexposed, otherwise similar groups of workers in the same society. Allowance should be made for the present state of the art, present-day objectives of health care, social acceptability and social habits" (Zielhuis and Notten 1979).

A distinction between "somatic health impairment" and "nuisance" should be rejected because (a) such a distinction is based upon a nonexistent dichotomy between soma and psyche, (b) perceived nuisance can just as well be assessed objectively in groups of workers as signs of somatic impairmant, (c) symptoms do not always occur before somatic impairment can be established and (d) symptoms and signs may restrict "normal" functioning in society and at work.

Adverse effects

An effect as such is a neutral concept: a biological change is observed. It is a matter of decision on the part of health experts *after* a study has been carried out to distinguish between "effects as such" and "adverse effects". Moreover, observation of a specified effect offers no guarantee that other relevant effects which one has not looked for do not exist. New studies may discover previously unexpected hazards.

The WHO (1978) defined "adverse" as changes that:

1. occur with intermittent or continued exposure and that result in impairment of functional capacity (as determined by anatomical, physical, biochemical or behavioural parameters) or in a decrement of the ability to compensate additional stress;

2. are irreversible during exposure or following cessation of exposure if such changes cause detectable decrements in the ability of the organism to maintain homeostasis; and
3. enhance the susceptibility of the organism to the deleterious effects of other environmental influences.

Sherwin (1983) recently proposed the following definition:

An adverse health effect is the causation, promotion, facilitation and/or exacerbation of a structural and/or functional abnormality, with the implication that the abnormality has the potential of lowering the quality of life, causing a disabling illness or leading to a premature death.

Both definitions correspond fairly well.

Monitoring programme

In 1980, the CEC, the National Institute of Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) organized a seminar on "Assessment of Toxic Agents at the Workplace" (Berlin et al. 1984). This seminar agreed upon the following definition:

Monitoring (in preventive health care) is "a systematic continuous or repetitive health-related activity, designed to lead if necessary to corrective action".

On the basis of this definition, the following definitions were presented:

Ambient (environmental) monitoring (EM) is "the measurement and assessment of agents at the workplace to evaluate ambient exposure and health risk compared to an appropriate reference".

Biological monitoring (BM) is "the measurement and assessment of workplace agents or their metabolites either in tissues, secreta, excreta or any combination of these to evaluate exposure and health risk compared to an appropriate reference".

Health surveillance (HS) is "the periodic medico-physiological examination of exposed workers with the objective of protecting and preventing occupationally related diseases. The detection of established disease is outside the scope of this definition".

In practice, EM, BM and HS are not always applied continuously or repetitively; however, repetitive measurements certainly add important extra information. The trends in time permit more reliable assessment of exposure and of the health risks (EM, BM) or of the state of health (HS).

Recently, a new type of programme was defined by Zielhuis and Henderson (1986):

Biological effect monitoring (BEM) is "the measurement and assessment of early biological effects, of which the relationship to health impairment has not yet been established, in exposed workers to evaluate exposure and/or health risk compared to an appropriate reference".

BEM differs from HS in that it does not assume a priori that the effects examined have an adverse character.

Toxicokinetics

Toxicokinetic data describe "how the body handles the agent": absorption, distribution, biotransformation, deposition and excretion. Toxicokinetic data do not give any information on the *state* of health, but – when internal exposure-effect/response relationships are known – on the health *risk*.

Toxicodynamics

Toxicodynamic data describe the "effect of the agent or its metabolites on the body". Toxicodynamic data give insight into the *state* of health, when adverse, and into the health *risk*, when not adverse.

Exposure-Effect/Response Relationships

Exposure has to be related (semi)quantitatively to health effects. In occupational exposure, the "dose" is much more difficult to establish than in pharmacology. The WHO prefers to use the term "exposure-effect/response" (E-E/R) relationships than "dose-E/R" relationships.

Exposure-effect (E-E) relationships describe the relation between exposure (intensity, duration and frequency) and a specified effect (quality and quantity) in an individual subject or between exposure and an average *graded* effect in groups of animals or humans. Because a "standard" worker does not exist, the 95% confidence interval is generally much larger in humans than in experimental animals. Some effects (events) are stochastic (*quantal*): they either do or do not occur, e.g. death, abortion, malformation and cancer. Exposure-response (E-R) relationships present the incidence rate of an effect; therefore, the interindividual difference in response at similar external or internal exposure levels is presented.

From the viewpoint of health protection, it is not the average effect in groups of workers that is important, but the relative frequency of exposed workers who exceed a specified intensity of a specified graded effect or who suffer a specified quantal effect at specified exposure levels. This percentage is expressed in the E-R relationships; those employees who are affected should first of all receive protection.

The responses actually studied often only present the tip of an iceberg. There exists a continuum of adjustment, compensation, breakdown, health impairment, disease, death. Whether one observes an effect depends first of all upon the *effects chosen* for study and the sensitivity and specificity of the *methods* applied.

Intake and Uptake

The *intake* refers to external exposure (EM), i.e. the level in inhaled air, eventually multiplied by the respiratory minute volume and the duration of exposure; mutatis mutandis, similar measures apply for chemicals ingested or potentially absorbed through the skin.

The *uptake* refers to the amount absorbed, i.e. intake multiplied by the fractional absorption factors.

Life Style

The various working documents discussed the following life style factors (in terms of quality, quantity and frequency):

1. Nutritional habits, maybe deviant habits, e.g. vegetarian diet, macrobiotics, overnutrition
2. Consumption of tobacco
3. Consumption of alcoholic beverages
4. Consumption of addictive drugs (even at work)
5. Consumption of coffee, tea, chocolate, mineral water and nonalcoholic beverages
6. Consumption of nonprescribed pharmaceutical drugs
7. Sports activities
8. Distribution of sleeping (rest) activity over the day and the week
9. Use of chemical anticonceptives
10. Personal hygiene off work
11. Hobbies with exposure to similar or other chemicals and physical factors

The relative importance of life style factors depends on ethnic and cultural background, level of education, SES, climatic conditions and choice of food.

Host Factors

The various working documents discussed the following host factors, not directly, although maybe indirectly, dependent on personal life style:

1. Age
2. Sex
3. Genetics
4. Pregnancy
5. Consumption of prescribed pharmaceutical drugs
6. Preexistent or intercurrent predisposition or manifest disease
7. Mode of transport and distance to and from work
8. Diurnal variation in toxicokinetics and/or -dynamics
9. Hygienic behaviour at work

Occupational Exposure Limits (OELs)

OELs is the generic term for threshold limit values (TLVs) and maximal acceptable concentrations (MACs). The definition of the American TLV can be used as an example. The TLVs refer to "Airborne concentrations (in workroom air) of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect". The TLV is the time-weighted arithmetric average concentration for a normal 8-h working day and a 40-h week for the whole working life. Some countries have also added protection of offspring.

Good Laboratory Practice

Good laboratory practice (GLP) refers to the organization process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported (WHO 1981).

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Theme I
Intra- and Interindividual Variability in External and Internal Exposure to Chemicals

Assessment of Variability in Individual Exposure to Metals

M. Piscator

1 Introduction

In the working environment, metals may enter the body via the lungs, the gastrointestinal tract or the skin. Dermal exposure will not be discussed in this section since it generally plays a minor role for systemic absorption; however, chromates may be absorbed from the skin.

The respiratory tract is the target for many metals as well as a portal of entry for metals causing systemic effects. Inhaled metal compounds can also be removed from the lung and transported to the gut by clearance mechanisms, which may cause further systemic absorption. There also exists the possibility of gastrointestinal exposure through direct ingestion of dust, through contact with contaminated hands or by other mechanisms.

However, there exist very large variations in how workers react to and handle hazardous materials. There are also large variations in how people behave during work. In addition, there is the problem of accurate measurements of exposure. Earlier occupational exposures were generally much higher than what could be found in the general environment, but with improved hygienic conditions in workplaces and an increasing pollution of the general environment, the gap has narrowed. These are some of the topics that will be treated in the following sections. Only exposure to metal particles will be discussed here.

2 Measurement of Exposure

To monitor the working environment, the concentrations of the metals in the air are measured, mainly to check whether MAC values are being complied with. For a long time, measurements were made by stationary or mobile high-volume samplers for short periods; only during the last decade has personal monitoring become more common.

Several studies have shown that the differences between measurements made by stationary and personal sampling may be very large (Adamsson 1979; Donaldson and Stringer 1980). Personal sampling generally results in higher measured concentrations than stationary measurements. That personal samplers sometimes give much higher concentrations may be caused by resuspension of dust collected on the worker's clothes (Cohen et al. 1984; Bohne and Cohen 1985). Table 1 shows results from a study in a Swedish battery factory.

Table 1. Stationary versus personal sampling. Arithmetic means of cadmium in air. (from Adamsson 1979; Hassler 1983)

Category	Period	*n*	Cd $\mu g/m^3$		*r*
			Stationary sampling	Personal sampling	
Briquette makers	December 1974	14	18.5	71.1	−0.03
	June 1975	26	9.3	8.9	+0.07
	Total	40	13.6	35.4	+0.55
Plate assemblers	December 1974	16	20.3	30.4	+0.44
	June 1975	20	10.9	10.7	+0.22
	Total	36	17.8	20.5	+0.39
Banders	December 1974	5	14.5	19.8	−0.67
	June 1975	4	6.4	5.9	−0.17
	Total	9	13.0	14.6	+0.32

It can be seen that in the month of December there are larger differences than in June. One explanation is that the lower humidity during winter increases electrostatic forces and causes more dust to settle on workers and their machines. There is also the problem of "respirable dust". Sometimes measurements are made with cyclones to get only particles of <5 μm, which are thought to be of most interest for estimating the risk of pulmonary deposition and absorption. However, it has been shown that some alveolar deposition and retention may occur after exposure to particles of up to 16 μm in size (Svartengren et al. 1987). Thus both total and "respirable" dust may be of interest for some exposure evaluations. For compounds like nickel subsulfide and chromates, which have an effect on the upper respiratory tract, it is obvious that the large particles may be important, since they contain the larger mass of the total particulate.

As mentioned before, there have been improvements in working conditions in many industries. Figure 1 shows the changes in cadmium concentrations in air in a Swedish battery factory.

It should be kept in mind that during the 1940s and 1950s few measurements were made, and the confidence limits of these early values were large, whereas during later years a large number of measurements were obtained. This also illustrates the problems epidemiologists face when they try to estimate individual exposures in the past to obtain dose-response relationships in cancer studies. Figure 1 also indicates that present exposure is below the Swedish MAC of 20 $\mu g/m^3$. However, when workers with only a few years of exposure to about 10 μg Cd/m^3 were examined, some were found to have very high blood cadmium levels. Further investigations showed that some of these workers had a very high faecal content of cadmium, which could not be explained by clearance of inhaled cadmium from the lung (Adamsson et al. 1979). Smokers had higher faecal cadmium than nonsmokers, and it had earlier been found that cigarettes and pipe tobacco could easily be contaminated if stored in working clothes or handled with dusty hands (Piscator et al. 1976). Evaluation of personal hygiene and behaviour

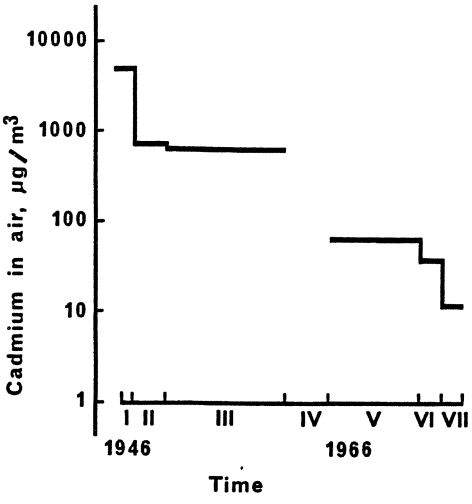

Fig. 1. Concentrations of cadmium in in workroom air from 1946 to 1977. There were no measurements 1961–1964. (From Hassler 1983)

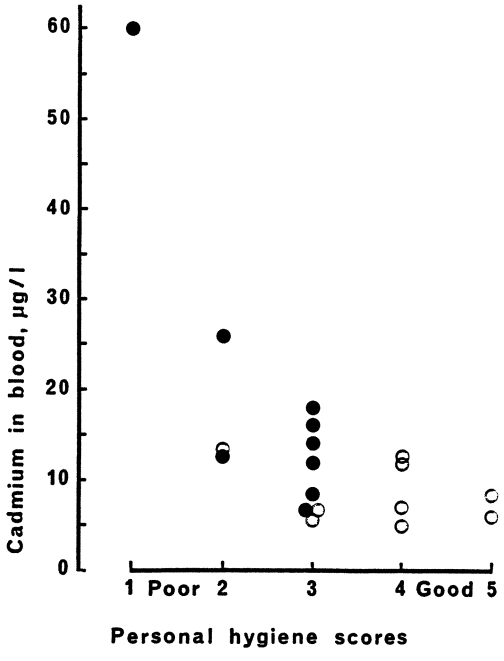

Fig. 2. Cadmium in blood in relation to personal hygiene score in smokers (*filled spots*) and nonsmokers (*unfilled spots*). (From Hassler 1983)

during work gave further indications of what may be more important than the acutal air concentrations, as shown in Fig. 2.

Similar experience has been gained in other studies on cadmium-exposed workers (Roels et al. 1982) and with regard to lead exposure. Chavalitnitikul et al. (1984) determined lead on hands, faces and working surfaces and found very high concentrations of lead. Unfortunately there are few data on the faecal content of metals in exposed workers, but it is not easy to perform such studies. It is of historical interest

that as early as 1926 Batchelor et al. determined zinc in faeces of smelter workers and found very high concentrations (Batchelor et al. 1926).

The conclusion is that in many workplaces a reduction in air concentrations of a metal dust may have little effect if the workplace is not kept as clean as possible and the workers are not informed about the importance of being tidy; smoking material and food especially must be kept from being contaminated. Respirators may be useful but will probably be of little use if these personal hygiene factors are not controlled.

3 Variability of Lung Physiology

Inhaled metal particles will be deposited in different parts of the respiratory tract. The deposition will depend on the bronchial diameters, especially for particles > 1 μm, and on the size of the lung, i.e. forced expiratory volume (FEV) and forced vital capacity (FVC). Workers with low FEVs may thus be at less risk than those with high FEVs. This implies that the deposition will be less in smokers, but on the other hand their mucociliary clearance might be impaired, which will cause higher retention (Svartengren et al. 1986a; Gerrard et al. 1986).

Bronchial constriction can be induced by many agents. Individual reactivity may vary by a factor of about 40 (Svartengren et al. 1986b). Where there is exposure to SO_2, NO_2 or other irritants, people with low reactivity will form a group of "healthy workers". On the other hand, if they do not react to SO_2 and there is simultaneous exposure to arsenic trioxide, they may get a large deposition of that compound.

There are thus many variations between individuals with regard to lung physiology, but there may also be an intraindividual variation. Bronchial constriction may cause variation in deposition, and a respiratory infection may cause a decrease of mucociliary clearance.

4 Exposure, from Other Sources

The studies on cadmium and lead in the United Nations Environmental Programme/ WHO study (Friberg and Vahter 1983) showed that in Japan there are high renal levels of cadmium in the general population, sometimes close to the so-called critical concentrations. This implies that a worker occupationally exposed to cadmium in Japan may have less capacity to handle additional exposure to cadmium than a colleague in, for example, Sweden.

With regard to lead, it was found that blood lead levels were quite high in Malta and Mexico (Bruaux and Svartengren 1985), compared with Belgium and Sweden. The higher the blood lead level from exposure via water or food is, the less the occupational exposure should be. In Europe there are also areas with a high background exposure to lead, e.g. in Scotland from water (Sherlock et al. 1984) and in Belgium from industrial pollution or water (Claeys-Thoreau et al. 1983). Another factor is the relatively high lead content of wine (Grandjean et al. 1981), which may partly explain the fact that lead levels in some countries in Southern Europe are generally higher than in

Northern Europe. This results in relatively high blood lead concentrations even without occupational exposure, which should be taken into account when setting a national MAC.

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The Impact of Life Style Factors and Consumption of Pharmaceutical Drugs on Toxicokinetics

P. E. Fournier and G. Thomas

The impact of life style and consumption of pharmaceutical drugs on toxicokinetics may be the subject of very different discussions. The first is the question of life style definition. The second deals with the impact of the use of pharmaceutical drugs by a normal worker with an apparently normal life style.

1 Life style

1.1 Assessment of Life Style

Life style can be described by using different trivial parameters. Social class, the traditional parameter in the last century, is characterized by economical status and association with cultural references, such as home, family life, rituals, level of education. Work class is another aspect, used in political science (Le Laidler 1986) and in occupational health epidemiology: workers without qualification, qualified workers, highly qualified workers, staff, managers and engineers, board members and directors. The category of independent workers (private or employed) and of occupational physicians is rapidly growing. However, for a sound epidemiology, health surveillance of other groups must be added: disabled workers, chronically ill workers (e.g. diabetics and hypertensives), retired and pensioned groups, part-time workers, workers without employment but with social aid, workers without employment without social aid. Obviously, in the EEC the last two classes have grown very quickly in the last 12 years.

Economic status and its distribution in a nation is a very important parameter of life style. With an average national product per year ranging from 7000 to 10000 fr. per capita, the life style of a family with a low income (say 4000 fr.) differs greatly from that of a family with a high income (e.g. 60000 fr.). Access to useful and pertinent medical care can vary from a strict observance of sound medical advice to faith in various natural or mild medicines. Generally in Europe, a national health system (medical services and insurance) maintains a high level of medical assistance, the results of which are very clear according to the demographic evolution and the development of old and very old groups (Santé-Solidarité no. 5 1986).

Many other classifications related to three approaches to a postindustrial society can be developed according to familial traditions which correspond to sleeping time, entertainment, degree of agressivity, flexibility, regular or aberrant social rhythms, incidence of prevalent diseases in old and very old groups and their relation to work and

social histories as well as to ethnic or geographical origin (Goyer et al. 1985; Roussel 1983; Suess et al. 1985).

1.2 Questionnaire Analysis

The analysis of life style in a nation can be more accurate if one takes into account some social characteristics, especially consumer data, as derived from national institutes for statistics dealing with:

1. Alcoholic beverages: general use, drinking habits, number of public distribution places, taxes, importance of abstinent groups
2. Smoking habits: general use, taxes, smoking patterns in the young
3. Life stresses: in the family, in sexual relations, at work, in relation with social events
4. Life loads: home and material maintenance, education and surveillance of children, care of old persons, obligatory use of traffic facilities, muscular or psychological load at work.

The description should be very complex in order to approximate to reality, because of the frequency of crises in an individual life.

However, it makes no sense to use very complicated forms or questionnaires in order to procure very comprehensive epidemiological data. Either the group is defined by very simple but specific parameters and, despite poor precision (lack of sensitivity), the data may be significant enough to allow a tentative conclusion, or the study is very sensitive and very specific, but the size of the group is frequently insufficient to draw a conclusion (Zielhuis 1984). When it is sufficient, the epidemiological enigma still exists. In the coal miners' group in France, for example, life style is rather uniform, the great differences being limited in coal regions to familial behaviour and clear-cut work qualification levels. A specific Miner Health System has been organized under the control of a National Board. It was found that the incidence of pneumoconiosis was quite different in the different regions, although the mechanical evolution in the mines and the organization of prevention were nearly the same all over the country, with a comparable pollution of silica in the air inhaled by the workers. Did differences in other pollutants, in life style, in genetic polymorphic response cause such observations?

1.3 Main Parameters of Life Style

After these preliminary remarks, we may consider the main toxicological, nonprofessional, life style-related parameters.

1.3.1 Use of Pharmaceuticals

The use of pharmaceuticals, cannabis or other addictive drugs by normal workers represents the main reference to a specific individual risk in life insurance reports.

1.3.2 Nutritional Life Style

According to what is known about pharmaceuticals, nutritional life style is certainly important, but we have very limited information on its role over very long periods, except in regard to alcohol abuse and overweight in life insurance documents. The absorption of fat may modify the kinetics of lypophilic chemicals (absorption and depots).

Gastric cancer is becoming less frequent, maybe as a consequence of direct observation by fibroscopy and of better treatment of gastritis and gastric ulcer. The morphological demonstration of gastritis and gastric ulcer could be a good marker of stress effects, of tobacco and alcohol abuse. The composition of gastric juice may be related to varying rates of absorption of chemicals. The increase in the incidence of colon cancer may be related to the modification of European nutritional habits and the reduction of alimentary fibres in the diet. It appears to be very difficult to analyse a whole life style in terms of normal nutrients, except perhaps in strictly vegetarian sects and among high milk or meat consumers or alcohol abstainers.

1.3.3 Coffee and Tea

The use of coffee, tea and chocolate is so different from one nation to another in terms of quality, quantity and frequency that a moderate use of purinic compounds cannot be interpreted, even when they can be related to uric acid metabolism and when they exert some influence on phosphodiesterase activity in the cell and on nuclear DNA repair. In the case of strong and permanent overdosage of caffeine, there are obvious actions on heart rate, muscular activity and arousal state, but there is no scientific conclusion about the possible action on toxicokinetics in normal subjects or chronically ill patients (Murphree 1974).

1.3.4 Drinking Habits

Ethanol is of great concern in modern life due to its generalized use as a mild sedative, anxiolytic agent. However, tolerance to and dependence (physical and behavioral) on alcohol are very important parallel effects, leading to disabling situations and irreversible defects.

1.3.4.1 Metabolizing Enzymes

Some differences may be found between groups of chronic alcoholics; this may lead to a discussion of new parameters. The induction of the microsomal ethanol oxidation system (MEOS) among chronic alcoholics is probably one very important marker of an adverse biological situation.

Normally, among nonalcoholics, ethanol elimination kinetics are roughly described as a zero order reaction (Widmark) and dependent on the liver cytosol enzyme alcohol

dehydrogenase (ADH), of which several isoenzymes are known. However, ethanol can be oxidized in the peroxisomes by catalase, the role of which is dubious, and by the MEOS. This can account for 10%–50% of the ethanol concentrations, depending on the concentration – the higher the concentration, the higher the percentage. MEOS is inducible, while ADH is not.

Clinicians currently use γ-glutamyl transpeptidase (γGT) activity as an index of liver parenchymal damage. It is possible to match controls in epidemiological studies and to differentiate workers with low from workers with high γGT levels, for example.

We observed important differences of kinetics in chronic alcoholics, some of them following a zero order graph, but most of them fitting the integrated form of the Michaelis – Menten equation corresponding to an open one-compartment model with a single elimination pathway (the zero order model is an extreme aspect of this). Differences between groups were tested by Wilcoxon's nonparametric t test for comparison of matched pairs. In that case, it was found, surprisingly, that the group with higher γGT levels had a lower daily alcohol intake before hospitalization and the test. But this finding may be correlated to a lower tolerance to the clinical effects of a certain dose of alcohol.

The other parameters, aspartate-aminotransferase activity, alanine-aminotransferase activity and erythrocyte mean corpuscular volumes, considered as the main parameters of alcohol intoxication with the liver as the target organ, were higher in the group with higher γGT. These results correlated with a higher metabolism of ethanol, 250 mg/ml h^{-1}, compared with 150 in the group with low γGT. The correlation between a modification of the enzymes and the appearance of a parallel metabolism leading in the organism to a significant elevation of dangerous metabolites, such as free radicals and aldehydes, can also raise the hypothesis of an important modification of the metabolism of the most important xenobiotics, related to the activity of MEOS (Thomas et al. 1987).

1.3.4.2 Neurotoxicological Target Esterase

In a recent study of alcoholics, we (Fournier et al. 1987) found a sharp reduction of the lymphocyte neurotoxicological target esterase (NTE) by comparison with non-alcoholics. The reduction was around 60% (from 1200 to 500 U) and correlated for the lower values with neurological diseases. If validated, this new parameter affected by life style could indicate an increased susceptibility to neurotropic chemicals (e.g. some solvents).

1.3.4.3 Interactions

Knowledge of interactions between alcohol absorption and metabolism of chemicals is mainly based upon theoretical evidence, e.g. (a) facilitation of the digestive absorption of solvents; (b) enhancement of vasodilators; (c) competition with the metabolic capacity of the liver; (d) enhancement of bone marrow toxicity; (e) interaction with the monoaminooxidase in the brain; and (f) reduction of metabolism due to liver dysfunc-

tion, fatty liver or liver cirrhosis. Such interactions ought to be confirmed by occupational exposures.

The metabolites interacting with liver enzymes can be alcohols other than ethanol, the most reactive with ADH, methanol with catalase, and numerous chemicals with MEOS, inter alia chloroderivatives, benzo[*a*]pyrene, aromatic amines and nitroderivatives. The acetaldehyde metabolism interferes with disulfiram, dithiocarbamates and chloroderivatives. A great deal of information is available from experimental protocols, without any toxicological correlation with chemical work situations.

1.3.5 Smoking Habits: Tobacco Smoking and Cannabis

1.3.5.1 Nicotine

Animal studies demonstrate the neurological action of nicotine. During smoking, nicotine acts on nicotinic, cholinergic receptors located in the mesencephalic-reticular formation. It activates the cholinergic pathway to the cortex, and in man it has been observed that after smoking, most fast-activity changes appear in the sensory evoked potential (SEP) of the cortex. Reduction of the latency of the positive peak P300 could indicate more efficient neural processing of information, probably related to reduced response latency.

The interference of nicotine metabolism and psychoactive chemicals can be relevant for this topic. The physiological effect should be related to the toxicokinetics of nicotine. This may support new information on the individual adjustment of smokers to their personal demand, in order to obtain either excitement or sedation. Behavioural studies are necessary to understand the reasons for choosing to smoke cigarettes, early in the morning, after meals, after alcoholic beverages or during free time (Russel et al. 1980, Henningfield et al. 1981). Habitual smokers extract almost 100% of the inhaled nicotine, and the urinary recovery of nicotine is 55%–70% in nonbiotransformation. Nicotine is an enzyme inducer in many biotransformation processes, with a marked increase of *N*-demethylation of substances like morphine and pethidine.

The cardiovascular effects of nicotine, including increased heart rate, stroke volume and myocardial contractility, result in increased myocardial oxygen demand, and may interfere with chemicals having such effects or counteract drugs used to limit the cardiac oxygen demand.

Other questions are still hypothetical: Is the smoking tendency constitutionally demonstrated? Is life style correlated with the intensity of smoking? Does smoking produce a real impairment of neural efficiency? Is continuous smoking necessary to maintain normal cerebral function? Can tobacco smoking be correlated with other smoking or sniffing habits? (Rosecrans 1979).

1.3.5.2 Metabolism: Toxicokinetics

The interference of smoking with the absorption of industrial chemicals is an important topic in occupational medicine. Tobacco smoke hampers the mucociliary transport of particles and will probably enhance the resorption of chemicals in dusts. It also hampers the transport of known carcinogenic chemicals like polycyclic aromatic hydrocarbons (PAH), asbestos and cumulative chemicals like cadmium. Therefore, in industrial and environmental epidemiological studies, it is necessary to take into account smoking habits (duration, level, type of tobacco). An important parameter in carcinogenesis could be the data of the start and of the cessation of smoking.

With respect to hepatic microsomal enzymes, the aryl-hydrocarbon-hydroxylase (AHH) is the most extensively studied. It has been found that AHH enhances the formation of carcinogenic epoxy-derivatives from PAH. The activity of this enzyme is strongly correlated with the hydroxylation of chemicals, e.g. antipyrine, hexobarbitone, zoxazolamine.

There exists evidence for genetic control of AHH inducibility and some data can be obtained by the study of lymphocyte AHH, although these assays are difficult and expensive.

1.3.5.3 CO and HCN

These chemicals may modify cellular metabolism, reduce enzyme induction and limit the effects of PAH and of nicotine (Hugod 1979). One must certainly add the effect of smoking to the inhalation of CO-polluted air, but this has not yet been quantified.

Cigarette smoke contains approximately 0.5 μg HCN per millilitre, and it has been thought that HCN inhalation could produce visual alterations. This topic could be studied in epidemiological studies of workers exposed to other chemicals which affect vision and function of the nervous system.

HCN itself does not alter metabolizing enzymes to any significant extent at the levels obtained during smoking. The main parameter is the level of thiocyanate in serum (13–18 mg/litre among smokers, 1–7 mg/litre in nonsmokers).

1.3.5.4 Mutagens in Urine

The excretion of mutagenic chemicals in urine during smoking can be matched with the general excretion of mutagenic substances in groups of exposed workers. However, the predictive value of such determinations is not yet confirmed because of the necessity for a very long follow-up. An increase in the excretion of mutagens in urine of workers must be considered as a signal of uptake of mutagenic substances.

The impact of synergistic drugs on urinary mutagenicity may be due to induction of enzymes involved in the biotransformation of cytostatic agents as a consequence of smoking (Bos et al. 1982). Besides, it cannot be excluded that this synergistic effect is caused by differences in working hygiene between smokers and nonsmokers.

1.3.5.5 Interaction Between Industrial/Drug Kinetics and Smoking

The extensive studies of the metabolism of phenacetin and antipyrine can be used as markers for hepatic microsomal metabolizing systems in man, e.g. the toxicokinetics of antipyrine half-life ($t_{1/2}$) and metabolic clearance rate (MCR): $t_{1/2} = 0.693/k_e$ (k_e = overall elimination constant), MCR = $k_e\, aV_d$ (V_d = apparent volume of distribution).

The metabolism of antipyrine is modified in cigarette smokers, but the effect looks limited (magnitude of 15%–25%); it is not correlated with the dose of nicotine and is reduced in old age.

1.3.5.6 Trace Metals and Tobacco

The major source of cadmium in the environment is tobacco smoke. It is estimated that smokers inhale 2–4 μg cadmium per pack; the estimated body burden is 19.5 mg cadmium in nonsmokers and 35.5 mg in smokers of comparable ethnic origin. This observations is comparable to the levels of zinc and cadmium measure in workers. The role of the radionuclides of tobacco smoke is unknown; polonium-210 could play a role in the formation of bronchial cancer.

1.3.5.7 Smoking and Alcoholism

Studies on the effect of smoking habits on the metabolism of ethanol are still conflicting, the first results being negative (no relationship between ethanol disposition and smoking). Further studies have shown that regular alcohol consumption and heavy smoking are correlated with an increased alcohol elimination rate. (For review see Tong et al. 1980).

A systematic assessment of the very frequent association among workers of the use (or abuse) of alcohol and tobacco has not yet been made (Leigh et al. 1977).

1.3.6 Pharmaceutical Drugs and Toxicokinetics

A number of pharmaceuticals used by workers may influence the toxicokinetics of industrial substances. Some drugs that may be used by workers demonstrate the existence of a genetic human polymorphism in metabolism and kinetics. Indications of individual or ethnic differences still remain limited, but they have been ascertained, as may be shown by the following examples:

1. Desipramine: clearance significantly lower in the Chinese population
2. Diazepam: variation of metabolism due to enzyme inducers
3. Digoxin: some subjects metabolize digoxin very rapidly into an inactive metabolite
4. Hydralazine: rapid and slow acetylators are known
5. Procainamide: rapid and slow acetylators
6. Lidocaine: long-term treatment produces a marked increase in plasma binding

7. Meperidine: slow metabolizers are known
8. Methotrexate: long-term treatment increases half-life
9. Rifampin: half-life is shorter after repeated administration
10. Valproic acid and antiepileptic drugs: enzyme induction
11. Verapamil: half-life is longer after long-term treatment
12. Warfarin: important differences in the clearance of enantiomers S^- and R^+

Smokers metabolize a wide variety of drugs more rapidly than nonsmokers (theophylline, warfarin, phenacetin, propanolol, caffeine and antipyrine). The pharmaceutical effects of opioids, benzodiazepines and antianginal drugs (nifedipine, atenolol, propanolol) may be reduced. Moreover, in acute or chronic alcoholism, the daily intake of folate in food may be severely restricted, and the enterohepatic cycle of this vitamin may be impaired or may interfere with antifolic chemicals.

The lack of information on the impact of pharmaceutical drugs on the metabolism in workers with exposure to industrial chemicals is obvioulsy linked to the ethical impossibility of testing a new drug in employees during work. The majority of clinical pharmacological data have been obtained from unemployed young volunteers (Gibbins et al. 1976). A similar lack of information on the impact on health risks and biological effects in combined exposure to industrial chemicals, drugs and chemicals used by consumers should lead to the development of a toxicovigilance system among the general population, as a complement to the pharmacovigilance systems already in operation.

2 Conclusion

Life style and the use of pharmaceuticals do not modify external exposure to chemicals. Direct contamination by uptake from hands, cigarettes and food absorbed during work, limited by education at the workplace, may strongly modify the individual uptake. The interindividual variability of this contamination may be very high.

The intraindividual variability in response may be due to important variations of metabolizing enzymes (MEOS for hydroxylation, acetylation and desacetylation enzymes, esterases). This variability may be amplified by alcoholic habits and/or tobacco smoking. There probably exists a genetic tendency to alcohol, tobacco and drug abuse. Great differences exist between individuals in the metabolism of xenobiotics.

The lack of information on the kinetics of industrial chemicals among alcoholics and smokers is almost absolute. The impact of tobacco smoking should be taken into account in the study of long-term exposure to CO, nicotine, PAH and mutagenic metabolities, HCN, amines and Cd and in all causes of chronic bronchopulmonary diseases.

Alcohol consumption has an important impact on hepatic enzymes and may modify the kinetics of solvents and of xenobiotics which are metabolized by the MEOS. It should be taken into account in all studies on the causal relation between work and chronic hepatic and neurological diseases.

Long-term studies on the biological effects of the very frequent alcohol-tobacco association are necessary. To date, the effects of pharmaceuticals on the toxicokinetics of alcohol and nicotine (and vice versa) are poorly recognized, and the choice of some experimental models could be useful.

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Variability in Toxicokinetics in Exposure to Solvents

J. J. G. Opdam

1 Introduction

Development of biological monitoring (BM) methods for solvents is mainly based upon field studies. These field studies have shown a lack of fundamental knowledge of individual kinetics; at the same level of exposure, the measured biological parameters, e.g. the level of solvent/metabolite in exhaled air, blood and urine, show inter- as well as intraindividual variability which cannot be explained.

There is still a lack of knowledge about (a) the magnitude of the inter- and intraindividual variation in kinetics; (b) the extent to which biological factors such as fat volume, age or hepatic clearance do have an impact upon the kinetics; and (c) the extent to which these factors are interrelated in the impact on the kinetics of an active solvent or metabolite. It is known from pharmacology that for most drugs the free drug serum level-effect relation closely corresponds with the drug target organ level-effect relation. Furthermore, the interindividual variability in the external dose-effect relation is much greater than that in the free drug serum level-effect relation for therapeutic and toxic effects (Koch-Weser 1975).

In the first part of this paper, the complexity of apparently simple variables such as body fat and age will be emphasized. In the second part, it will be emphasized that a true individual appraoch starts in the laboratory with the aid of physiologically realistic models.

2 Experimental Data

2.1 Exposure Experiments

In the literature, the individual time courses are hardly emphasized, as some examples illustrate. During the 47-h postexposure period after 6 h exposure to styrene, the intersubject variation of four subjects showed a 95% confidence interval within a four fold range of the styrene blood concentration. The elimination half-time ($t_{1/2}$) was 13 ± 0.7 h (Ramsey and Young 1978). In a recent paper (Löf et al. 1986), the concentrations of styrene and the nonconjugated styrene glycol in blood were measured for two groups: preexposed workers (n = 7) and nonpreexposed volunteers (n = 7). In both groups, the 95% confidence interval for intersubject variation was within a four fold range. In the first hour post exposure, the styrene glycol concentrations were within a seven fold range; beyond this hour, the intersubject variation decreased to a four fold

range. During the first 2 h post exposure, both styrene and styrene glycol were eliminated faster in the preexposed workers; the concentrations were about 30% lower.

Experiments with 4-h exposure (n = 6) to 1,1,1-trichloroethane yielded a four fold 95% confidence interval of the postexposure concentration of the solvent (up to 150 h), of trichloroethanol (up to 24 h) and of trichloroacetic acid (up to 150 h) (Monster et al. 1979).

The difference in kinetics between men and women was studied for solvents such as toluene, acetone and trichloroethene (Nomiyama and Nomiyama 1974). During the postexposure period of 5 h, the average time courses of the sexes were parallel, but those of the women were lower. The reason was not explained. It may be suggested that the women had a lower uptake due to a lower minute volume ventilation, or that they had a larger fatty distribution volume.

Blood ethanol and acetaldehyde were compared in male and female subjects (n = 20) after an intravenous infusion of ethanol for a duration of 75 min (Arthur et al. 1984). After the infusion was completed, females had a significantly higher ethanol concentration in blood than males. There was no difference in elimination rate. For both sexes, the 95% confidence interval was about a four fold range. Acetaldehyde was significantly lower in females than in males. For both sexes, the 95% confidence interval of the acetaldehyde level was about a ten fold range. The differences were explained by a sex difference in the metabolism of acetaldehyde by the liver. In the experiments, the subjects seem to have a parallel time course within the confidence interval; however, the true courses are not shown, thus the individual half-times may be quite different.

In our experiments (Opdam and Smolders 1988), six subjects (three males and three females) were exposed two or three times simultaneously to tetrachloroethene (PER) and trichloroethene (TRI). The individual concentration/time profiles were determined by means of alveolar sampling. The sampling method has been described in detail (Opdam and Smolders 1986). The duration of exposure was about 1 h, the postexposure period for PER 350 h and for TRI 100–160 h. For both TRI and PER, the intersubject variation in the solvent concentration was within a two fold range. However, one male subject showed a lower concentration: for TRI beyond 20 h, the concentration became ten fold lower, and for PER beyond 140 h about four fold lower. The intraindividual variation was studied with data obtained from two or three exposures; the intraindividual variation of PER concentration during the whole postexposure period was within 10%–20%. For TRI, some subjects showed a small intraindividual variation ($\simeq$ 10%), while for some subjects a 50% variation was found.

A number of elegant exposure experiments with lipophilic solvents have been published. Some general conclusions are:

1. The uptake during exposure is somewhat higher in obese subjects than in slim subjects.
2. At the end of exposure and during the first postexposure period, the concentration in blood is lower and the decline is more rapid in obese subjects.
3. In the later postexposure period, the decline is slower and the concentration in blood tends to be higher in obese than in slim subjects.

It is interesting that for toluene for example, the half-life in subcutaneous adipose tissue seems to increase with an increasing amount of body fat. A decreasing concentration of toluene in adipose tissue with an increasing degree of obesity was also found. This was explained by the fact that the blood perfusion in subcutaneous adipose tissue declines with increasing subcutaneous thickness. Hence the estimated amount of toluene in the total adipose tissue was higher in the obese people (Carlsson and Ljungquist 1982). Another experimental study with toluene showed that the uptake rate was not significantly influenced by the amount of body fat (Veulemans and Masschelein 1978).

In general, some comments should be mentioned: (a) for some solvents, the postexposure period did not exceed 24 h and (b) the number of subjects was small, and they were healthy and young; solvent studies on aging subjects were not found.

In conclusion, exposure experiments with human subjects show an intersubject variation in blood concentration with a 95% confidence interval with a magnitude of about a four fold range. The fat volume may be a source of the variation, but to what extent is not clear. Also, any relation between the rate of metabolism and fat volume cannot be quantified. The intersubject variation might be larger in a population aged 20–65 years.

2.2 Age and Kinetics

Age as a variable is rather complicated because chronological age may not necessarily correspond to physiological age. An increased biological variation may be a characteristic of older people (Vestal and Wood 1980).

A number of physiological changes in man are known which occur with aging and which contribute to alterations in kinetics. They include an increase of relative body fat and a reduction of lean body mass, total body water, serum albumin concentrations, liver mass, cardiac output and apparent liver blood flow, renal plasma and glomerular filtration rate. For example, in a subject aged 65, the hepatic blood flow may be reduced by up to 40%–45% compared with a subject aged 25. This decline is partially the result of the decline in cardiac output. For compounds with high hepatic extraction ratios, one might predict an effect of age on hepatic drug clearance. Furthermore, the glomerular filtration rate may fall by about 30%, and the age-related decline of renal plasma flow is about 50%. A higher blood pressure may affect the ratio between the glomerular filtration rate and the renal plasma flow. The changes produced by age in hepatic and renal clearance affect the rate of formation and the rate of elimination of metabolites. Therefore, the metabolite concentration/time profile may be age related and thus will become obvious when measuring the concentration in blood. Excreted metabolites in urine collected over one 4-h period, for example, will probably not reflect the intersubject variation with sufficient accuracy; urine gives an integrated measure.

Studies on experimental animals have demonstrated reduced activity of liver microsomal enzymes with aging. There is also some evidence that the aging process in man may result in alteration of the intrinsic metabolic capacity of the liver for some drugs. For example, several authors observed that the half-life in blood of the low-clearance

model compound antipyrine was 45% longer in elderly subjects (aged 70–100 years) than in young subjects (aged 20–40 years). Furthermore, the age-related decrement in antipyrine metabolism was greater in men than in women, emphasizing the need for sex stratification in pharmacokinetic studies of old age. On the other hand, in one study the intersubject variation exceeded the effect of age, and only 3% of the variance in metabolic clearance could be explained by age alone.

2.3 Prediction

2.3.1 Solvents

Some elegant simulation models have been developed (Fiserova-Bergerova 1985). These models are useful in predicting a concentration/time profile of a solvent or metabolite by means of changing physiological variables. However, for a true "individualization", these models have their limitations. Some simple predictions can be made regarding the impact of hepatic and pulmonary clearance on the intra- and intersubject variation of the solvent concentration/time profile. A solvent will be eliminated by respiratory excretion and/or by biotransformation mainly in the liver but probably also in other tissues, e.g. lungs and kidneys. The respiratory excretion depends upon the blood/air partition coefficient (λ) and the alveolar ventilation. The total systemic clearance and the distribution volume determine the elimination $t_{1/2}$ in blood. For solvents with a low λ (<10), the respiratory excretion may be substantial. For high biotransformed solvents, changes in biotransformation hardly affect the $t_{1/2}$; for low biotransformed solvents, changes in biotransformation have only a minor effect on $t_{1/2}$. For solvents with a high λ ($\gg 10$), the respiratory excretion may be low. For high biotransformed solvents, changes in biotransformation have a minor effect on $t_{1/2}$, but for low biotransformed solvents the changes in biotransformation do indeed affect $t_{1/2}$. In conclusion, intra- and intersubject variation in the solvent time course can be expected from changes in the respiratory excretion and the rate of biotransformation; the relative impacts depend upon the solubility of the solvent.

For example, simulations by Fiserova-Bergerova (1985) show that for TRI (λ = 10), the difference between zero and normal biotransformation yields only a 25% change in the elimination $t_{1/2}$; 50 W physical activity during the period of desaturation will shorten the $t_{1/2}$ by about 75%. An unknown minute volume of ventilation may strongly affect the concentration/time profile. This profile provides only minor information about the changes in hepatic clearance and consequently about the rate of formation and the kinetics of the metabolites. The solvent concentration in blood seems only of primary interest if it is the acutal toxic agent.

2.3.2 Metabolites

Intra- and intersubject variation in the level and time course of the metabolite depends upon the rate of formation and the kinetics (i.e. distribution and elimination). A change in the rate of formation or differences in the ratio of formation of two or more metabolites directly affect the levels. Elimination mostly occurs through the kidneys. The

three mechanisms of renal clearance are glomerular filtration, active and passive tubular transport. Renal clearance is a flow-limited process, and the numerical value of the clearance cannot be greater than the renal blood flow but can be any value between that and zero. The renal plasma flow (600 ml/min) includes the glomerular filtration rate (150 ml/min).

Intersubject variation in the rate of formation and in the kinetics of metabolites may be large. To take an example from a review paper by Calabrese (1985), debrisoquine, an antidepressive drug, has a range of oxidative metabolism of up to 20000-fold, but the majority (75%) falls within a ten fold range.

3 Discussion

The intra- and intersubject variation in the solvent concentration/time profile can be strongly affected by differences in respiratory uptake and excretion due to physical activity, for example. For metabolites, the relative magnitude of the contribution to the intra- and intersubject variation made by both the rate of biotransformation and of metabolite elimination (e.g. renal clearance) is not clear; however, they might both be of significant magnitude.

In pharmacology, rational drug therapy demands that the extensive interindividual variations in rate of drug elimination be considered in arriving at the right dose for each patient – individualization of drug therapy. Also, the investigation of sources of interindividual variation in drug disposition has become an independent new area of research. The study of toxicokinetics and of the magnitude and sources of intra- and intersubject variations will be a great help for BM in occupational practice.

In this respect, it is helpful to consider solvents and metabolites separately. The time course and the level of the solvent (together the concentration/time profile) are determined by (a) the solvent kinetics and (b) the rate of respiratory or dermal input (milligrammes per minute) respectively. The metabolite concentration/time profile is determined by metabolite kinetics (distribution and, for example, renal and metabolic clearance) and the rate of formation (rate of metabolic input). If should be noted that in this context, the rate of metabolite formation is proportional or equal to the hepatic excretion rate of the parent solvent. At the same rate of input, any intra- and intersubject variation in the time course is due to variability in kinetics and vice versa.

The magnitude of intra- and intersubject variations in kinetics in a population of men and women aged from 20 to 65 years becomes obvious if one compares the concentration/time profiles as a whole of both the solvent and the metabolites at an equal rate of input. This includes study of the variations in (a) solvent concentration/time profile in blood at an equal rate of solvent input and (b) metabolite concentration/time profile in blood at an equal rate of solvent input and equal rate of metabolite input.

Such experiments yield individual kinetic characteristics which completely imply all interrelating variables such as fat volume, age and nutritional and environmental factors. In the following, the usefulness of the individual characteristics will be described. Furthermore, the dependence of hepatic clearance upon metabolic enzyme activity and liver blood flow will be described as an example of a study of the sources of variation.

3.1 Physiological Models

In the past, pharmacokinetic experimental data have frequently been interpreted by compartmental analysis and usually according to linear kinetics. These models were sometimes applied to problems in industrial toxicology. The redundancy and limitations of the use of these models in most kinetics problems have been shown (Wagner 1975). In recent years, model-independent physiological approaches have been used which allow more realistic physiological predictions.

The theory of linear dynamic systems deals with the relation between the input (rate of intake) and the output (concentration/time profile of solvent or metabolite). This relation is a transfer function. When two of the three (input, output and transfer function) are known, the third can be calculated with a suitable method of convolution and deconvolution.

The transfer function is an individual characteristic and implies the complete kinetics of a solvent or metabolite in the body. The movement of the individual molecules through the body is governed by probability, since they will not all be metabolized or excreted at the same time. The time course of the plasma concentration following a single dose (i.e. transfer function) can be regarded as a statistical distribution curve. Analysis of the distribution curve can be made by use of the method of statistical moments: the area under the curve (AUC), the mean residence time of the intact molecules (MRT) and the variance of the MRT are the zero, first and second moments respectively (Yamaoka et al. 1978). The MRT can be defined as the mean time for the intact molecules to transit through the body; it involves a composite of all kinetic processes.

The statistical moments offer the advantage of showing clearly the overall properties of the time course because these moments can be calculated by simple numerical integration of experimental data without an arbitrary pharmacokinetic model.

In order to characterize the intra- and interindividual variations in kinetics, the use of the statistical moments can be helpful. In fact, in contrast with the $t_{1/2}$, the MRT of a solvent or metabolite depends upon the whole concentration/time profile. The first three moments appear to be quite suitable for characterizing the complete individual kinetics of a solvent or a metabolite.

3.2 Intra- and Interindividual variability due to Hepatic Enzyme Activity

The intra- and intersubject variations in hepatic enzyme activity are due not merely to genetic properties but also to enzyme induction or inhibition, competition and disease states.

To study these variations in hepatic enzyme activity by means of blood concentrations, the solvent concentration/time profile must be sensitive to changes in the enzyme activity. In principle, the intrinsic clearance is the only parameter that reflects the enzyme activity: it indicates the maximal ability of the liver to remove a compound in the absence of flow limitation.

The hepatic clearance – that is, the volume of blood cleared per minute – depends upon liver blood flow (Q) and the intrinsic clearance (CL_{int}). In a physiological approach

to hepatic drug clearance by Wilkinson and Shand (1975), it was made clear that the AUC and/or the elimination $t_{1/2}$ are of importance for assessing the intra- and interindividual variation in liver enzyme activity. For a compound with a low intrinsic clearance ($CL_{int} \ll Q$), the hepatic clearance does not depend on liver blood flow. The $t_{1/2}$ in blood will be independent of changes in liver blood flow but highly sensitive to the liver's ability to metabolize. An example of this type is antipyrine. For compounds with a high intrinsic clearance, the hepatic clearance and $t_{1/2}$ in blood will predominantly reflect liver flow rather than metabolizing capacity. Such a compound will exhibit significant presystemic hepatic clearance after an oral dose, and the AUC of the compound in blood will reflect variations in the intrinsic clearance.

In conclusion, in order to study differences in the metabolizing activity, the use of the $t_{1/2}$ after an intravenous injection or pulmonary exposure is only appropriate for solvents with a low intrinsic clearance. For solvents with a high intrinsic clearance, oral administration and AUC are preferred. For example, to investigate intra- or intersubject differences in the metabolic enzyme activity of a high-clearance solvent such as TRI, the fraction metabolized of the dose in exposure experiments is not sensitive; oral administration is required.

The magnitude of intraindividual variation in the kinetics caused by enzyme activity depends upon the drug or solvent. In our experiments with simultaneous exposure to TRI and PER and simultaneous alveolar sampling of TRI and PER, the residual error of the sample points around the postexposure fitted line equals about 11% for TRI and 7% for PER (Opdam and Smolders 1988). TRI and PER have a high and low intrinsic clearance respectively, and, therefore, the intrasubject variation of TRI around the fitted curve can probably be explained by variation in the liver blood flow and not by variation in the enzyme activity. On the other hand, any physical activity may affect the time course of TRI to a larger extent than that of PER.

4 Conclusions

In the literature, experiments have been carried out with young and healthy subjects, and in addition the number of subjects was mostly very limited; increased biological variation has been avoided.

Physiological simulation models might be suited to predict with some error the concentration/time profile for the majority of subjects. However, the minority calls for a true kinetic individualization for both solvents and metabolites, which cannot be achieved by just changing some simple variables in a simulation model.

Knowledge is needed about the magnitude of the intra- and intersubject variation in the kinetics of solvents and of metabolites. Controlled experiments have to be carried out with arbitrarily selected male and female subjects aged 20–65 years. A relevant biological variation will be reflected in the individual characteristic transfer function of the solvent and of the metabolites and quantified by means of parameters such as $t_{1/2}$ and statistical moments. In this way, the magnitude of the intra- and intersubject variation in kinetics will be known.

Furthermore, knowledge can be obtained on the sources of the variations by appropriate methods to investigate hepatic or renal clearance. The time courses of metaboli-

tes in blood and urine are important. The design of the experiments depends on the solvent or metabolite.

In this experimental field, the theoretical knowledge and experience from clinical pharmacokinetics is of great value. In achieving an optimal clinical response, under- and overdosing have to be avoided. With regard to overdosing, toxicokinetics and pharmacokinetics are expected to handle the same problems. Furthermore, both toxico- and pharmacokinetics have to extrapolate their results in the laboratory to the field situation, i.e. to exposure of a variable population.

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Variability in Toxicokinetics in Exposure to Metals

T. Norseth

1 Introduction

Even if the main objective of this paper is to discuss the variability in toxicokinetics of metals in relation to metal speciation, age and sex, a number of other sources of variation may be of importance for occupational practice. Factors causing variability in the utilization and effects of essential metals are not discussed in this paper. A sometimes difficult descrimination in favour of occupational factors should be borne in mind.

2 Host Factors

2.1 Age

Age seems to be a minor interacting factor in metal toxicokinetics from the occupational health point of view. Increased risk has been claimed for young children and for the elderly, both being outside the usual working age. So far, data are available only for young animals and children, whereas data on the elderly are still lacking. Age-related reference values may have to be taken into consideration, e.g. for cadmium.

Prenatal and neonatal exposure may relate significantly to occupation. Increased values for lead in blood up to toxic levels have been demonstrated in children of fathers occupationally exposed to lead. Prenatal exposure to lead has been suggested to cause mental retardation (Sager et al. 1986), and prenatal exposure to methyl mercury may cause a generalized brain damage (Amin-Zaki et al. 1974a). Postnatal accumulation of methyl mercury from mothers' milk has been described as causing delays in motor and speech development in children (Amin-Zaki et al. 1974b). The exposure was not occupational in any of these examples.

Experimental data for prenatal and postnatal exposure have in particular been described for lead and methyl mercury but can be found for a number of metals. For many metals, but in particular for lead, an increased uptake is found during the period of milk diet (Kostial et al. 1978). Interaction with a number of trace metals on absorbtion has been described (Tsuchiya and Iwao 1978). For methyl mercury, a high retention in the postnatal animal may be related to a decreased biliary excretion and to different biotransformation with a decreased rate of demethylation.

Risk assessment during working age should take into consideration that toxic effects may first be demonstrated at a later age. This is typically demonstrated for cancer. The relationship between dose, latency time and development of cancer is not clear, nor

whether older people are more susceptible than the young. The question whether metals may be important for other diseases in old age such as dementia has been discussed in relation to aluminium and lead, but no definite answers can be given. Some metals, such as lead or cadmium, are, however, deposited with age in certain organs.

In conclusion, age seems to be of limited importance as a source of variation for the toxicokinetics of metals during the period of active working life, but age factors may be important and indirectly related to the duration of occupational exposure.

2.2 Sex

Sex differences in metal toxicology can be discussed from three different aspects. When women are referred to as a high-risk group, it is most often meant that exposure of pregnant women results in exposure of the fetus. This is probably the most important aspect. Another is possible effects on the male and female reproductive system, and finally we have a possiblity of other unspecified sex-related differences.

Prenatal and postnatal exposure have been discussed to some extent in the previous section. Interference with the reproductive system may involve a direct action on the organs, but indirect hormonal disturbances may also be important. Decreased fertility associated with oligospermia, teratospermia and asthenospermia has been described in lead workers, and historically stillbirths and abortions have been reported in heavily exposed women (Sager et al. 1986). More recently, abortions and decreased fertility have been suggested in women exposed to a mixture of metals including lead. Corresponding effects have been demonstrated experimentally for both lead and cadmium. Hormonal mechanisms have been discussed in connection with the suggested risk of prostate cancer with cadmium exposure, but supporting data are limited (Piscator 1981).

Differences in the toxicokinetics of metals related to size and fat distribution may be unspecifically sex related but have not been systematically described. Females seem to be more sensitive than males for effects of lead, based on free erythrocyte protoporphyrin (FEP) and δ-aminolaevulinic acid (ALA-U) in urine after exposure. This may be of importance when evaluating the effects of lead exposure (Tsuchiya 1986).

In conclusion, sex seems to be of limited importance for variation in the toxicokinetics of metal exposure except for prenatal and postnatal exposure and effects on sex-specific organs.

2.3 Organ Damage

Few data exist on the impact of impaired organ function on the toxicokinetics of metals. Theoretically, uptake, metabolism/distribution and excretion, as well as target site reaction, may be influenced.

Thus far, the most important reports from the practical occupational health point of view are the increased excretion of cadmium in urine after cadmium-induced kidney damage (Friberg et al. 1986). Less documented is a relative increase in chromium excretion with increasing chromate exposure, even if chromates are known to produce

kidney impairment (Mutti et al. 1979). As renal handling of metals depends on glomerular function and tubular function, any change in these may influence distribution or excretion of metals. The acid-base equilibrium may also have such an effect.

The increased uptake of lead in smoking lead workers compared with nonsmokers is probably related to external contamination of hands and fingers and not to lung impairment; even so, working habits and contamination are factors which should be taken into consideration with metal exposure (Tola and Nordman 1977). Altered particle deposition and clearance in the respiratory tract may theoretically cause variability in kinetics, but no data have been found for metals. Such effects may be caused both by lung diseases and by mixed exposure to irritant gases.

Diseases of the gastrointestinal tract influence metal absorption, as documented for iron in the malabsorption syndrome. A direct effect on the mucous membrane is possible, but the mechanism may also include interrupted enterohepatic circulation or changed biotransformation, as for methyl mercury. There is a complicated interrelationship between the absorption of different essential and nonessential metals, but these interactions seem to be without practical occupational health implications, Milk (calcium) has, however, been given to lead workers to decrease lead absorption. This is based on the demonstration of a high lead uptake with low calcium, but a correspondingly decreased lead uptake does not seem to occur with high calcium. The high cadmium uptake in Itai-Itai patients seems to be partly related to a simultaneous calcium deficit.

Theoretically, organ impairment may greatly influence the toxicokinetics of metals with occupational exposure, but only few data have been reported. It is possible that the so-called normal variation in uptake, distribution and excretion could to some extent be explained with a more thorough clinical examination.

2.4 Other Factors

A diurnal variation of urinary mercury excretion in persons without occupational exposure has been demonstrated. The mercury excretion oscillated by as much as 25% of the daily mean excretion rate for the individual (Vokac et al. 1980). Even this magnitude of variation should probably disappear in most occupational exposures, but it should be taken into consideration when setting reference values. The circadian rhythm was not influenced by changing the sleep/wake schedule for 2 days. Circadian rhythms have been described for a number of physiological parameters and probably should also exist for metals other than mercury.

It is well known that immunological factors influence dose-effect and dose-response for many metals and may change the susceptibility to cancer, but whether the toxicokinetics of metals is influenced is not known. Immunological and hypersensitivity factors are, however, important for the practical occupational health evaluation of exposure to metals.

3 External Factors

3.1 Metal Speciation

Different kinetics for species of the same metal is by far the most important source of variability in metal toxicokinetics. Speciation must be taken into consideration for uptake, distribution, biotransformation and excretion. In addition, speciation is an important problem for the analytical chemist.

Single metals relevant for occupational health may behave differently depending on different valencies. Organic compounds defined by a covalent carbon-to-metal bond usually behave differently from inorganic salts or the metal itself; inorganic salts may have different solubility. It is important to note that water or buffer solubility may not be representative for the solubility in biological fluids with an abundance of chelating ligands. Metals are often found as particles in the occupational environment, and even particles of the same chemical species may have different effects, based on physical properties such as crystal modification or surface charge. Metals may also be found in gaseous form in the occupational environment.

The toxicology of chromium and nickel presents interesting problems related to valency, solubility of inorganic salts and particle physics. For a long time, trivalent chromium has been assumed to be the carcinogenic agent in exposure to chromates. Chromium in the trivalent form only passes the cell membrane to a very limited degree, whereas the chromate ion is readily taken up by cells and rapidly reduced to the trivalent form inside the cell. Recent results have, however, indicated that even if trivalent chromium can be introduced into the cell, DNA lesions comparable to those caused by the hexavalent form presumably after reduction could not be demonstrated. These results indicate that some short-lived compound, probably a penta- or tetravalent form, is responsible for the effect (Norseth 1986a).

For both nickel and chromium, only slightly soluble particles (in buffer solutions) seem to cause cancer in occupational exposure, while the soluble salts of hexavalent chromium, but not of nickel, cause bacterial mutations. Salts of both metals cause cellular transformation in vitro. This problem is probably related to the microkinetics of metals in the cells. A sufficiently high concentration of metal in the cell can only be reached by phagocytosis of a particle, with subsequent dissolution inside the cell. The physiochemical properties of the particle in question in the respiratory tract then become important. Soluble particles are dissolved before phagocytosis can take place. This theory is supported by data which indicate that nickel oxide particles with different surface properties have different effects in vivo in cell transformation systems. A correlation was demonstrated between degree of phagocytosis and effect. It is important to note also that the degree of phagocytosis did not correlate to the solubility of the particles in water or inorganic buffer solutions. To complicate this picture, even trivalent chromium has been demonstrated to cause cytotoxic and mutagenic effects after in vivo phagocytosis of particles (Norseth 1986b).

Variable kinetics of organic and inorganic compounds of the same metals can be demonstrated for lead, mercury, arsenic and tin. I shall give some comments on mercury because the stability of the carbon-to-mercury bond in methyl mercury induces a highly different kinetics, and because metallic mercury in vapour form also demon-

strates a problem. Methyl mercury has a long biological half-life compared with inorganic mercury and is predominantly excreted in faeces, while inorganic mercury is excreted in the urine. The importance for occupational health practice is evident. Other organic mercury compounds are less stable (methoxyethyl mercury, phenyl mercury). It is also important to note that when inhaled, vapour of metallic mercury is not immediately oxidized to mercuric mercury, but can be taken up by the central nervous system as such, with subsequent oxidation. This causes a higher concentration than after exposure to mercuric mercury. The oxidation which also takes place in blood can be delayed by simultenous exposure to alcohol, and such combined exposure delays uptake (Nielsen Kudsk 1965).

Stibine and arsine are other examples of volatile metal compounds, but different kinetics compared with inorganic salts can be more easily understood for these than for mercury vapour.

3.2 Mixed Exposure

Mixed exposure is the rule rather than the exception in the occupational setting. The practical importance of such exposure for metal toxicokinetics seems to be limited. The mixed exposure to alcohol and elemental mercury has been mentioned, but the alcohol exposure is probably most often nonoccupational. Interaction between metals on intenstinal absorption, specifically the calcium-iron interaction, has also been mentioned, as well as the problem of nutritional interactions on the essential metals level.

The interaction between some metals – mercury and cadmium – and selenium has been specifically studied and may have occupational health implications. Selenium seems to protect experimental animals against effects of mercury and cadmium by formation of selenosulfide complexes with low reactivity. Practical applications have not been demonstrated in occupational health, but they have been discussed in relation to uptake of methyl mercury from the food chain as a general population problem (Nordberg 1978).

A specific case of mixed exposure is exposure which induces synthesis of metal-binding proteins. The occupational health significance of such induction is uncertain. Cadmium, for example, induces synthesis of metallothionein, which in turn binds increased amounts of cadmium and thus protects toxicologically critical binding sites. The amount of metallothionein also depends on the amount of zinc in the cells, and other metals such as mercury may also be involved (Nordberg et al. 1986). Some gold complexes also induce metallothionein. Such induction has been discussed as a possible meachnism for development of resistance in patients treated for rheumatoid disease with gold (Glennås and Rugstad 1985).

3.3 Other External Factors

Diet, drugs and smoking are other external factors which should be discussed in relation to variability of toxicokinetics of metals. Some possible examples of the influence of diet and smoking have already been mentioned. Dietary variation may influence

biological samples, as for arsenic (organic arsenicals in seafood), but as a source for kinetic variation – except on the trace metal levels – it is probably unimportant. Alcohol as a part of the diet has been mentioned and should also, in extreme forms in alcoholics, be of general interest because of liver disease and deficit of sulphur containing essential amino acids and vitamins. No relevant examples have been found for occupational health.

Some drugs such as oral contraceptives and antihypertensives are taken by a large number of the population and may be important. Alterations in trace metal metabolism have been described in consumers. Such drugs are probably without significance for occupational exposure to metals. Diethyldithiocarbamate, a metabolite of disulfiram used for treatment of alcoholism, increases nickel excretion and influences the distribution of lead and mercury. Thiocarbamates are also used as pesticides, but the effect of such exposure on agricultural workers or from eating contaminated food is not known. Other chelating agents such as nitrilotriacetic acid (phosphate substitute in detergents) can also be found in the environment. Even if no effects of such exposures have been demonstrated, influences on trace metal metabolism in particular should be discussed when approval for use is given. Working in hot environments may influence metal toxicokinetics; for example, high nickel concentrations can be demonstrated in sweat.

4 Conclusions

Metal speciation is at present the most important single factor for variability of the toxicokinetics of a single metal. Sex and age are important in relation to prenatal and postnatal exposure. A number of other factors have been discussed, but these seem at present, except in specific cases, to be of limited importance for occupational exposure. For trace metal metabolism, however, these factors may be important.

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Screening Models in Occupational Health Practice for Assessment of Individual Exposure and Health Risk by Means of Biological Monitoring in Exposure to Solvents

A. C. Monster and J. J. van Hemmen

1 Introduction

In routine occupational health surveillance, both the occupational hygienist and the occupational physician usually assess (individual) exposure and health risks from group data (e.g. mean, median). It is well known that the actual individual exposure and health risk may differ considerably from the mean.

In the case of systemic effects, the level of a toxic agent in biological specimens will, at least in theory, be more indicative of actual internal exposure – and consequently of the health risk – than the level of external exposure as measured in the breathing zone of the worker. To date, the health risk has usually been estimated directly from the levels of external exposure on the basis of epidemiological studies. The biological limits of occupational exposure are usually estimated from the relationship between parameters of external and of internal exposure.

However, in order for these limits to be meaningful, the relationship between external exposure, internal exposure and (adverse) response should be known. Both the effector/target organ and the physicochemical and toxicokinetic and -dynamic characteristics of the chemical (solvent, metabolites, intermediates, specified effects) should have been established. These data are – if available – usually obtained from animal experiments. Human data may be obtained from controlled experiments with oral or respiratory exposure, from field studies or from clinical intoxications. However, for most chemicals such data are scarce. It should be noted that often in modern industry, with rather low exposure levels, dose-effect/response relationships can hardly be obtained any longer.

In this paper, we discuss factors and variables that are relevant for the assessment of internal exposure of solvents by means of biological monitoring (BM), with due attention to interindividual variability.

2 Individual Variability in Uptake and Metabolism

It should be emphasized that in practice, BM is meant to estimate both the external exposure and the potential health risk on the basis of levels of chemical agents and/or their metabolites in biological specimens. For several chemicals, there is some evidence that BM methods may be useful for detecting an excessive internal dose on an individual or group basis, although they are mostly based on the relationship between external and internal exposure (Lauwerys 1983).

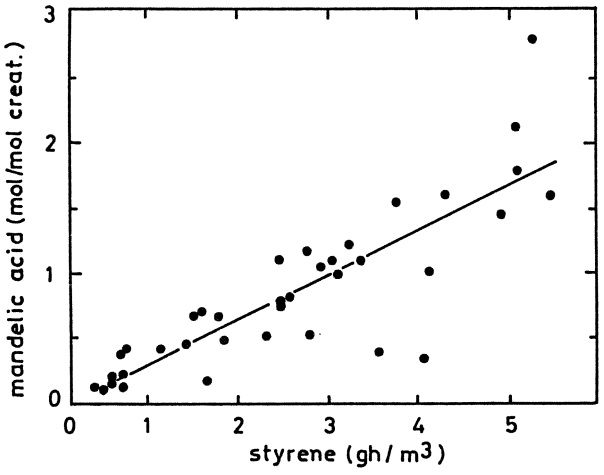

Fig. 1. The relation between (average airborne exposure to styrene, gram/m^3) x (exposure time, h) and the amount of mandelic acid in urine (mol/mol creatinine) collected at the end of the shift (data from 39 workers). (From Van Hemmen and De Mik 1987)

Figure 1 (Van Hemmen and De Mik 1987) shows as an example the relation between (exposure to styrene) x (duration of exposure) and the concentration of mandelic acid in urine collected at the end of the shift. The estimate of internal exposure at an exposure level of 100 ppm/8 h is 1.12 mol/mol creatinine with a range of 0.44–1.80 mol/mol creatinine.

The large interindividual variation of mandelic acid excretion in urine in workers with about the same external exposure to styrene is not specific for that solvent. The variation may result from the following factors:

1. The amount of solvent inhaled by each worker depends to a large extent on his *physical workload.* However, measurement of pulmonary ventilation during a whole work shift is not feasible in practice. It may suffice to take samples at random, albeit only when the work load is well defined and reasonably stable. Indirect measurements such as the rather simple heart rate measurements, movement and acceleration meters or time and movement studies are all more or less deficient for estimation of pulmonary ventilation. Particularly when the heart rate is below 100 beats per minute, many factors such as drinking coffee, smoking and stress have an impact on the heart rate. When both pulmonary ventilation and the concentration in inhaled air fluctuate, one can achieve a realistic estimate of the intake only when both are measured simultaneously. This is particularly important when the highest workload and highest concentrations coincide.
2. Furthermore, the amount of styrene absorbed by the body is influenced by *retention* (Engström et al. 1978), which may differ slightly between persons, probably in relation to the levels of, for example, lipids, proteins in blood, blood flow to tissues and tissue content (fat, muscles). As shown by Droz and Guillemin (1983) and Åstrand et al. (1974), pulmonary ventilation is directly related to the uptake of styrene. For solvents with a smaller solubility in blood and with less biotransformation, retention decreases as the duration of exposure increases.
3. *Personal behaviour,* such as holding one's breath near points of high concentrations of solvents, may be important.

4. A factor that may be important for many compounds is *dermal absorption* through the skin (hand-washing with solvents). In practice, this is relatively unimportant for styrene, but it may be very important for water-/lipid-soluble solvents such as dimethyl formamide (Lauwerys et al. 1980). The uptake through the skin also depends on the individual condition of the skin (thickness, chaps) (Stewart and Dodd 1964).
5. *Nonoccupational intake* of solvents and metabolites (e.g. from paint, glues, drugs, food) increases the levels of solvents or metabolites in biological media. The metabolites hippuric acid and 0-cresol occur in urine of subjects who are not occupationally exposed to toluene, and the metabolite phenol is present in urine of subjects not exposed to benzene or phenol. In this case, comparison of the concentration in pre- and postshift samples may be useful because in nonexposed controls there are usually no significant differences between the concentrations in morning and afternoon samples, at least when no other occupational or nonoccupational exposure exists, e.g. phenol excretion due to drugs.
6. There exists a considerable interindividual variation in the *capacity to metabolize* foreign substance. In exposure to methyl chloride, the findings strongly suggest the existence of two populations: a minority of "poor converters" and a majority of "converters" (low blood concentration, high excretion of metabolite in urine) (van Doorn et al. 1980; Putz-Anderson et al. 1981). It is not yet clear whether the difference in metabolism indicates a difference in health risk.

Substantial evidence indicates that the human variation in metabolism of various xenobiotics may grossly exceed a factor of 10 (Calabrese 1985). This may be particularly important in exposure to solvents which are hardly metabolized and less so for (the metabolites of) solvents which are almost totally metabolized, because 95% biotransformation does not differ much from 90% or 100% biotransformation. In addition, consumption of alcohol may inhibit the biotransformation of some solvents (e.g. trichloroethene, toluene and styrene) to a large extent. This may also be true for combined exposure to some solvents. Moreover, the biological half-time and excretion velocities of metabolites also show an interindividual variability.

3 Urinary Excretion

Possibilities to take the individual kinetic differences in urinary excretion, at least partly, into account are:

1. Sampling urine over a long period, preferably over 24 h, which is usually not feasible in practice. This should diminish interindividual variation in urinary levels due to variations in exposure concentrations during work and individual variations in excretion velocity.
2. Frequent sampling of urine during and after the work shift. This should emphasize some individual differences in kinetics, such as slow or fast excretion.
3. Frequent sampling of both solvent and metabolites in several biological specimens (urine, blood and exhaled air). This should give a more or less complete picture of

the differences in individual metabolic capacity and excretion rates, but it is very laborious.

After experimental exposure of six volunteers to trichloroethene (70 ppm, 4 h a day for 5 days), the concentration of trichloroacetic acid (TCA) in blood in one subject was always relatively high, whereas the amount of TCA excreted in urine was always relatively low in comparison with the other five volunteers (Monster et al. 1979). Obviously in this subject, the TCA was more firmly bound to some plasma protein than in the other subjects.

A combination of concentrations of metabolites in urine may sometimes improve the estimate of the (daily) external exposure, e.g. the combination of the metabolites mandelic acid and phenylglyoxylic acid in urine the morning after exposure to styrene. The combination of the concentrations in urine of the metabolites trichloroethanol and TCA after exposure to trichloroethene is not recommended because of the difference in biological half-time (10 h and 100 h respectively); the trichloroethanol level is an indicator for daily exposure, and the level of TCA for long-term (weekly) exposure.

Since the production and excretion of urine largely depends on the concentration capacity of the kidneys and the intake of fluids, the level of most compounds in urine has to be adjusted for the amount of dilution. In practice, various methods have been developed, such as specific gravity, osmolality and creatinine adjustment. The correction for urine dilution by means of the concentration of creatinine is in most cases the best choice. However, the concentration of creatinine in urine also depends on age, sex, muscle mass and food consumption (meat). Very satisfactory results were obtained by Šedivic and Flek (1976) after experimental exposure to xylenes, when the amount of metabolites excreted within a defined time (8 or 24 h) was recalculated according to body weight in kilogrammes. However, for methanol, the retained dose of methanol correlated very well with the concentration of methanol in urine (Šedivic et al. 1981).

Although in the case of trichloroethene and styrene, for example, the urinary levels of metabolites may reflect the time-weighted average (TWA) exposure or external dose, a relation between these levels and health effects does not necessarily exist because the metabolites of solvents excreted are generally conjugated (nontoxic) compounds.

4 Concentrations in Blood

In blood, the solvent and its metabolites are generally in an unbound form and not in the usually nontoxic conjugated form. It is likely that the level of the free (unbound) active chemicals in blood is better related to the toxic (therapeutic) action than to the external dose or to the conjugated amount excreted in urine (Koch-Weser 1975). The concentration in blood reflects the concentration in (target) organs with a high blood flow, such as brain (CNS) and kidneys.

In exposure to trichloroethene (TRI), the Deutsche Forschungsgemeinschaft (DFG) has chosen as biological tolerance value for a working material (BAT value) the concentration of free trichloroethanol (TCE) in blood at the end of the work shift because

the effect on the CNS appears to be mainly due to free TCE. TRI itself appears only to be narcotic at very high concentrations. TCE reaches its maximum concentration in blood almost directly after the end of exposure (in a more or less constant exposure concentration of TRI). The choice of free TCE in blood as BAT value is a good example of a relation between the concentration of the actual toxic agent in blood and in the possible target organ (CNS).

However, this individual BAT value is not based on the individual relationship between the free TCE concentration and the narcotic effect, but on the mean concentration of TCE after exposure to constant concentrations of TRI (Henschler and Lehnert 1983).

Similarly to TRI the biological limit in exposure for more than 3–4 h to dichloromethane (methylene chloride) is based on the toxic action of carbon monoxide (CO), the metabolite of dichloromethane. Dichloromethane only has a narcotic effect in very high concentrations. Because of the $t_{1/2}$ of about 10 h, the carboxyhaemoglobin (COHb) level reaches its maximum within 1 h after the end of exposure. It is more or less proportional to the product of the exposure concentration and the duration of the exposure (as for TCE). However, the no-adverse-effects level of COHb is derived from data on exposure to CO, with a shorter $t_{1/2}$, of about 6 h.

The concentrations of the solvents in blood *during* exposure mainly reflect the external exposure concentration, whereas the concentrations of the solvents the next morning (16 h after exposure) are more related to the (TWA) external exposure and to the total uptake per work shift. After the weekend, the concentration has become proportional to the cumulative concentration in adipose tissue for example. In occupational exposure to tetrachloroethene, the concentrations in blood and exhaled air decrease faster from Friday to Monday in slim subjects than in more obese subjects (Monster et al. 1983). Sato et al. (1975) showed that in rats of both sexes with a large body fat content, benzene was eliminated more slowly and remained in the body for a longer time than in rats with a small body fat content. In accordance with this finding, the decrease in white blood cell numbers during a chronic benzene exposure was observed only in the groups of rats with a large volume of fat tissue. In human volunteer exposure, the elimination of benzene was slower in females than in males. The kinetic study revealed that the slower elimination in the females was primarily due to the higher fat percentage in women (at least on the average).

For tetrachloroethene, a high correlation ($r = 0.976, n = 21$) exists between the individual concentration of tetrachloroethene in blood 15–30 min after the end of the work shift on Friday and the TWA external exposure level over the entire working week (Monster et al. 1983). This can be explained by the accumulation of tetrachloroethene in the body, due to its high solubility in blood and adipose tissue and the almost complete absence of metabolism (<3%). The biological $t_{1/2}$ of tetrachloroethene is about 140 h.

For other solvents, such as 1,1,1-trichloroethane, this relation is much weaker (Monster 1987), probably due to the lower solubility in blood and adipose tissue. For tetrachloroethene and trichloroethane the blood/air and fat/air partition coefficients are 15 and 5 (blood), and 2000 and 360 (fat), respectively. The principal effects of tetrachloroethene and 1,1,1-trichloroethane are the action of the solvent itself on the CNS. However, is the course of the toxic action determined by the concentration as

such or is it the product of concentration and time (during exposure and also after exposure)? The strategy of BM depends on the answer to this question.

5 Concentrations in Exhaled Air and Saliva

In exhaled air, only relatively volatile substances such as the solvents themselves can be measured, but generally no metabolites are found in exhaled air [exception: (free) TCE after exposure to TRI]. The level in alveolar air reflects the concentration in mixed venous blood; therefore, the level in exhaled air is indirectly related to concentrations in the (target) organs with a high blood flow, such as CNS and kidneys. An advantage of sampling exhaled air is that the specimen can be obtained and analyzed relatively easily; however, this only applies for volatile compounds. Saliva is also quite easily obtainable in the occupational setting. It is probably a proper medium for compounds which are not bound to proteins and which are distributed over the total body water content, such as methanol and ethanol.

Droz and Guillemin (1986) observed a strong relationship ($r = 0.956$, $n = 38$) between expired air concentrations on the next morning and exposure to tetrachloroethene (parts per million x hours) for dry-cleaning workers. Such relationships also exist for other solvents. These relationships are important because most of the time the solvents themselves cause the toxic action (e.g. toluene, xylene and styrene), and not the nontoxic conjugated metabolites. Again the question arises, when should we measure these concentrations: during or after exposure, the next morning or after the weekend? At present, however, the required knowledge is lacking for most solvents, at least with regard to the relationship between the level of the toxic compound and the health effects.

6 Discussion and Conclusions

It may be evident that there are hardly any data concerning the relationship between the concentration of the actual toxic compound in the target organ and its health risk. If it is true that the interindividual difference in toxicokinetics is much greater than the variability in response of the target organ, then the measurement strategy of BM should aim to measure or to approximate as much as possible the concentration of the *active compound* in the most feasible biological specimen.

The first choice in BM always remains the active toxic compound (solvent or metabolite) in the target organ. This is because in subjects with the same concentration of the toxic compound in the target organ, the individual differences in uptake, biotransformation, excretion and coexposure are no longer of much consequence – apart from the interindividual variability in response of the target organ. If the relation between an early health risk and a biological measurement of the active toxic compound in the appropriate biological specimen is not yet known, one should try to determine the relationship between the uptake in the body and the concentration of the relevant compound in the biological specimen. This can be done in controlled animal and volunteer experiments. In that case, BM is possible since all relevant data are avialable for

estimation of the internal dose on a group basis. BM should not merely be used to estimate the degree of external exposure, apart from estimating relatively low or high exposure.

Therefore, screening programmes in practice should preferably be based upon measurement of the active toxic compound in blood and the corresponding health risk should be estimated from the (known) relation between the active toxic compound in the appropriate biological medium and the response of the target organ.

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Screening Models in Occupational Health Practice for Assessment of Combined Exposure to Chemicals at Work

G. de Mik, P. Th. Henderson and P. C. Bragt

1 Introduction

In any situation, humans are exposed to a variety of xenobiotic chemicals present in the environment, in food and in drinking water. Also in the occupational environment, most situations involve exposure, not to a single, but to several chemicals. There may be prior, coincidental or successive exposure to a multiplicity of chemicals. The nature and conditions of exposure may lead to a significant alteration of the toxicity of the single chemical components. Even in a workplace situation where only one chemical is handled, combined exposure may occur when workers use drugs, alcohol or tobacco.

Evaluation of health hazards from multiple chemical exposure is much more complex than evaluation of these from single chemicals exposures. Many interactions are possible before and after absorption. Not only chemicals may be involved, but several other environmental factors can play a role in the increase or decrease of health risk (Table 1).

In this brief presentation, only a few factors can be described, particularly chemical factors, which illustrate possibilities for screening models in occupational health practice. In this context, health practice also includes industrial hygiene activities.

2 Nature of Multiple-Exposure Interactions in the Exposure Phase

The working atmosphere may contain gases, vapours, fibres and liquid or solid aerosols. First of all, it is necessary to have data of the exposure pattern. What is the composition of the inhaled air, and what are the fluctuations in the relative concentrations of the individual components? Is it an intermittent or a continuous exposure, and what is its duration?

In occupational exposure, the route of entry is mostly by inhalation or by skin contact. For skin contact, liquids present the greatest hazard. The composition of workplace air may be different from the liquids from which it is produced, so there may be a difference between the hazard after absorption by skin contact and that after absorption by inhalation. Special attention must be paid when heating or combustion is involved in a process, since thermal degradation products of unknown toxicity may be released into the atmosphere (Table 2).

To determine the hazard from mixed exposure, the toxicity data of the single chemicals in question are evaluated using the knowledge of potential interaction. It is important to realize that minor constituents, such as trace additives, contaminants

Table 1. Some examples of environmental factors involved in multiple exposure

Chemical factors	Exposure to various chemicals at the workplace or other places (hobby, drugs, smoking and food additives).
Physical factors	Exposure to heat, radiation and humidity influencing chemical exposures.
Biological factors	Increased risk of infectious disease due to combined exposure to chemicals and micro-organisms.
Psychological factors	Stress may increase biotransformation capacity, the perception of odour, irritation of mucosae.

Table 2. Some examples of interactions in the exposure phase

Photolysis	Degradation products may be either more or less toxic. Methylene chloride, for example, decomposes by the influence of UV light into the highly toxic phosgene.
Photosynthesis	Toxic organic peroxides are formed from carbohydrates, nitrogen oxides and oxygen in the air by the influence of sunlight (photochemical smog).
Pyrolysis	Heat degradation products can be more toxic than the parent compounds (e.g. phosgene, HCl); heat degradation products may rearrange into new toxic substances, e.g. polycyclic aromatic hydrocarbons.
Hydrolysis	Decomposition in water (pH-dependency), esters, amides
Adsorption	Dust or smoke particles are ideal vectors for other substances, for example, facilitating deposition and uptake of radon by the bronchial epithelium.

or residuals from a synthetic process, often have a high toxicity (e.g. benzene in toluene) and may contribute to the health effects.

In summary, the following major considerations should be taken into account in assessing the hazards from the exposure conditions (Ballantyne 1985):

1. Chemicals entering into mixture: chemical nature, chemical reactivity
2. Mixture constituents: chemical properties, physical properties and state, concentrations
3. Exposure characteristics: route of exposure, concentrations, frequency, duration, sequence

Knowledge of each of these factors and its relevance for a special workplace situation is a useful tool in predicting the possible health effects. In view of this, the first priority should be given to research topics that can contribute to monitoring and controlling the environment not only for a single chemical but specially for mixtures of chemicals that are typical for certain industrial processes.

3 Toxicokinetic Interactions

3.1 Interference with Absorption

As stated earlier, the respiratory tract and the skin are the predominant routes of entry in the work environment. Since the rate of absorption through a biological membrane is determined by the physicochemical properties of the chemicals, interactions during the absorptive phase may result in an increase or a decrease of the amount absorbed. The keratin layer of the skin is covered by a film of lipoidal material derived from the sebaceous glands. This surface film provides a barrier in particular for polar chemicals. It is readily removed by several organic solvents. Thus, previous contact with solvents may facilitate the entrance of other chemicals.

It has been recognized that hydration of the horny layer of the skin also accelerates the penetration of several chemicals. Elevation of the ambient temperature results in an increase of percutaneous absorption. This is due to increased sweat production, resulting in a highly hydrated skin. Moreover, elevated temperature also causes hyperemia, with consequent increase in the rate of transport of the penetrated chemical into the blood stream.

Absorption of pesticides through the skin can be enhanced by special formulations. Therefore, it is recommended to carry out the toxicity experiments with the products or formulations as they are used in practice, and not only with analytical grade chemiclas. Special attention should be paid to deviant ambient temperature, humidity and pressure.

3.2 Interference with Distribution

Several factors govern the distribution of absorbed chemicals: blood flow to the tissue, tissue mass, tissue fat content, affinity of the chemical for the tissue, binding to plasma proteins and binding to special carrier proteins. Many examples can be given of interactions of chemicals, for instance by competition for the same binding site in plasma proteins. In this respect, it is recommended to pay special attention to the interaction of work-related chemicals with drugs which have a high protein-binding percentage, since in a normal working population as many as 25% of the workers may use drugs. Many drugs are bound to plasma albumin, and by competing for the same binding site, the drug may displace a chemical. This displacement will increase the plasma concentration of the free form, leading to an increased biological effect. This holds true in particular for those substances that bind to plasma proteins at very high percentages. For instance, the pesticide dieldrin can be bound at about 99% to plasma proteins. If this binding percentage is decreased to, for example, 98% by the presence of a competing drug, the concentration of unbound dieldrin that can reach the target tissue is doubled. Another important feature is that drugs are present in the body in physiologically active concentrations, whereas for chemicals, "effective" concentrations are to be avoided.

The interactions in distribution are widely studied in pharmacology, but not in industrial toxicology. More research is needed, especially for determination of the ratio

between free and bound chemicals in plasma and the influence of other chemicals on this ratio. It is recommended for BM purposes not only to measure the total amount of the chemical(s) in blood but to speciate the freely available and the bound concentrations.

3.3 Interference with Biotransformation

Many chemicals undergo biotransformation by a variety of oxidative, reductive and conjugating mechanisms, such as hydroxylation, dealkylation, deacetylation and conjugation. As the duration of toxicity of a chemical agent depends on the body's effectiveness in transforming and eliminating the chemical, any interaction will lead to a reduction or an increase of toxicity. In the report of a WHO Expert Committee (WHO 1981), a number of examples of industrial chemicals are given. Of special relevance is the chronic use of ethanol, which can enhance the toxicity of several xenobiotics (see Sect. 6.2). On the other hand, various industrial chemicals, including dithiocarbamates, trichloroethylene, calcium cyanamide and dimethylformamide can interfere with the metabolism of ethanol. Combined exposure may cause alcohol intolerance ("Antabuse syndrome").

In recent years, methods have become available to measure certain microsomal enyzme activities, and both stimulation and inhibition have been shown. Together with methods for measuring the chemical or its relevant metabolite, this seems to be an adequate model for predicting (adverse) health effects.

3.4 Interference with Elimination

Apart from biotransformation, elimination is effected mainly by excretion via urine, bile or exhaled air. The most important interaction occurs in renal excretion. It is well known that changes of pH affect excretion. For BM urine sampling is the method predominanty used. It is recommended to measure also pH and density to be aware of deviant values.

Inhaled airborne particulates can be cleared through the mucociliary transport moving the particles form the deeper parts of the respiratory tract to the oral cavity. After being swallowed, they may be excreted. This elimination mechanism can be affected by tobacco smoke, for example, which inhibits the activity of the ciliated epithelial cells.

4 Toxicodynamic Interactions

Toxicodynamic interactions are based on the fact that interference between two or more chemicals occurs at the target or receptor level. In some cases, the susceptibility of the target cells is increased by previous exposure. For instance, exposure of the bronchial epithelia may decrease resistance against infections.

Particular attention should be given to toxicodynamic interactions due to multiple exposure to various types of carcinogens. It is generally assumed that initiator (genotoxic) carcinogens activate oncogens through irreversible DNA modifications. However, this initiation step does not necessarily lead to cellular transformation. Cell transformation can be achieved by the action of promoter substances. Therefore, simultaneous or successive exposures to different types of carcinogens may considerably enhance the carcinogenic risk.

Another example of a toxicodynamic interaction is the potentiation of the anxiolytic action of diazepam in the rat by toluene.

5 Consequences of Toxicological Interactions

Toxicological interactions are based on the fact that the response to two or more chemicals given together or after each other cannot be explained by the action of the single chemicals, but is due to their acting simultaneously. The overall resulting response is classified as synergism, potentiation or antagonism.

The term "synergism" is used in different ways. The word itself simply means "working together" and was originally used to refer to a similar action of two substances when given simultaneously. Nowadays, it is used for the situation in which two chemicals produce a greater effect together than equivalent doses of each given individually. To prevent misunderstanding, the following definitions are given for terms used in this paper to express the possible effects when an organism is exposed simultaneously to a mixture of chemicals:

1. *Independent:* when each chemical produces a different effect owing to a different mode of action
2. *Additive:* when the magnitude of the combined effect is equal to the sum of the effects produced by each chemical separately
3. *Potentiating:* when the magnitude of the combined effect is more than the sum of the effects produced by each chemical separately
4. *Antagonistic:* when the magnitude of the combined effect is less than the sum of the effects produced by each chemical separately

From the point of view of health care, the potentiating effects are the most important ones. The above-mentioned effects describe the overall response, irrespective of whether interactions occur in the working environment, in the toxicokinetic phase or in the toxicodynamic phase.

The likelihood of toxic responses and their nature and severity depend on the absolute concentrations of the chemicals themselves or of the metabolites at the target site. Part of the additive, potentiating and antagonistic effects can be explained by toxikinetic interactions which increase or decrease the concentrations at the target site and in this way the toxicological response. Often, potentiating and antagonistic effects are the result of toxicokinetic as well as of toxicodynamic interactions. Examples are the induction or inhibition of microsomal enzymes resulting in increased or decreased concentrations of the toxic agents.

Interactions of drugs are widely studied in pharmacology. From these studies, it is clear that at a given dose the interindividual variability in plasma concentration is extremely large. This variation is due to the variability of biotransformation reactions, which are affected by different factors such as nutrition, hormonal status, age and sex. This large biological variability makes it very difficult to detect the interactions unless these are very strong. For this reason, the detection of interactions in cross-sectional epidemiological studies seems unlikely. Therefore, longitudinal studies are needed, using people as their own controls.

6 Personal Characteristics

Much information on the effects of combined exposure derives from animal experiments, and only a little from humans studies. One should be careful in extrapolating the animal data since the interactions in animals and humans may be totally different. For example, short-term exposure to ethanol induces the metabolism of solvents in rats but inhibits solvent metabolism in man. Phenobarbitone is a strong inducer of solvent metabolism in animals but fails to change the metabolism of xylene in man (David et al. 1979). The interindividual variability in inbred animals is also much less than in man. Some exogenous factors influencing variability will be mentioned briefly.

6.1 Nutrition

There is no doubt that nutrition, malnutrition and overnutrition affect the toxicity of chemicals. Much of the scientific evidence is based on animal studies. In rats exposed to toluene, a 9% protein diet reduced the excretion of hippuric acid to half the amount excreted by rats on a normal diet. Starvation was shown to increase the severity of liver lesions induced by carbon disulfide (WHO 1981).

6.2 Drugs, Alcohol and Smoking

In general, 20%–25% of workers may be under treatment with one or more therapeutic drugs. Animal studies show that some drugs taken by ambulatory patients, such as sedatives, activate the microsomal enzyme system, thereby increasing the rate of the biotransformation process. On the other hand, inhalation of chemicals at the workplace may enhance the activity of drugs.

There are several investigations on the combined effects of alcohol and industrial chemicals. Since alcohol consumption is common and increasing in Western society, this phenomenon is of importance for industrial health care. Alcohol can increase the toxicity of parent toxic chemicals by blocking biotransformation. This has been found for trichloroethylene and styrene. On the other hand, exposure to chemicals can also increase the susceptibility to alcohol consumption and thus increase accidents in the workplace, in traffic or at home. Special attention should be paid to the Antabuse syndrome.

Isolated hepatocytes derived from a heavy drinker appeared far more active in metabolic activation in vitro of premutagenic arylamines than those of nondrinkers. This supports the idea that the susceptibility to certain genotoxic compounds might be dependent on previous exposure to inducing chemicals.

Smoking is an important factor in the development of many disorders. In the workplace, tobacco serves as a vector by contamination with different chemicals such as metals, dust and other products. Sometimes, smoking adds to the effects of workplace exposures since the same chemicals are present in tobacco, as has been shown for CO, aldehydes, cadmium, nickel and polycyclic compounds. The potentiating effect of smoking was clearly shown by the lung cancer incidence of asbestos workers.

6.3 Implications of Combined Exposure

As mentioned above, there are many factors influencing the ultimate toxicity of chemicals. From this point of view, exposure to a single chemical does not exist since there are always other xenobiotics which may interact. The interactions can be studied in animal experiments, but extrapolation to man should be done very carefully, as the number of modifying factors in humans is very large. It is of great importance to have knowledge of the biological variability, both inter- and intraindividually, of the normal working population. One should know the prevalence of the most important hereditary diseases, the nutrition pattern, use of drugs and alcohol and smoking habits. Workers reacting with an increased or decreased susceptibility to chemical exposure may have a different life style which explains their susceptibility.

7 Screening Models

In occupational health practice, the main goal is to prevent (adverse) health effects due to chemical exposure. This implies a hazard evaluation, involving a determination of whether the known toxicity of the chemicals will occur under specific occupational exposure conditions. Evaluation of hazards from combined exposure is a much more demanding and a currently less satisfactory procedure. As mentioned above, different factors have to be taken into account, particularly those resulting in a potentiating toxicological effect. The following screening models may be used as an approach to the evaluation of the combined hazard.

7.1 Industrial Hygiene Survey

Chemicals are only toxic when there is a contact with the organism or when they are absorbed to a certain amount. Only for some genotoxic carcinogens is it assumed that there is no threshold limit. For all other chemicals, a safe level can be defined, below which no adverse effects occur. Surveys are required to characterize the nature of the different chemicals, their variations in concentrations. Compliance with expo-

sure guidelines such as MAC values and precautionary measures such as protective clothing and equipment are also essential.

7.2 Toxicity Data

In some workplace conditions, exposure is reduced to a few chemicals, and the individual components have well-documented toxicological information. In that case, it may be possible to make a rational and reliable prediction of adverse health effects under the specific conditions of use. However, there are more complex situations of which the toxicology is not well appreciated. Ideally, combinations of chemicals – in the way they are absorbed – should be subjected to appropriate investigations to determine their overall toxicity. This is practically impossible, due to the multitude of combinations of chemicals that may occur and the variations in concentrations. However, priorities can be set: for instance, health effects of inherent mixtures (polycyclic aromates, petroleum distillates and white spirits) and frequently encountered combinations of chemicals in distinct occupations.

7.3 Biological monitoring

BM offers the possibility to assess potential interactions, especially toxicokinetic interactions. For this purpose, it is necessary not only to measure the exposure chemicals or their metabolite(s) in body fluids but to differentiate between protein-bound and free concentrations in plasma. In most cases, it is the free concentration which determines toxicity. Interaction may be shown by an altered ratio. Special attention should be paid to nonspecific tests such as thioethers and mercapturic acids in urine, which can show the overall exposure to a variety of electrophilic agents.

7.4 Biological effect monitoring

An indirect estimate of the degree of exposure to a specific substance, or a particular functional class of substances, may be possible by determining enzyme activities. Exposure to mixtures of organophosphates can be monitored by the degree of inhibition of blood cholinesterases, which indicates the overall effect. Special attention should be paid to recent developments in methods for detection of enzyme induction and inhibition. With these methods, both toxicokinetic and toxicodynamic interactions may be shown.

7.5 (Early) Health Effect Monitoring

Different methods exist for the detection of early health effects. They are available for neurotoxic, nephrotoxic, genotoxic and hepatotoxic effects. When the exposure pattern is very complex, these methods may be very useful.

7.6 Medical Examination

An occupational history and full physical examination of each worker is required. In certain circumstances, it may be necessary to undertake special investigations to detect organ injury. One should have insight into personal characteristics such as drug use, alcohol consumption, smoking habits, leisure activities and hereditary diseases.

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Theme II
Intra- and Interindividual Variability in Response

Intra- and Interindividual Variability of Biochemical and Haematological Parameters in Periodical Health Surveillance*

F. van Geen

Introduction

One of the potential uses for biochemical and haematological parameters in occupational health is periodical health monitoring of workers with potentially hazardous jobs. One of the objectives of health monitoring of a target population is to permit one to discriminate between health and disease, ultimately in order to prevent disease.

However, there are many unanswered questions about the scientific basis (and cost-effectiveness) of health monitoring. When using nonselective biochemical and haematological parameters, we should know the sensitivity, specificity and predictive value of the screening procedures. But the prevalences of the diseases we are looking for are low, even those diseases which permit preclinical detection. So, what risk factors or diseases can reasonably be found in asymptomatic, ostensibly healthy persons in relation to their working conditions?

Usually, we apply the probability concept of normal or the percentile distribution for interpreting results simply in terms of normal or abnormal. But the usual upper/lower limit of normal tells us nothing about health or disease, which is the main reason why these concepts have to fail (Galen and Gambino 1975). The board distribution of test results in an apparently normal population does not define the limits of anyone's personal state of health.

If we accept the concept of biochemical individuality as an important factor determining a medical fate, then an accurate description of normality for an individual is fundamental for the assessment of his or her state of health and for early recognition of abnormal trends in the individual's physiology and chemistry (Grasbeck and Alstrom 1981).

2 Significance of Intra- and Interindividual Variability in Occupational Medicine

After the introduction of, for example, TLVs, there are no longer any heavy exposures. The response in the dose-response relationship will become increasingly nonspecific, reflecting more and more a kind of general response, as a characteristic of toxicological

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and nontoxicological, work-related and nonwork-related factors. It will be very difficult to express the most significant event as a direct reflection of the disturbance brought about by a toxicological agent.

If we accept the presupposition that repetitive measurements of one worker over a period of time add extra information, then we must refine the selection of standards of normality for biochemical variables. To interpret the statistical and clinical significance of a change or the difference between successive measurements, we have to go beyond normality to see the individual homeostatic and compensatory capacities in the light of additional modifying factors.

3 Historical Perspective

In the 1960s, Williams et al. (1970) demonstrated a "profile" of 15 chemical constituents of a normal subject. By comparing different profiles, it appeared that (a) no two profiles were the same; each individual showed a characteristic set of mean values and patterns of fluctuation of his blood constituents; (b) the individual mean concentrations of a given blood constituent were consistently within the limits of the normal range; and (c) the individual range of variation of most results of each test was smaller then the accepted range in a normal population.

These observations led to an extremely interesting long-term study of the characteristics of individual normal ranges of blood constituents and of their consistency. A study of blood constituents in 68 selected subjects was undertaken to (a) estimate the contribution of biological and analytic factors to the variation of constituents over an extended period of time; (b) explore whether such tests can be used to derive meaningful personal blood profiles; and (c) determine when analytic variation may become large enough to assure medical significance.

Because the analytic variability may obscure the true physiological variation, Williams et al. (1970) concluded that it is essential to know the contribution of analytic variability to the overall variability in order to achieve meaningful interpretations of differences in intra- and interindividual results. In the second report, Harris et al. (1970) defined the components of variance. They introduced an algebraic method to analyze these components in a statistical way in order to estimate the biological components. They made the assumption that the separate components of variance are additive and independent of mean values.

The major finding was that a chemical test will contribute to individuality only if the combination of personal and analytic variance components is substantially less then the interindividual variability.

Cotlove et al. (1970) examined the types of variation more precisely in the third report. They charted the magnitudes of five types of variation as coefficients of variation. In addition, they calculated the "subject mean" of each particular constituent, which represents the "set point" concentration of homeostatic regulation. Not surprisingly, they supported that the isolated personal variation, separated from analytic deviations, measures the extent of fluctuations above and below the set point that is allowed by the subject's homeostatic mechanism. Subsequently, the isolated interindividual variance, separated from both personal and analytic components, reflects differ-

ences in homeostatic set points of different individuals, arising from such factors as genetic characteristics, diet, physical activity and age.

The concepts developed in this study indicate that a subject mean may be a better discriminating measure to detect mild states of abnormality than a group mean. Besides, the intraindividual variation may also be useful since an impaired regulatory mechanism may manifest itself by an abnormal degree of variation as well as by an abnormal mean concentration.

Young et al . (1971) reported a way to analyze and minimize the analytic variation for estimating the personal variation. The long-term analytic variance component increased over many days, and in most tests it was the major contributor to the total analytic variance. They investigated the analytic day-to-day vs within-day variance and the biological component of variance of nine subjects with fairly uniform demographic characteristics. The within-day variance component did not achieve significant levels in most tests. The day-to-day variance was evident in the determination of enzymes in pooled sera. They expected that the nine subjects would show minimal interindividual differences; however, in most parameters these individuals showed a purely interindividual variation that was greater than or as great as the one found among the diverse group of 68 subjects studied earlier. Young et al. (1971) concluded that certain blood parameters depend more on personal characteristics than on broad demographic factors.

In the 1970s, the above-mentioned authors and others studied the same components of variance and their medical implications in order to explore and develop statistical models suited for long-term studies of healthy individuals. Harris and De Mets (1972) observed that a distribution of single measurements may have any form or shape, depending on the characteristics of the intra- and interindividual distributions from which it sprang. The shape of the distributions of interindividual mean values plays a major role, but the distribution of intraindividual variances is also an important factor. Harris (1974) proposed a numerical index combining intra- and interindividual variation for use in judging the appropriateness of applying a conventional normal range to an individual measurement of some biochemical constituents. This index (R) discriminates between an individual distribution curve and the overall distribution curve in terms of in- and oversusceptibility when compared to the normal range. Stratifying a sampled population into homogeneous subgroups did increase the magnitude of R, but it failed to produce a substantial improvement in sensitivity. For this reason, Harris (1976) introduced three statistical time-series models, to use the individual as his own reference. The "random walk model" postulates fluctuation of the biological component in a random manner. The "homeostatic model" postulates homeostasis over a period of time. The "intermediate model" postulates regulation towards a set point. The crucial issue among the three models is the meaning of the value of previous results in testing a new observation from the viewpoint of the equation between biological variance and analytic variance, the physiological control and the number of equispaced observations over a certain period of time.

With a word of caution against their own conclusions, Winkel et al. (1975) ended their report about the intrasubject correlations of three combinations of serum constituents. They found from subject to subject different and low correlation coefficients and, therefore, they concluded that studying relationships between laboratory tests may yield no meaningful clinical information.

After the development of multichannel analyzers and their consequences for long-term analytic variance, Pickup et al. (1977) studied the problem once again. In this excellent study, the subjects were not students, colleagues or patients, but employees of a plant. Pickup et al. used the same statistics as in the earlier studies. Their results in determining the appropriateness of population-based reference ranges or computing correlation coefficients for all possible pairs of analytes for each individual generally confirmed the previous studies.

Although Williams et al. (1978) were not able to develop new points of view, they showed that dividing the demographic groups into six classes according to age and sex reveals statistically significant differences between the means of many variables of the different classes. They used data from 1105 healthy subjects. After examining the sensitivity of the ranges of variation within these classes to individual variation, their conclusions about the usefulness of accepted normal ranges affirmed the former studies.

Harris and Brown (1979) studied the observed change between two successive measurements in an individual. Using the data described by Pickup et al. (1977), they focused on the within-person standard deviations and their frequency distributions. All distributions of the ten serum constituents studied appeared to be lognormal. They calculated the coefficients of variation of the within-person standard deviation and observed heterogeneity of the within-person deviations of values for a constituent. After ranking the within-person deviations, the results showed highly significant differences within the subjects with respect to their variabilities in the concentrations of the analytes. After discussing a statistical way to describe the general pattern of variations over time within a subject and to test the appropriateness of a threshold difference between two serial measurements, Harris and Brown (1979) concluded that the variance heterogeneity could be a critical factor in assessing the importance of a change between two successive measurements of an analyte. A quantitative change may become statistically and physiologically significant in a subject whose biological variability for that analyte is relatively small, but not important in one with large random variation. Harris and Brown conjectured that factors which influence within-personal variances include fluid intake, diet and physical or psychological stress. A very stable or very erratic life style would be expected to display small or large within-person variances respectively.

Harris et al. (1980) demonstrated the homeostatic and random walk models again. They postulated strict homeostasis for every constituent and calculated F-values to detect the nonhomeostatic behaviour. Significantly large F-values would indicate rejections of the strictly homeostatic model. The enzymes had large F-values by chance alone of 40%–60%, so the nonhomeostatic model should be accepted. Close to the homeostatic model were Ca, P, glucose, urea, creatinine, uric acid and triglyceride. For haematological constituents, the stationary variability was more frequently rejected than for the clinical chemical constituents. Especially the erythrocyte parameters mean corpuscular haemoglobin (MCH), haemoglobin concentration (MCHC) and volume (MCV) were nonstationary, whereas the white blood cell count (WBC), haematocrit (HT) and red blood count (RBC) were homeostatic.

Finally, whichever model was chosen, many investigators computed ranges on the basis of laboratory results already observed in a given subject. Harris et al. (1980) and Winkel et al. (1975) introduced the terms "subject-specific prediction intervals" and

"subject-specific reference intervals": previous laboratory results are used to estimate an interval which will contain the value as measured in a future specimen with a specified probability p, subject to the condition that the person is still in the same state of health. Stamm's (1982) critical difference is more realistic to indicate the range which covers the great majority (e.g. 95%) of the differences between low values of one parameter obtained in one individual.

4 Ecology of Haematological and Clinical Chemical Values

We use the term "homeostasis", invented by Cannon (1929), in the physiological sense as formulated by Claude Bernard. In the light of individual susceptibility, the question is: what are the individual conditions to be kept constant? After calculating individual means and variances of constituents, and even if there is concordance among the data of several persons, do these data indicate the same assumed individual regulation of homeostasis (statistical and biological masking)? Cells of a given organ have distinct resonance characteristics, such that they are tuned to a particular biological clock associated with the homeostasis of that organ (Wasserman 1976). Homeostasis should include the possibility of a "milieu interieur" spontaneously changing over time. So, within a work cycle for instance, measurements of many fundamental indices must be considered not only in the relationship of the work cycle to the environment but also in the light of the tuning system which controls the intrinsic rhythmicity. We have to know a great deal on many levels, including cellular levels, about the ecological background of ostensibly healthy persons before we are able to classify persons working in potentially hazardous jobs as at risk before we can interpret test results. Table 1 presents some factors influencing laboratory data (indications): (Grasbeck and Alstrom 1981; Costongs et al. 1984; Winsten 1975).

5 A Try-Out

For 2 years (October 1984–October 1986), haematological and biochemical data were sampled from 191 male blue-collar workers of a large Dutch steel company. These volunteers were stratified according to age (born 1930–1939 vs born 1950–1959), work schedule (nonshift work vs shift work with rotation every 3 days), occupational energy expenditure (high/low) and selected/nonselected (by medical history). Figure 1 presents the study design.

Each month, on a normal working day, a blood sample was taken under controlled conditions: between 8.15 and 8.45 am. after 15-min rest, venepuncture/vacuum technique, light pressure, seated, the same laboratory technician. The following constituents were analyzed: WBC, RBC, haemoglobin (Hb), Ht and MCV (using a Coulter Counter) and urea, creatinine, uric acid, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), γ-glutamyl transpeptidase (γ-GT), alkaline phosphatase (AF), total cholesterol, lactate dehydrogenase (LDH) and total bilirubin (using a Cobas Bio centrifugal analyzer). Because we wanted to examine a real-life setting, there were no restictions on life style before the time of blood sampling. Nevertheless, during the 2 years,

Table 1. Factors influencing laboratory data

	White blood cells	Erythrocytes	Haemoglobin	Haematocrit	MCV	Urea	Creatinine	Uric acid	ASAT	ALAT	γ-GT	Alkaline phosphatase	Cholesterol	LDH	Total bilirubin
Race	x					x		x					x	x	
Sex (♂ > ♀) (adults)	+		x			+	+	+	o	o	o	+	x	o	−
Age	♂+ ♀−		−			+	+	+	o	o	o	−	+	−	+
Circadian periodicity	x					±	±	+	±	±	±	±	±	±	±
Seasonal variation						+2	o	+2	o	o	o	+3	+1 −2	+2 +4	+3 −1
Diet (nonfasting)						+	+	+	+	−	o	+	+	±	±
Caffeine ingestion															
Ethanol ingestion					+			+	+		+				
Tobacco smoking	+			+	+	−	o	−	o	o	o	o	+	o	o
Exercise	+		−	−		+	+	+	±	±	o	o	o	+	+
Psychological stress	+		+			+	+	x	+	−	o	+♀	+	+	o
Overweight	+					o		+		o		+♀	+♂	+	o
Genetic differences															
Phenotype differences															

+, increase; −, decrease; o, no influence; x, there is a difference; 1, spring; 2, summer; 3, autumn; 4, winter
The influence on erythrocytes is not known.

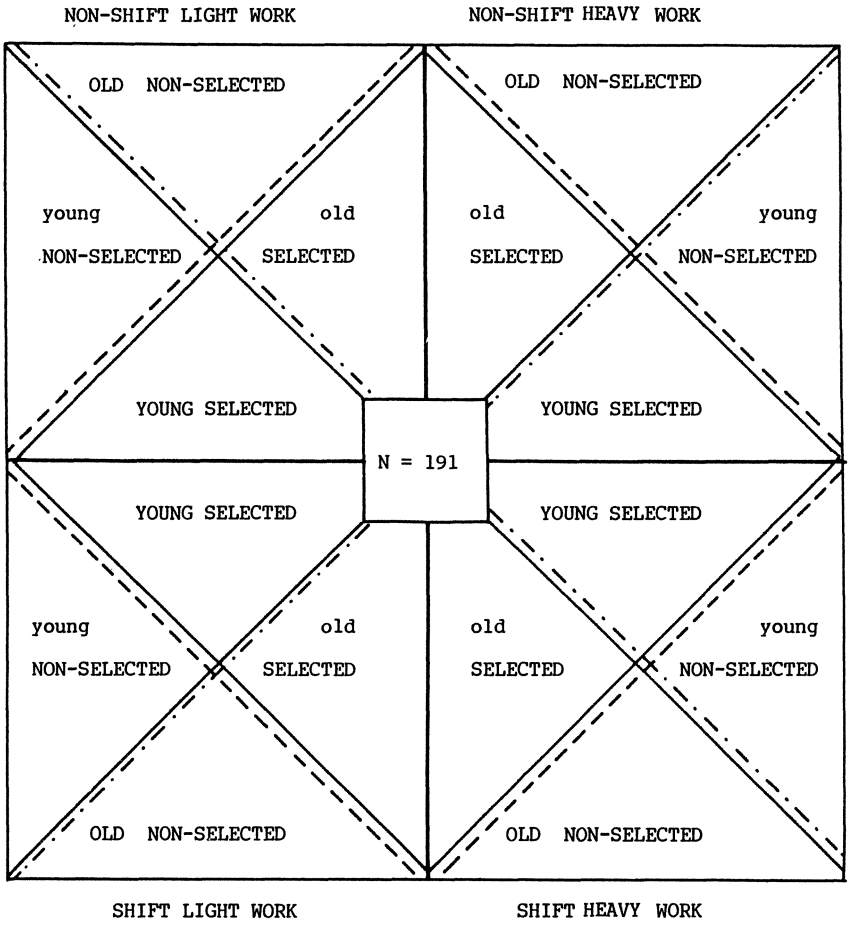

Fig. 1. Design of the study

we have tried to assess individual life-style by means of questionnaires on dietary habits (including drinking and smoking habits), nonwork energy expenditure and stress factors (Michigan model). The purpose of this study is to establish:

1. The overall means and range of variation among the groups and subgroups
2. The individual mean and intraindividual variation
3. The overall means of the individual means and the range of variation within the groups and among the groups
4. The overall variations of the intraindividual variations and the range of variation within the group and among the groups

This is necessary in order to study (a) the impact of statistical characteristics in the light of the modifying factors mentioned earlier and (b) the impact of the results on health monitoring programmes.

At this moment, we cannot yet present our results. However, to demonstrate the importance of the individual approach, we made, as an example, some calculations for the Hb values [coefficient of variation (CV) about 2%] of 142 participants (selected participants excluded) sampled during the first year. One way to identify high-risk persons and groups is to find "extreme" values for a constituent having a broad distribution in the population (Smith 1975). The question is: which value do we indicate as an extreme value?

To study this problem, we used the following statistical procedure. We calculated:

1. The overall mean (M_t) and the overall standard error (S_t)
2. The personal mean (M_p) and the personal standard error (S_p)
3. The mean of all M_p indices (M_n) and their standard error (S_i)
4. The mean of all S_p indices (S_n) and their standard errors (S_m= the standard error of the standard errors)

The variances of Hb values are shown in Fig. 2. We assumed different numbers of extreme values among the groups (different susceptibility?). To indicate and to discover the number of extreme values within and among the groups, we have to select a reference standard error. To solve this problem, we have chosen S_n as reference standard error. For about 50% of the subjects in the total given population, S_p will be smaller than S_n, and for 50%, S_p will be larger than S_n. So this standard error will have to select that difference between consecutive values that would indicate one or more extreme values in roughly 50% of all persons. The consequences are shown in Fig. 3. It is not surprising that about 50% of the individuals are indicated to have one or more significant changes. However, Fig. 4a suggested no differences among the groups.

However, 50% of the changes will be "upward" changes, and 50% will be "downward" changes, supporting a normal distribution around M_p. Therefore, we examined the

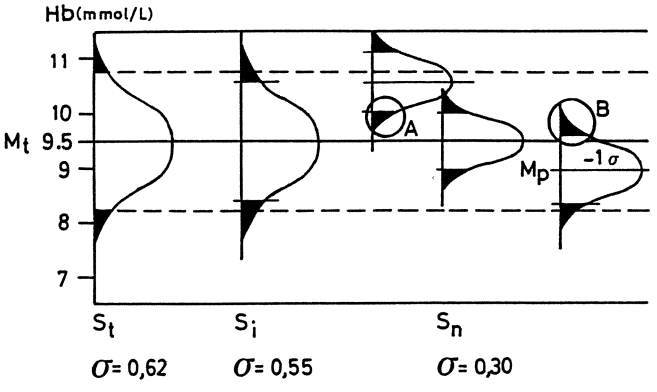

Fig. 2. Variances of haemoglobin (*Hb*) values: overall standard error (S_t) $\sigma = 0.62$; standard error (S_i) $\sigma = 0.55$; mean of all personal standard error (Sp) indices (S_n) around the personal mean (M_p) $\sigma = 0.30$. Note that $S_n < S_t$ and $S_i \approx S_t$. The influence of S_i on S_t is much larger then the influence of S_n. So M_p is very important to S_t. Almost the same values of a constituent may have a different significance to individuals *A* and *B*; moreover, *A* and *B* are within 2 x S_t and are near the overall mean (M_t) in this case

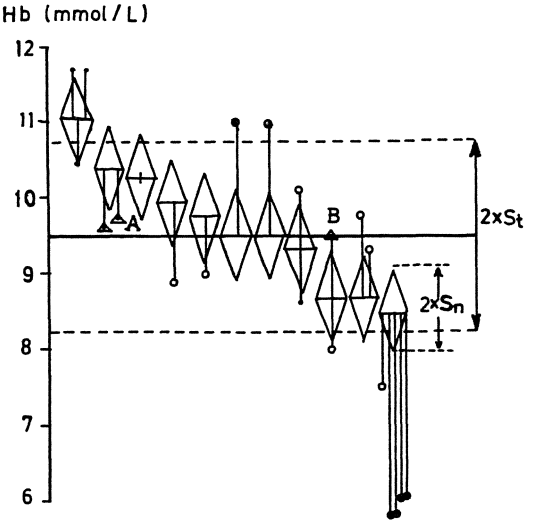

Fig. 3. Detection of deviations outside 2 x S_t limits and 2 x S_n limits. Note that *A* and *B* show that a result which is high for one individual is low for another, although both are within 2 x S_t and in this case are near the overall mean of all results! In this way, we simply counted the number of persons who have one or more significant changes

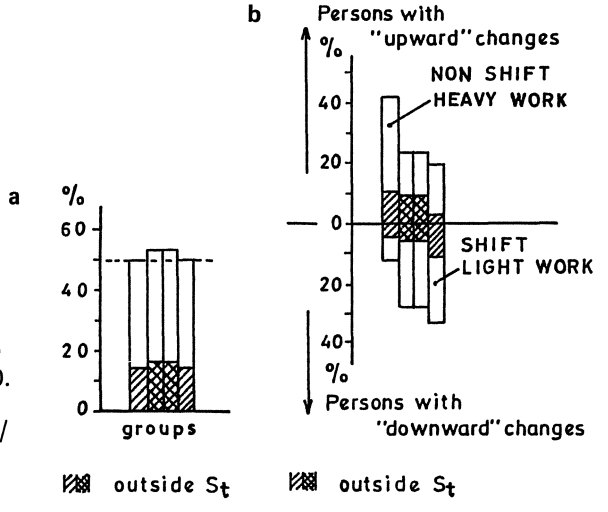

Fig. 4. a Percentage of persons with one or more changes in Hb values during 1 year, S_n: $\sigma = 0.30$. S_t, overall standard error. b Percentage of persons with upward/downward changes in Hb values during 1 year, S_n: $\sigma = 0.30$

number of extreme values now specified in upward and downward changes, as shown in Fig. 4b. Seeing Fig. 4b, we determined an important difference between the two groups nonshift/heavy work vs shift/light work ($p \sim 1\%$). It might be suggested that the difference is due to a higher or lower M_n (in the light of the total M_n within the groups). To verify this, we examined the M_n of each group. Surprisingly, the M_n of shift/light work was even larger than the M_n of nonshift/heavy work. So shift/light work undoubtedly inclines to show more downward changes.

Another interesting question is: in which month did we indicate most changes? Figure 5 shows that the largest number of upward and downward changes appear in approximately the last 6 months of the year. Again, we were not able to indicate this

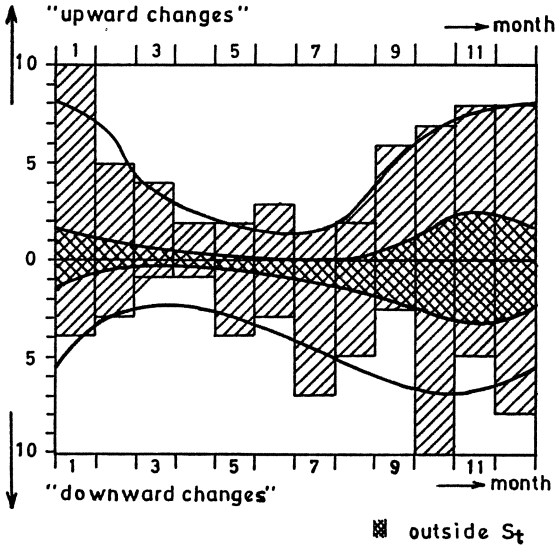

Fig. 5. Numbers of upward and downward changes in Hb values during each month of 1 year

phenomenon by using the usual statistical procedures of calculating the overall means of the groups and their standard errors ($2S_t$ limits); we did not see any difference among these statistical indices, for the same reasons as mentioned before.

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Enzyme Induction: Its Relevance for Internal Exposure and Health Risks

B. Kolmodin-Hedman

1 Introduction

The activity of the hepatic microsomal enzyme system, which may be of great importance for metabolic activation and the activation of hepatotoxic agents and carcinogens, is changed by exposure to commonly used in industrial chemicals.

Previously, it has been shown in animal experiments that exposure to chlorinated hydrocarbon pesticides induced the microsomal hydroxylating enzymes in the liver. Hart et al. (1963) reported shortening of hexobarbital sleeping times in rats exposed to chlordane, which was sprayed in the animal stalls. Chronic feeding of rats with DDT similarly produced a long-lasting effect. Street et al. (1969) have shown that dieldrin is also capable of inducing enzymes. Kolmodin-Hedman et al. (1969) and Kolmodin-Hedman (1974a) showed in one of the first observations in humans that workers exposed to a mixture of pesticides, mainly lindane and dichloro-diphenyl-trichloroethane (DDT), had significantly decreased plasma antipyrine and phenylbutazone half-lives after single doses administered orally. They also showed reversible changes in the hyper-α-lipoprotein metabolism caused by exposure to lindane.

Ideally, as in animals, an induction of the liver microsomal enzymes should be shown directly to increase the metabolism of the test substance, leading to speeded elimination. As this is difficult to accomplish in human beings, various indirect ways of showing an effect of the microsomal enzymes have been used.

1.1 Direct Measurements

Microsomal enzyme activity can be measured directly in vitro in humans. Davies and Thorgeirsson (1971a, b) have studied the antipyrine half-life in plasma ($Pt_{1/2}$) in vivo and nicotinamide adenine dinucleotide phosphate (reduced) (NADPH), cytochrome P_{450} reductase, cytochrome *c* reductase and ethylmorphine *N*-demethylase in vitro in four volunteers. High in vitro rates of oxidation correspond to short plasma antipyrine half-lives and vice versa. Cytochrome P_{450}, NADPH, cytochrome *c* reductase, *O*-demethylation of *p*-nitroanizole and *N*-demethylation of aminopyrine were shown by Schoene et al. (1972) in liver obtained by needle biopsy. Such experiments cannot be done in healthy occupationally exposed men for ethical reasons.

2 Indirect measurements: Estimation of Plasma Clearance or Other Metabolic Rates of Test Drugs

2.1 Antipyrine Half-lives

The most commonly used substance has been antipyrine (phenazone), as this drug is predominantly metabolized in the liver and thus not excreted unchanged to any great extent in the urine and not appreciably bound to plasma protein.

Our own investigations (Kolmodin-Hedman et al. 1969) tested antipyrine in workers exposed to DDT and lindane. Twenty-six Swedish male workers sprayed a solution of 4% lindane, 1% pyrethrum, 0.125% piperonylbutoxide and 2.5% malathion in kerosene. Previously, they had also been exposed occupationally to DDT during a period of 5 years. Gloves and respirators were not used regularly. They worked from daily to once weekly and the employment period varied from 1 to 15 years. Thus, both dermal and respiratory exposure occurred. In the first study, the plasma levels of lindane could not be detected in such low amounts, but in later studies of antipyrine and phenylbutazone half-lives in DDT workers, the mean plasma lindane levels were 18.4 ± 26.8 ng/ml (range, 1–90). In a series of animal experiments in rats given various levels of lindane in their food, the inductive limit in food would be 4 ppm, corresponding to a plasma level of 40 ng/ml. As in a later investigation of oxazepam glucuronidation the mean lindane levels were less than 10 ng/ml (mean 6.9 ± 3.0), no effect on oxazepam glucuronidation could be found. So, Kolmodin-Hedman (1974b) postulated the inductive plasma level of lindane in humans to be 10 ng/ml.

In these early studies, invasive methods were used, taking repetitive blood samples four to five times per day over 24–72 h, respectively. To avoid this, Dϕssing et al. (1984) developed the antipyrine test for estimation of a single dose of antipyrine in saliva with a sample taken after 18 h (Dϕssing et al. 1983b). According to these authors, based upon the formula estimating body weight and height and thus giving the volume of distribution, antipyrine clearance (Cl) was calculated as follows:

$$\mathrm{Cl} = \frac{\ln (V_D/D) - \ln c_t}{t} \times V_D,$$

where V_D is the volume of distribution, D is the dose and c_t is the concentration of antipyrine in plasma or saliva at sampling time t. Dϕssing et al. also pointed out the importance of paired observation, thus the same person before and after exposure or after cessation of exposure.

For details on Dϕssing's series of experiments, see Dϕssing (1982, 1983, 1984); Dϕssing and Andreasen (1981), Dϕssing and Weihe (1982); Dϕssing et al. (1982, 1983a–c, 1984, 1985). However, other influences should also be taken into account when evaluating antipyrine clearance. There is a considerable genetic variation in the half-lives and, as Vesell et al. (1971) studied, in drug metabolism in monozygotic twins. The consumption of drugs, especially hypnotics, tranquillizers, analgetics and oral contraceptives (in females), smoking and alcohol may also influence the half-lives. Compare the discussion in Kolmodin-Hedman (1974a) and the review by Park and Breckenridge (1981).

The interindividual differences in antipyrine half-lives may thus be decreased by exposure to, or pretreatment with, inducing agents. Vesell and Page (1969) showed that persons with an initially long $Pt_{1/2}$ of antipyrine were more prone to decrease the half-life after pretreatment with phenobarbital than those with initially short half-lives. Breckenridge et al. (1971) also found that persons with a long $Pt_{1/2}$ of antipyrine lowered their warfarin steady-state concentration more if pretreated with dichloralphenazone than those with a short $Pt_{1/2}$ of antipyrine. Vesell (1979) has reviewed the application of the antipyrine test, mainly in clinical pharmacology.

2.2 Phenylbutazone Half-lives

Poland et al. (1970) studied workers exposed to DDT and estimated phenylbutazone $Pt_{1/2}$: total DDT compounds over 500 ng/ml significantly shortened the phenylbutazone half-lives compared with controls. In conifer workers, exposed to low levels of DDT, Kolmodin-Hedman (1974a) showed that no effect was exerted on the antipyrine half-lives at DDT plasma levels ranging from to 25–100 ng/ml [Σ DDT (DDE + DDT), [DDE: dichloro- 2,2 bis (*p*-chlorophenyl) ethane]; nor was there any effect in fishermen indirectly exposed by diet (Σ DDT = 125 ng/ml). From these data, Kolmodin-Hedman postulated that the no-effect level of total DDT in plasma for induction would be above 200 ng/ml. [Extrapolation to experimental data in rats showed that 0.5 mg DDT per kilogramme in food corresponded to an effect level of 10 mg/kg in fat, which increased the hexobarbital oxidation in the liver (Schwabe and Wendling 1967)].

Phenylbutazone and warfarin have also been used as model compounds in occupational research (Ghoneim et al. 1975) for workers exposed to pesticides (Kolmodin-Hedman 1973; Poland et al. 1970). Phenylbutazone, however, is not an ideal drug, as it is transported in plasma appreciably bound to plasma proteins, and both the single dose and multiple doses change the $Pt_{1/2}$. Whittaker and Price Evans (1970) showed that about 60% of the variability of the plasma half-lives of phenylbutazone could be accounted for by genetic differences, and the remainder by environmental factors. Even higher genetic dominance was reported by Vesell (Vesell and Page 1968a, b, 1969; Vesell et al. 1971).

2.3 Endogenous Substances as Indirect Indicators of Enzyme Induction

2.3.1 D-Glucaric Acid

D-Glucaric acid is an end product of carbohydrate metabolism produced via the glucuronic acid pathway, mainly in the liver. D-Glucaric acid excretion is assayed after boiling urine at pH 2. This converts the D-glucaric acid into D-glucaro-1,4-lactone, which is measured by its specific inhibitory effect on β-glucuronidase. Adjustment for the variable excretion of urinary creatinine is necessary for correction of urine production. The urinary excretion of D-glucaric acid is increased by many, but not all drugs, which stimulate microsomal enzyme activity. It is not known whether D-glucaric acid

excretion is decreased by inhibitors of microsomal enzyme function. Thus, one has not been able to establish the mechanism by which enzyme-inducing agents increase urinary D-glucaric acid excretion. Hunter et al. (1973) showed an increase in men occupationally exposed to endrin.

2.3.2 Excretion of 6β-Hydroxycortisol

In the liver, cortisol is partly converted to 6β-hydroxycortisol, which is excreted in urine. This endogenous product has been shown to be increased after occupational exposure to chlorinated pesticides, DDT (Poland et al. 1970) and endrin (Jager 1970). Lately, Ohnhous and Park (1979) have developed a method of measuring 6β-hydroxycortisol by radioimmunoassay using HPLC. The results are often expressed as the ratio between the levels of 6β-hydroxycortisol and urinary 17-hydroxycorticosteroids. The latter is assayed by a colorimetric method. Ohnhous and Park (1979) have used the estimation of 6β-hydroxycortisol excretion as an in vivo parameter in the clinical assessment of the microsomal enzyme-inducing capacity of antipyrine, phenobarbitone and rifampicin. Park and Breckenridge (1981) have also surveyed studies using 6β-hydroxycortisol.

6β-Hydroxycortisol may be excreted by the adrenals; the urinary excretion of the cortisol metabolite is influenced by factors that do not necessarily affect the microsomal enzyme function. However, urinary 6β-hydroxycortisol is reasonably well correlated to other in vivo and in vitro indices of microsomal enzyme activity during treatment with inducing drugs. It is not affected by cigarette smoking, in contrast to the above-mentioned antipyrine test, which is enhanced in cigarette smokers (Hart et al. 1976).

The following advantages and disadvantages of the estimation of 6β-hydroxycortisol excretion should be considered. The existing method of estimating 6β-hydroxycortisol in 24-h urine samples is often used. This is rather complicated in field studies. However, it is a noninvasive method; urine is easy to sample, and sampling could be repeated as often as desired. Dϕssing et al. (1982) suggested this as the method of choice, "especially in studies, where the complete time course of changes in microsomal enzyme function with daily measurements is the object of the investigation".

3 Discussion

3.1 Effects of Tobacco Smoking

The inductive effect of smoking on drug metabolism was first shown by Pantuck et al. (1974), who found that the plasma concentrations of phenacetin were lower in smokers than in nonsmokers. Jusko (1978) has more recently reviewed the effects of smoking on in vivo drug biotransformations. He found that the metabolic rates of nicotine, antipyrine, theophylline, imipramine and pentazocine were increased, while the metabolism of diazepam, pethidine, phenytoin, nortriptyline, warfarin and ethanol were unchanged.

If has recently been suggested that the effect of cigarette smoking on drug metabolism predominantly occurs in the young rather than the elderly. Of the 3000 chemicals so far identified in cigarette smoke, the polynuclear aromatic hydrocarbons are probably the agents responsibe for the hepatic enzyme induction. Animal experiments have shown that agents that induce P_{448} enzymes, such as polynuclear aromatic hydrocarbons, are much more potent on a molar basis than inducers of P_{450} enzymes such as phenobarbitone.

Vestal et al. (1975) showed a decreased clearance of antipyrine in elderly people and increased clearance after smoking in a population study of 307 males, grouped according to age, taking into account the intake of caffeine and alcohol and smoking habits.

3.2 Effects of Alcohol (Ethanol)

Chronic administration of ethanol induces the microsomal ethanol-oxidizing system, while on the other hand acute administration of ethanol to volunteers decreased the clearance of pentobarbitone, meprobamate (Rubin et al. 1970) and warfarin (Breckenridge et al. 1971). Ethanol, however, is normally metabolized in the cytosol by alcohol dehydrogenase, but sometimes also by an inducible microsomal enzyme.

3.3 Inhibition of Microsomal Enzymes

Dϕssing (1984) has shown that exposure to lead decreased the antipyrine metabolism. A decreased urinary output of 6β-hydroxycortisol was shown after exposure to lead (Saenger 1983). Alvares et al. (1976) showed a slight increase of antipyrine half-lives in two out of eight workers heavily exposed to lead. Hart and Fouts (1963) and Rao and Anders (1973) have shown that exposure to malathion increased hexabarbitol sleeping times, indicating an inhibitory effect on the microsomal enzymes.

3.4 Health Hazards of Prolonged Exposure to Chlorinated Long-Lived Pesticides

Severe effects of exposure to DDT have been reported for birds at the end of an ecological chain. This is partly a consequence of increased oxidation of sex hormones, mediated by increased activity of liver microsomal enzymes (Peakall 1969; Heath et al. 1969). Peakall (1967) found an increased conversion of testosterone and progesterone to more polar metabolites in pigeons given low doses of DDT and dieldrin (10 ppm and 2 ppm in food, respectively). The deleterious effects on the reproduction of birds, resulting in thinner eggshells and reduced hatchability, may also be due to a change in vitamin D metabolism followed by a defect of calcium uptake (Peakall 1969; Bitman et al. 1969). A disturbed calcium uptake and increased vitamin D metabolism have been postulated by Richens and Rowe (1970) and Dent et al. (1970) in patients treated with long-term phenobarbital and diphenylhydantoin. O'Hare et al. (1980) showed

evidence of osteomalacia with prolonged carbamazepine intake (referred to in Dϕssing 1984).

In summary, exposure to environmental factors such as chlorinated hydrocarbon pesticides, causing decreases of half-lives of the test drugs antipyrine and phenylbutazone and changes of serum lipoproteins, has so far not affected the subjects clinically. The findings may be regarded as early biological responses to exposure to low levels of chlorinated pesticides. However, little is known about the consequences in humans of long-lasting induction for the state of health, as was stated in my dissertation (Kolmodin-Hedman 1974b). Dϕssing (1984), having followed the literature for the next 10 years, state: "it seems justifiable to regard changes in microsomal enzyme activity as biological changes with potentially harmful consequences to the human organism".

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Variability in Response of the Nervous System (Central, Peripheral) to Workplace Chemicals

A. M. Seppäläinen

1 Introduction

The contemporary way of studying responses of the nervous system to workplace chemicals is the epidemiological approach. That is, of course, the way to study causal relationships between certain chemicals and adverse or subclinical nervous effects. We accept that the exposed and nonexposed (control) groups contain some individuals who have positive signs or otherwise belong to those with slightly deviant test results, but we assume that those deviant subjects are evenly distributed in both groups and thus do not prevent us from finding true causal relationships.

In suitable conditions, exposure-response relationships can be studied epidemiologically, but when dealing with nervous system effects, this is often difficult. Most chronic nervous effects are a result of long-term exposure, which has usually lasted for several years, whereas exposure levels from previous periods are poorly known. Consequently, previous exposure often has to be assumed or deduced from external data such as general use of, for example, solvents in the type of workplace in question and effectiveness of ventilation. In that kind of study design, individual variability is a factor that weakens the exposure-response relationships because it increases the standard deviation. Usually, each exposure category contains several persons with a "wrong" kind of response: some perfectly normal individuals in the most-exposed group and, on the other hand, some with severe symptoms and clear positive findings even in the least-exposed group.

Reasons for these variations in epidemiological studies may arise from two directions: (a) the exposure has been miscalculated; consequently, some subjects have been erroneously placed in wrong exposure groups. This may even happen when the overall exposure in a workplace has been correctly estimated since the exposure levels of individual workers may have varied to a large extent; (b) true interindividual variation in the reaction may have caused the variations noted. In large series, both these factors are probably effective, particularly when past exposure has been evaluated on a group basis.

Clearer exposure-effect relationships have usually emerged from epidemiological studies in which the individual internal exposure has been measured, preferably over a longer period of time (Seppäläinen and Härkönen 1976; Araki and Honma 1976; Seppäläinen et al. 1979). However, even then a researcher often finds workers who do not resemble their colleagues with similar exposure indices. That has been clearly demonstrated, for example, in the study by Seppäläinen et al. (1975), which presents subjects, blood lead (Pb-B) level ranges during exposure periods which lasted for years

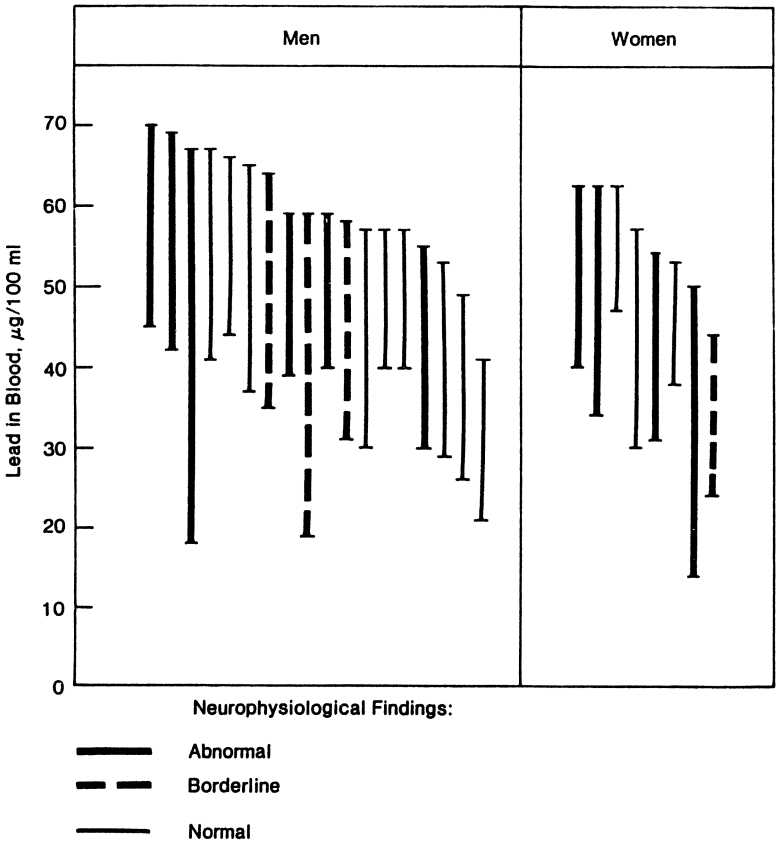

Fig. 1. Neurophysiological findings for lead-exposed workers and the range of individual blood lead values. (From Seppäläinen et al. 1975, published by Heldry Publications, 4000 Albenmarle Street, NW, Washington, DC 20016, Copyright © 1975. Reprinted with permission of the Helen Dwight Reid Educationar foundation.)

(Fig. 1). The small sample of women in that study seemed to be more sensitive towards lead neuropathy; they had abnormal results at Pb-B levels where men had no positive findings. At Pb-B levels around 70 µg/100 ml some men had normal findings, while a few showed signs of neuropathy at even lower levels. In these cases, the variation in results seems to be more individual in type since internal exposure has actually been measured and biologically monitored, although not directly in the effector tissue. Even in cases with biological monitoring, we have to keep in mind the variation of exposure between working days; it is almost never possible for someone to be constantly monitored in a workplace.

2 Factors Which Affect Variability

2.1 Sex

Is there a biological feature in women that would make their nervous system more vulnerable to toxic exposure? Usually, studies reporting the use of medical services by sex and age reveal that women seek medical help more often than men. On the other hand, in most industrialized countries the life expectancy of women is longer than that for men. This could be based on the fact that women are more conscious of minor ailments, while men are more negligent about those as a psychological trait.

This sex difference in reporting symptoms does not apply for those studies where the peripheral nervous system has been studied with objective measures, such as that on lead mentioned above (Seppäläinen et al. 1975)). Concerning the peripheral nervous system, we must thus investigate possible sex differences in toxicokinetics.

When we are dealing with questionnaire studies with self-reported symptoms, we must consider as one possibility for explaining sex differences the general trait that women are more apt to seek medical help and express more concern about health effects. (Is one reason for this the fact that as mothers, women are used to feeling responsible also for the health of their future babies?) This trend towards sex differences in health questions may, however, be changing, if we think of the prevalent fashion of jogging and health clubs, which seem to attract men more than women.

Rather rarely have CNS effects been studied in both male and female populations with the same methods and after similar exposure, which makes it difficult to compare the sexes. For example, in certain studies on solvent-exposed workers, EEG findings have been reported without sex differentiation (Seppäläinen 1973; Seppäläinen et al. 1980; Seppäläinen and Antti-Poika 1982), or the exposed population has only been of one sex (Elofsson et al. 1980; Giuliano et al. 1974; Seppäläinen et al. 1978). No significant difference between women and men was noted in the overall neurological prognosis in a follow-up study of patients with diagnosed solvent poisoning (Juntunen et al. 1982). Most studies with pneumoencephalography or computer tomography of the brain have concentrated on male workers (Juntunen et al. 1980).

In psychometric studies on solvent-exposed workers, certain differences have emerged between men and women. The responses to solvent exposure described were noted in part in separate tests for men and for women (Seppäläinen et al. 1980). Actually, there was a greater range of impairment in test results among female workers, but the exposure level of women was slightly higher, and they were more often exposed to halogenated hydrocarbons. However, the differences in exposure were quite small.

2.2 Age

Age as such may cause variations. Among styrene-exposed workers, young people in their early twenties during the first 1–2 years of exposed work were more apt to show EEG abnormalities than workers in their thirties and forties with several years of styrene-exposed work (Dolmierski et al. 1974). Is the reason for this that the younger brain is more sensitive towards toxic influences, or is it because less sensitive workers

stay in exposed work and those with possible problems change to another job at a young age? Or is the cause adaptation to toxic influences, so that with longer exposure, the individual develops adaptive measures to counteract ill effects? At least in the case of lead, children usually develop lead encephalopathy with convulsions and possible mental defects, while in adults lead neuropathy is usually the first neurotoxic sign (Seppäläinen 1984). Lead encephalopathy is rare among adults and is mostly seen in connection with excessive use of alcohol, often illegally distilled with leaded pipes.

Old age also seems to be a predisposing factor for toxic or other ill influences. Toxic chemicals may accelerate normal aging phenomena and arteriosclerotic changes (Vigliani and Pernis 1955). With age, the plasticity of the nervous system decreases, and corrective and compensatory mechanisms start failing. An elderly worker thus has less capacity to cope with all kinds of problems. Part of this failure is no doubt caused by factors other than chemicals, namely, increasing demands of modern society, stress from social factors and new working methods which may be hard to learn.

Also, chemical exposures throughout life may have slowly caused minor defects, which may not have emerged earlier, but have eaten up the extra capacity of the nervous system. Any further damage then creates an imbalance in the delicate situation, and the person starts experiencing some decreased functional capacity and increasing symptoms. Failing physical capacity is also tilting the balance between health and non-health towards disease.

2.3 Genetic Aspects

Intellectual functions, as well as many psychic traits, seem to be genetically determined; i.e. some persons have an inborn ability to learn easily and also a drive to learn and increase their knowledge. For others, learning new things is difficult, and they may also lack the drive to utilize all their abilities. A person with a high capactiy is more able to compensate for possible losses and to find new ways of functioning with certain acquired handicaps. Also, more intelligent people may be more apt to use protective measures and good hygienic manners to avoid possible chemical hazards. That way they are more protected and less exposed than coworkers who may not realize the value of protective equipment.

Similarly, factors which are probably genetically determined may explain large differences noted in coping with external injuries caused by traffic accidents for example. Some persons with extensive physical handicaps – paraparesis, for example – may lead a very active and productive life, while others are completely defeated by similar traumas and accept the role of a sad invalid.

Other genetically determined factors in the response of the nervous system to chemicals are a possible lack of certain enzymes needed in detoxification of neurotoxic chemicals. One well-kown example is the lack of aldehyde dehydrogenase in a large proportion of the Japanese. Similar enzyme defects of less well known or unknown enzymes may explain some interindividual variation.

In similar working conditions, some persons may increase their body load of a toxic substance faster than others – whether through varying absorption, excretion or detoxification of the chemicals or neglect of hygienic measures – and such persons

acquire a harmful concentration faster. In a prospective follow-up study of lead-exposed workers, it was noted that those persons whose Pb-B rose quicker changed to another kind of work in a shorter time than others. After these workers left, the remainder did not exhibit slowing in their nerve conduction velocities, such as was noted during the two first years of lead-exposed work among those whose Pb-B was above the median value of the whole group (Seppäläinen et al. 1983).

2.4 Life Style

Life style varies between individuals, especially concerning the use of alcohol and drugs. Both psychotropic drugs and alcohol affect the nervous system and also induce the hepatic enzymes which take part in the toxicokinetics of workplace chemicals. We can assume that excessive use of alcohol may potentiate the effects of solvents and probably other chemicals as well. Consequences of alcohol abuse are similar to neurotoxic effects of other chemicals. Alcohol is one cause of dementia, decreasing mental capacity and loss of memory, as well as polyneuropathy; thus, problems arise in the differential diagnosis of occupational diseases.

It has also been suggested that certain chemical exposures at work may promote increased use of alcohol; for example, rotogravure printers exposed to toluene showed a greater alcohol consumption than their controls (Juntunen et al. 1985). Exposure to solvents and alcohol abuse may, therefore, be a two-way road, each leading to the other.

Alcohol may also increase the accident risk at work and thus also cause excessive exposures by accident: this can happen when the worker has consumed alcohol during the working day or is working during a hangover. Drugs may similarly increase the accident risk, and drugs compete for the same detoxification system as toxic chemicals. Psychic lability is often behind the use of drugs or alcohol, and the same lability also accentuates central nervous symptoms.

The real use of alcohol or drugs is often unknown to those who do medical or psychological studies on workers with chemical exposure either for research or for occupational health purposes. Many subjects and patients prefer to hide all kinds of abuses. These effects are also difficult to study scientifically because of the notoriously poor reliability of information given on alcohol and drug consumption. Susceptibility to effects of alcohol also varies greatly as everybody has seen from acute alcohol effects in social situations. Similarly, it appears that actual alcohol diseases vary among people, and the total amount of alcohol consumed before serious symptoms and signs appear may vary considerably.

Other life style factors, such as nutritional habits, play a role in modifying chemical effects. If the nutritional state is good and vitamins and trace substances stay in correct concentrations, people are more apt to cope with chemical exposure. If something is lacking, they are more sensitive towards external hazards.

The physical condition of the worker is also a modifying factor. A fit person who exercises outdoors is more apt to exhale residues of chemicals, and physical activities may also increase other ways of excretion of the toxic substance. Jogging may also increase inhalation of toxic substances: it has recently been shown in France that ur-

ban joggers have higher Pb-Bs than rural joggers. The body burden of fat-soluble chemicals such as organic solvents depends on the amount of body fat. Large reservoirs of fat keep solvents longer in the body and thus lengthen the period of exposure. As there are sex differences in the distribution of fat tissue, this may partly explain some sex differences in the response to solvent exposure.

3 Conclusions

It seems that the variability in response of the nervous system to workplace chemicals partly depends on actual variability of exposure conditions – especially the occurrence of high peak exposure periods which may greatly deteriorate health – and partly on actual individual variability in response.

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The Impact of Nonwork-Related Impairments of Organ Functions on the Toxicokinetics and Toxicodynamics of Industrial Chemicals

R. Lauwerys

1 Introduction

The "acceptable exposure levels" to industrial chemicals recommended in many countries usually intend to prevent the occurrence of adverse health effects in the majority of the exposed workers. In view of the type of scientific information on which they are based (e.g. experimental studies on healthy inbread animals; cross-sectional epidemiological studies on active workers; retrospective morbidity and mortality studies on cohorts of workers), these acceptable exposure levels mainly apply to healthy persons.

No biological or environmental limit value takes into consideration the possible increased susceptibility of certain individuals because of genetic or acquired biological or functional impairments. At first sight, this approach seems reasonable, as long as a regular surveillance programme permits the early detection of hypersusceptible individuals. The occupational physicians, however, should be aware of the few industrial chemicals which have already been shown or suggested to be more deleterious to workers with preexisting disease states than to healthy subjects.

This paper intends to illustrate, through a few examples, the interest of further assessment of the genetic and acquired health impairments which may exacerbate the toxic effects of chemicals or increase the risk of adverse effects.

2 Nonwork-Related Factors

2.1 Genetic Factors

There exist few, if any, known genetic factors which have been clearly demonstrated to be linked with increased susceptibility to industrial chemicals. So far, only suggestions of possible interactions between genetic factors and toxicity of industrial chemicals have been offered.

Genetic differences in the ability to metabolize carcinogenic chemicals (e.g. polycyclic hydrocarbons) might influence the risk of occupational cancer (Kellerman et al. 1973). It has been reported that subjects with lung cancer have an increased ability to metabolize (hydroxylate) debrisoquine (Ayesh et al. 1984). Workers with this characteristic might produce more ultimate carcinogenic metabolites following exposure to polylcyclic hydrocarbons (e.g. coke oven workers). Likewise, subjects who have a reduced ability to acetylate (inactivate) aromatic amines (slow acetylator phenotype)

may be more at risk of developing bladder carcinoma when exposed to arylamines or related compounds (Cartwright et al. 1982; Hanssen et al. 1985).

It has been suggested, but not yet clearly demonstrated, that subjects with partial genetic deficiency (heterozygotes) in α_1-antitrypsin are more prone to develop emphysema or chronic obstructive pulmonary disease when exposed to irritant gases, dusts and mists (Cooper 1973; Mittman et al. 1974; Morse et al. 1975; Stokinger and Scheel 1973).

It is known that atopic subjects are more likely to develop allergic reactions (asthma, urticaria) when exposed to occupational allergens (e.g. platinum salts, organic dust) (Hughes 1980).

2.2 Disease States

Pathological conditions may influence the response to toxic chemicals either by mofifying their metabolism (toxicokinetic interaction) or by increasing the susceptibility of the target organs (toxicodynamic interaction).

2.3 Toxicokinetic Interaction

It is evident that any disease (e.g. hepatic or renal insufficiency) which alters the absorption, biotransformation, distribution or excretion of industrial chemicals may modify their toxicity. If examples of such interactions in animals are numerous, well-documented human data are limited. We have found that the methylation of inorganic arsenic is different in patients with hepatic insufficiency (decreased monomethylarsonic acid and increased dimethylarsinic acid production) than in control subjects (Buchet et al. 1984). It is not yet known, however, whether this effect has any influence on the long-term toxicity of inorganic arsenic. We have observed the occurrence of a fulminant hepatonephritis in an epileptic treated with phenobarbital who had been slightly exposed to carbon tetrachloride (CCl_4) (Mahieu et al. 1983). In this case, however, it is not the previous disease which is responsible for the increased susceptibility to CCl_4, but its treatment. Microsomal enzyme induction by phenobarbital has led to an increased CCl_4 activation.

2.4 Toxicodynamic Interaction

Previous disease states or a reduction of organ function with age may exacerbate the toxicity of some industrial chemicals. It has been suggested that persons with myocardial conduction defects due, for example, to coronary sclerosis may be more susceptible to the arrythmogenic activity of trichloroethylene. It has been recommended to remove persons with ECG changes from trichloroethylene exposure (Lilis et al. 1969).

Clinical studies have suggested that asthmatic patients are more responsive to various lung irritants (H_2SO_4, SO_2 and O_3) than control subjects (Bethel et al. 1983;

Jaeger et al. 1976; Koenig et al. 1981, 1983; Linn et al. 1983; Sheppard et al. 1981; Spektor et al. 1985; Uttel et al. 1983).

The reactivity of the airways to short-term (2-h) exposure to O_3 (0.12 and 0.3 ppm) is not increased in subjects with chronic obstructive pulmonary disease (COPD) (Linn et al. 1982; Solic et al. 1982). However, contrary to control volunteers, COPD patients exhibit a transient reduction of the blood oxygen saturation (Solic et al. 1982).

It has been demonstrated that slight exposure to CO favours the occurrence of acute angina pectoris or intermittent claudication in patients suffering from coronary or peripheral arterial sclerosis, respectively (Anderson et al. 1973; Aronow et al. 1974; Aronow 1981). The physical working capacity of patients with COPD is reduced following exposure to 100 ppm CO for 1 h (Aronow et al. 1977). Calverley et al. (1986) have also reported that a carboxyhaemoglobin level of 9% significantly decreases the work capacity of patients suffering from chronic bronchitis or emphysema.

3 Conclusions

The progress in medicine has increased the proportion of handicapped subjects in the active population, but our knowledge of the impact of acquired or genetic deficiences on the toxic response to industrial chemicals is still very limited.

Occupational physicians frequently find it difficult to advise workers suffering from various diseases on the possible risk associated with specific chemical exposure. Questions such as the following are sometimes raised and are still without clear answer. Can an epileptic or a patient with multiple sclerosis in remission or a subject treated for depression be kept exposed to organic solvents? Can exposure to tetrachloroethylene in a dry-cleaning shop modify the evolution of chronic active hepatitis or chronic glomerulonephritis? Can a young worker who has had a valvulotomy for mitral stenosis be exposed to halogenated hydrocarbons? Can a worker with moderate hypertension be maintained at a workplace involving exposure to Cd or to CO? Which industrial chemical exposures are contraindicated for patients with a history of chronic duodenal ulcer? Should a diabetic with preclinical signs of peripheral neuropathy keep a job involving exposure to lead or mercury vapour or aliphatic hydrocarbons? Should a 50-year-old worker treated for hypothyroidism be removed from lead exposure when his plombemia exceeds 40 μg/100 ml? Should a nurse who has had a previous abortion be kept exposed to volatile anaesthetics when pregnant?

Several approaches might be considered to improve our knowledge in this area. Experimental models could be developed to assess the possible interactions between health impairments and chemical exposure. It is certainly more difficult to design epidemiological studies for assessing interaction phenomena. Frequently, cross-sectional studies are designed in such a way that workers with preexisting diseases are removed from the examined populations before statistical analysis (elimination of confounding factors); this prevents the study of possible interactions. However, it is likely that the small number of subjects with specific health impairments and also exposed to specific chemicals will be the main limiting factor for the epidemiological approach. Occupational physicians, therefore, should be encouraged to report cases of possible interactions

between preexisting disease and exposure to industrial chemicals. This requires the development of toxicovigilance systems at the national or international level. Case reports do not usually prove the existence of an association, but they may stimulate other physicians to look for similar situations and toxicologists to set up experimental studies for testing the suggested hypothesis.

It should be realized that the detection of health impairments or biological factors which may increase the susceptibility to some industrial chemicals raises an important ethical issue. There is a risk that this information is mainly used for preemployment selection. Before initiating any preemoployment screening programme, the occupational physician should discuss this ethical problem with employer and worker representatives and attempt to formulate specific guidelines on which both parties can agree.

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Screening Models in Occupational Health Practice to Detect and to Assess Individuals and Groups at Risk Because of Exposure and/or with Decreased Capacities to Cope with Workplace Chemicals

D. Lahaye

1 Health Surveillance

Health surveillance in the workplace can be tackled in two ways: lowering of exposure to toxic agents and/or screening of populations of workers for identification and removal from risk of susceptible individuals. In modern Western countries, much has been achieved in the control of exposure in the workplace. Meanwhile, the medical scientists have focused their efforts on new screening methods and more sensitive laboratory tests for the detection of susceptibilities.

2 Medicolegal Consequences

In the Belgian Insurance Fund against Occupational Diseases (FOD), this trend had major consequences from the medicolegal point of view:

1. The typical occupational disease pattern is becoming less frequent. There is a shift towards a more vague or even latent symptomatology, leaving the occupational physician or medical advisor of the insurance in a position in which no clear-cut diagnosis can be made. Therefore, general criteria are being applied with caution.
2. New "work incompatibilities" towards toxic environments are being observed due to the application of more sensitive screening laboratory tests in otherwise healthy worker's populations.
3. The diagnosis cannot easily be fitted into the "list of prescribed occupational diseases" [e.g. occupational cancers, cobalt lung (extrinsic allergic alveolitis)]. This list urgently needs a thorough revision.

In Belgium, the FOD is in charge not only of the compensation for disability due to occupational diseases but also of the prevention of these by withdrawal of workers from their occupational environment. Belgian law encourages proposing to an individual worker that he or she be removed from the hazardous occupation. This legal procedure can only be motivated on medical grounds. The withdrawal may be temporary or permanent. For the temporary withdrawal, one has to produce legal proof of what is called *the first symptoms* of the disease.

According to Hatch (1973), it may indeed be possible to recognize some health defects before "breakdown" occurs (Fig. 1). In this way, a permanent impairment which is more difficult to repair might be avoided. Here we touch the borderline between health and disease, between normality and impairment. If we consider the me-

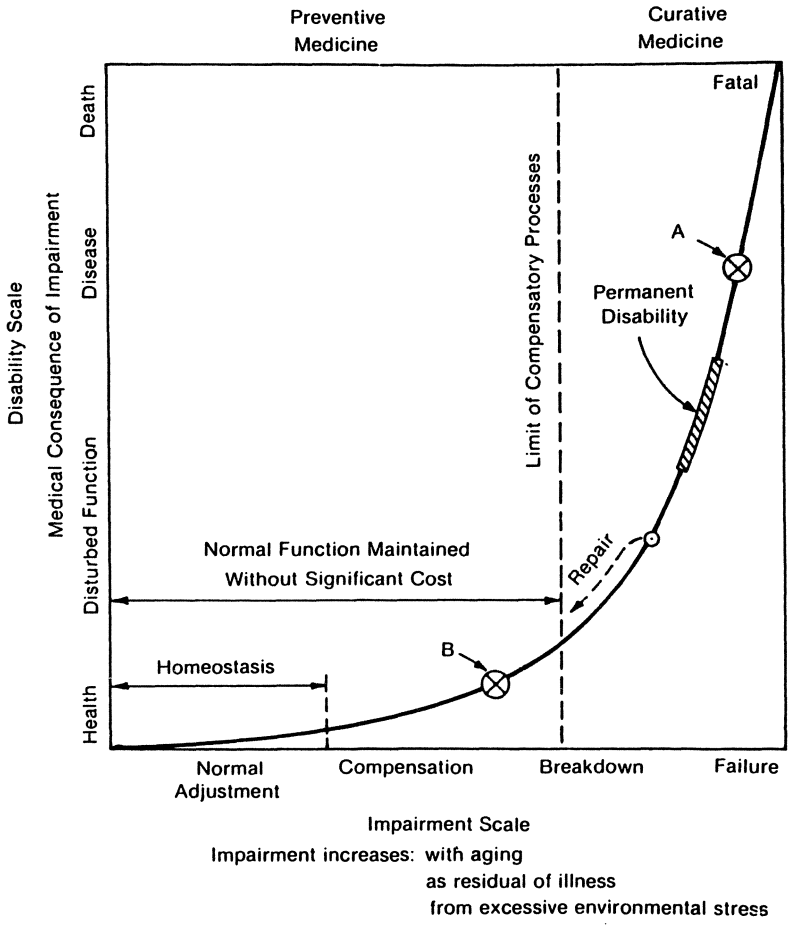

Fig. 1. Suggested relationship between impairment and consequent ill health. Because of the protection afforded by homeostatic and compensatory processes, considerable movement along the impairment axis is accompanied by relatively little disability. Thus, a state of health is maintained with no threat of potential ill health over a substantial portion of the homeostatic and compensatory zones. (Adapted from Hatch 1962)

dical criteria of the FOD on temporary withdrawal (Table 1), we can easily ascertain that only a few biological (effect) monitoring [B(E)M] data are accepted as a criterion for removal of the worker. The question whether BEM belongs to the "homeotasis" or to the "compensation" part of Hatch's curve remains unanswered. Although B(E)M can be used as a criterion for temporary removal of the worker at risk, it does not give us any idea about the existence of ill health or impairment. For the insurance, however, this distinction is of capital importance.

For permanent withdrawal of workers from occupational exposure, the FOD uses a set of criteria in order to establish the *predisposition* for the most frequent occupational diseases (Lahaye 1984) (Table 1). The uncommon occupational diseases (intoxi-

cations: first group of EEC list) are evaluated by analogy. The medical advisor of the FOD here faces a difficult problem: is the medically established susceptibility reason enough to let the worker lose his job permanently and put him in a weak professional situation in times of economic recession and high unemployment? If the answer is affirmative, then the insurance has to propose a professional rehabilitation programme resulting in re-placement in a job in which the previous occupational hazard does not exist. The FOD has until now used this preventive measure cautiously. The results are shown in Table 2.

Table 1. Medical criteria for withdrawal of workers from the harmful occupational environment. (From Lahaye 1984)

Intoxication	Criteria for withdrawal	
	Temporary withdrawal	Permanent withdrawal
Lead (at least 2 positive criteria)	Pb-U $>$ 80–100 µg/l ALA-U $>$ 6–8 mg/l Pb-B $>$ 60 µg/100 ml Positive EDTA provocation test (Lahaye et al. 1968) Positive FEP or ZPP	Renal dysfunction Hypertension Chronicity Ulcerative colitis
Mercury	Hg-U $>$ 50–100 µg/l Hg-B $>$ 0.8–1 µg/100 ml	CNS disturbances Renal dysfunction (impaired creatinine clearance)
Cadmium		Cd $>$ 10 µg/g creatinine (3 positive tests) β_2 Microglobulin $>$ 200 µg/g creatinine Retinol-binding protein $>$ 170 µg/g creatinine Albumin $>$ 12 µg/g creatinine Total protein $>$ 250 mg/g creatinine, all in urine Cd $>$ 1–3 µg/100 ml in blood
Benzene		WBC $<$ 2500/mm^3 RBC $<$ 4000000/mm^3 Granulocytes $<$ 1500/mm^3 Thrombocytes $<$ 150000/mm^3 Aplastic or hypoplastic bone marrow Chromosomal anomalies Leukaemia in remission
Dermatosis	Orthoergic	Allergic (positive skin test)
Occupational Asthma		Obstructive syndrome Positive provocation test
Byssinosis		Phase I and II

Table 1. (continued)

Intoxication	Criteria for withdrawal	
	Temporary withdrawal	Permanent withdrawal
Pneumoconiosis		Evolutive cases Presence of tuberculosis Bronchitis or asthma (obstructive syndrome) Pseudotumoral stage
Hypoacusis		Evolutive cases (loss of 15 dB/in 1 year (at frequency 1000–2000–3000 cycles/s) Stapedectomy Epilepsy Unilateral deafness
Diseases due to vibrations	Raynaud phenomenon	Rheumatoid arthritis Burger's disease Sciatic nerve disease Arthrosis of upper limbs

Abbreviations: Pb-U, lead in urine; ALA-U, aminolaevulinic acid in urine; Pb-B, lead in blood; EDTA, ethylenediaminetetraacetate; FEP, free erythrocyte protoporphyrin; ZPP, zinc protoporphyrin; Hg-U, mercury in urine; Hg-B, mercury in blood; dB, decibel.

Table 2. Survey of the number of cases that have been withdrawn from the occupational environment since 1965. (From Lahaye 1981)

	Temporary withdrawal	Permanent withdrawal		Total
		Re-placement after professional rehabilitation	Re-placement without professional rehabilitation	
Absolute number of withdrawals since 1965	3974	116	2096	6184
Percentage of the total (1965–1980) number of cases examined by the FOD in 1980	1.99	0.06	1.01	3.1
Percentage of the total number of withdrawals (n = 688) of claims (± 10000) per year (1980)	4.4	0.13	2.3	6.8

The results of such rehabilitation programmes appear to be poor. An adequate solution is only reached for a minority of workers. The others remain exposed until they are too much impaired to carry on occupational activities. The final result is total disability.

Although we recognize the necessity of this procedure as a solution for obvious cases of individual susceptibility (e.g. allergy), the figures prove the inadequacy of the measure as a tool for prevention.

3 Genetic Susceptibilities

How far can one go in the detection of susceptibilities? Is it necessary, for example, to screen a population of a genetic susceptibility (Omenn 1984) and to withdraw all workers with a positive result from the toxic environment (Table 3)?

There is obviously a significant difference between the criteria for permanent withdrawal proposed by the FOD (Table 1) and this list of susceptibilities. The latter means a further step towards early withdrawal from occupational hazards. It could put the occupational physician in a difficult position, especially in small factories where job permutations are often impossible.

4 Conclusion

If a medical restriction regarding some risk environment is discovered, the individual's chances of being rejected from any lucrative job in industry increase considerably. But if the occupational physician does not propose to withdraw the worker from the toxic occupational environment for minor susceptibilities, then it is possible that the worker may still remain able to work regularly in the toxic environment for quite some time. The question then arises what the purpose of costly screening examinations is if positive results do not lead to adequate preventive measures for the individual.

Much effort in occupational medicine is spent on screening methods. However, identification and withdrawal of a small number of hypersusceptible individuals provides no solution for the real problem: the widespread exposure of workers to a harmful occupational environment. The better the work environment can be controlled, the less likely are susceptible individuals to lose their job.

The title of the paper suggests a description of several alternative screening models. Although some susceptibilities have been mentioned, it has mainly focused on the opportunity of screening as a tool for prevention. Obviously, primary prevention of exposure must be considered as more effective in health surveillance of workers than screening programmes.

However, one may argue that this is not a matter of science but a matter of policy. The scientist can only describe the relationship between exposures and their effect on human health. The choice of criteria is up to the parties involved: employers and employees. There is always a risk acceptance (a notion well known in safety sciences), which is mainly based on nonscientific arguments.

Table 3. Genetic variation in human susceptibility to environmental agents. (From Omenn 1984)

Drugs	
Metabolism: *N*-acetyltransferase, plasma pseudocholinesterase, C-oxidation	
Sensitivity: G6PD deficiency, methemoglobin reductase deficiency	
Inhaled, pollutants/pesticides	
α_1-Antitrypsin deficiency	
Aryl hydrocarbon hydroxylase inducibility	
Metabolic conversion of nicotine	
Plasma paraoxonase activity	
Foods	
Lactose intolerance	Fava beans
Wheat gluten/celiac disease	Goitrogens
Saturated fats/atherosclerosis	Catecholamines
Food additives, and stimulants	
Iron, ethanol, caffeine	
Physical agents	
Cold weather, motion sickness, metal poisoning, colour vision, ultraviolet radiation, X-radiation	
Infectious agents/autoimmune disorders	
Malaria: Duffy blood group; sickle haemoglobin, thalassemia, G6PD deficiency	
Predispositions due to imparied antibody production or cellular immunity	
Predispositions associated with histocompatibility phenotypes	

Finally, a major difficulty for screening programmes lies in the lack of congruence between on the one hand the list of occupational hazards for which screening is imposed and, on the other, the list of prescribed occupational diseases allowed for compensation. Also, the use of the EEC list does not stimulate more systematic research into new or potential occupational risks. This is illustrated by the current inadequacy of the EEC list in the problem of registration of occupational cancer (Lahaye and Van Sprundel, 1988).

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Analytical Variability of Biological Parameters of Exposure and Early Effects

R. F. M. Herber and K.-H. Schaller

1 Introduction

In occupational medicine, the objective of any examination is to obtain a finding which can be related to the individual subject. In the case of exposure to hazardous substances, this finding is usually the result of an analytical determination of:

1. The concentration of the substance itself in various biological media (blood, urine, expired air, hair, fingernails, adipose tissue and saliva)
2. The concentration products (metabolites) in the same media (1 and 2: biological parameters of exposure) (Lauwerys 1983)
3. Biological parameters of early effects that are the result of the reaction of the organism to exposure (biological parameters of early effects) (Lauwerys 1983)

and/or the assessment of the health risk by estimating the external exposure to the chemical, i.e. ambient monitoring of the airborne concentration of the chemical (Zielhuis 1985).

The analytical result is influenced by the preanalytical phase and the analytical determination. Both stages are associated with specific errors. Interference factors can modify the results of the analysis in vitro. These factors must be differentiated from biological factors which in vivo may lead to alterations in the concentrations of the toxicological parameters, e.g. toxicokinetic behaviour, circadian rhythm, influence of alcohol, smoking and variability of matrix (diuresis) (Angerer et al. 1983; Keller et al. 1985). From the analytical point of view, the interpretation of the errors due to interference factors and matrix variability in relation ot intra- and interindividual biological variability of parameters is relevant.

2 Biological Parameters of Exposure

Biological monitoring (BM) of exposure assesses the health risk through the evaluation of the internal doese. The assessment is normally performed on an individual basis but may be done on a group basis. Internal dose estimation involves several critical steps in the *preanalytical phase* (sampling, storage, shipment, processing of urine, whole blood, serum or plasma, hair and fingernail specimens) and *analysis.* The final result depends of course on how well these procedures have been performed (Kneip and Friberg 1986).

2.1 Preanalytical phase

A very important step in the preanalytical phase that can contribute to a large variability of results is the time of specimen collection. Some industrial chemicals have a long biological half-life in various body compartments, and the time of sampling is not critical. For other chemicals the time of sampling is critical because after exposure the compound and/or metabolites may be rapidly eliminated from the organism. In these cases, the biological sample is usually collected at the end of the working shift after at least 3 consecutive days of work or just before the next morning shift (16 h after the end of exposure).

In the case of inorganic substances, the sources of error are, inter alia, contamination of the sample during collection and further contamination or loss of analyte during both storage and subsequent procedures used to prepare the sample for measurement of its trace metal contents. In the case of numerous organic substances, it is primarily their volatility or chemical reactivity that can influence the results of the analysis (Berlin et al. 1979).

Before the collection of biological material, subjects should change their clothes, and in the case of exposure to inorganic substance and the determination of metals in urine, extensive washing is recommended. Great care must be taken in the selection and preparation of sampling equipment. Disposable collecting instruments and containers should be employed. Acid-cleaned test tubes or tubes certified by the manufacturer must be used for collection of blood samples. However, freedom from contamination for a particular substance must not be assumed until proven. Urine should be collected in plastic bottles cleaned with acid, particularly when heavy metals are to be determined. For the detection of organic substances in blood and urine, which are frequently volatile, it is expedient to use glass ampoules closed with teflon-coated rubber stoppers for collection, transportation and analysis containers.

Periods ranging from several days to several weeks often elapse before the specimens are finally analyzed in the laboratory. An important factor is, therefore, the storage temperature. For the majority of relevant parameters, it suffices to store the specimens in the refrigerator (at +4 °C). Addition of acid to urine is often necessary. Storage for more than 3 weeks should occur at a temperature of −18 °C to −29 °C. When a precipitate forms by cooling, care must be taken that the samples are stirred, so that any deposits are dissolved or evenly distributed (Angerer et al. 1983).

There are many potential sources of error in sampling and processing of biological material prior to analysis. These errors cannot be detected or controlled by statistical quality assurance. However, it is possible to obtain reliable results when these sources of error are known, and their presence and/or effect can be reduced by as much standardization of the preanalytical phase as possible.

2.2 Analytical Phase

Assuming that correct sampling has been performed, the next step is the quantitative analysis. Analysis of biological material such as whole blood, serum, urine, fingernails, hair and expired air involves many steps from the moment the sample arrives at the laboratory until the final reading is obtained. The main steps are homogenization, sam-

ple preparation (digestion and extraction) and chemical and/or physical analysis. The media to be examined may exhibit large differences in both matrix composition and analyte content. There are no standard procedures applicable to all types of media. However, for all these methods, the analytical reliability criteria must always be carefully considered. The accurary, precision and detection limit of the analysis should be satisfactory. Several intercomparison programmes for the analysis of industrial chemicals in biological materials have indeed stressed the analytical difficulties sometimes associated with these measurements. Therefore, a rigorous programme of quality control is needed to confirm the reliability of the results (Kneip and Friberg 1985).

A biological parameter of internal dose has to fulfil a lot of criteria (e.g. sufficient analytical specificity, adequate analytical sensitivity, little discomfort to the subject and ethical aspects). Furthermore, the analytical and biological variability of the test must be acceptable.

The data on the precision of the BM methods for some important industrial chemicals are given in Table 1. Estimates of precision should be accompanied by information as to how they are obtained, and an effort should be made to make these correspond

Table 1. Present analytical reliability criteria for the determination of some relevant parameters of internal dose

Parameter	Analytical technique	Imprecision		Recovery of amount added (%)	Detection limit
		Within series (%)	Between days (%)		
Pb-B	ET-AAS	3 – 6	4.5– 6	97	10 µg/l
Hg-U-B	Cold vapour	1.7– 6.2	3.1– 4.9	98	0.1 µg/l
Cd-U	ET-AAS	3.7– 4	6.8–10.5	106	0.1 µg/l
Cd-B	ET-AAS	5.5–12.3	6.6– 8.4	95	0.1 µg/l
Cr-U	ET-AAS	5.6	5.5– 8.5	95	0.3 µg/l
Co-U	ET-AAS	4.7– 8.6	5.3–11.2	101–108	0.1 µg/l
F-U	Ion-selective electrode	1.6	2 – 4	93	0.1 mg/l
Benzene-B	Headspace-GC	5.4– 6.0		101–117	0.02 mg/l
Toluene-B	Headspace-GC	2.5– 7.0		100–101	0.04 mg/l
Xylene-B	Headspace-GC	5.6– 8.9		97–105	0.04 mg/l
PCP-U-S	GC	1.6– 6.4		77–102	0.05 mg/l
Tri-B	GC	1.5		98	0.1 mg/l
PGA-U	HPLC	5 –10	2.7– 5.4	86–108	15 mg/l
MA-U	HPLC	4 – 9	5.8– 1.6	91–102	25 mg/l
HA-U	HPLC	3 – 7	3.4–12.8	99	25 mg/l
MHA-U	HPLC	5 – 9	9.2– 1.6	100–116	15 mg/l
TCE-B-U	GC	1.5– 3.6	4 – 8.5	97	0.05 mg/l
Phenol-U	HPLC	2.3– 3.8	2.1– 4.5	86–101	1 mg/l

Abbreviations: -B, in blood; -U, in urine; Co, cobalt; F, fluorine; PCP, pentachlorophenol; PGA, phenylglyoxylic acid; TCE, trichloroethanol; GC, gas chromatography; Tri, trichloroethene, MA, mandelic acid; HA, hippuric acid; MHA, methylhippuric acid; ET-AAS electrothermal atomic absorption spectrometry.

to the precision prevailing in regular analytical work. Most tests show an acceptable precision (within series as well as from day to day). This is acceptable in view of the biological variability (intra- and interindividual) of these parameters. In clinical chemistry, it is proposed that analytical goals should be derived from biological variation data. For analyses used in monitoring an individual, it has been proposed that the allowable analytical variance should be less than or equal to half of the average intraindividual variation (Shepard et al. 1981). To our knowledge, this can also be applied to the presently used methods in BM.

The quality of analytical data depends mainly on the accuracy of the analytical methods. The use of inappropriate methodology and unsuitable equipment may be a major source of error. It is important to emphasize, however, that there is no definite method of BM which always gives accurate and precise results. Inaccurate results may also be related to lack of competence or concern among the analysts. Human factors are often very important and can introduce errors. The risk of contamination during analysis is particularly great when monitoring concentrations of substances which are widely present in the environment (e.g. Cd, Pb, Cr, Ni annd Al). Similarly, losses of the substance to be monitored can occur (adsorption to equipment and volatilization). These errors can only be recognized by different specific quality assurance (internal and external quality control) procedures. Internal quality control is conducted by the laboratories themselves, while an outside laboratory or agency is involved in the external quality control procedures. Analytical procedures can be checked by analyzing reference samples or by carrying out duplicate analysis at reference laboratories.

2.3 Conclusion

The quality of analytical data of the internal dose depends on the reliability of the analytical methods and the quality of several steps related to procedures prior to the analysis. Recording and treatment of data is included in both the preanalytical and the analytical phase. Analytical procedures can be checked by internal and external quality control. The preanalytical phase is more difficult to control by procedures giving a quantitative measure of the quality. There is a need to standardize sampling procedures and to have good programmes to monitor the quality control of analytical data.

3 Biological Parameters of Early Effects

3.1 Introduction

As many effects may occur as a response of the human body, some types of effects are chosen which can be related to different agents:

1. *Effects on heme synthesis.* Agent: Pb, Cd, hexochlorobenzene, polybromated biphenyls (PBB), polychlorinated biphenyls (PCB), alkyl benzenes, halogenated phenoles, chlorodibenzodioxins (e.g. tetrachlorodibenzo-dioxin), vinyl chloride, methyl chloride, chloroform, octachlorostyrene, dibenzofurane and endrin (these compounds are of course not all equally important).

2. *Effects on kidney function.* Agent: Cd, Pb, Hg, Cr and Ni, and many solvents such as phenols, alkyl benzenes, alkanes, esters and styrene.
3. *Effects on cholinesterase.* Agent: organophosphates (e.g. parathion) and carbamates.

It will be clear that an enzyme, an organ and/or a system have been chosen. The effects on heme synthesis are mostly on enzymes, e.g. 5-aminolaevulinic acid dehydrase (ALA-D) and synthetase; indirectly on porphyrines such as zinc protoporphyrin (ZPP) and coproporphyrin, and on precursors such as 5-ALA and porphobilinogen; and finally, on haemoglobin itself.

The effects on kidney function can be divided into (a) effects on tubular function, e.g. on the enzymes *N*-acetyl-β-D-glucosaminidase (NAG), β-galactosidase and β-glucuronidase, and on the proteins β_2-microglobulin and retinol-binding protein; and (b) effects on the glomerular function, e.g. on albumin, immunoglobulin G, orosomucoid and transferrin.

3.2 Preanalytical Phase

3.2.1 Whole Blood, Serum

Venepunctures are preferable to finger or ear punctures in the case of blood or serum. No special requirements will be necessary in the case of whole blood. Enzymes and some other compounds have to be determined directly after venepuncture. Common anticoagulants can be used. The storage depends on the compound, but most compounds must be determined directly. Generally, it can be said that the more complex a compound is (e.g. enzymes), the sooner the determination should be completed.

3.2.2 Urine

In theory, 24-h or 6-h urines are to be preferred to spot urines; however, as the measurement time is critical – which even in hospitals seems to be problematic – spot urines are the most easily obtained samples. Preservation against bacterial growth and fungi formation can be done by adding a solution of sodium azide. Determination of enzymes must be done preferably within 24 h, but at least within 1 week when stored at 4 °C. Proteins can be stored for months if stored at –20 °C. In urine, typical problems, such as sedimentation, can arise. The sediment should be resolved by techniques such as carefully heating to 37 °C and/or ultrasonification. Containers for both blood and urine samples should be soaked in diluted acid. The preferable material for freezing is polyethene or polystyrene.

3.3 Analytical Phase: Precision and Accuracy

In general spectrophotometric methods are used for the determinations. Spectrophotometric measurements must generally be preceded by a separation technique to separate the compound or enzyme of interest from the matrix. This separation technique ap-

pears to be the weakest point. Incomplete recovery and inadequate separation are responsible for faulty determinations. It is astounding that, contrary to the determination of BM parameters, data in occupational health papers about precision are rare; data about accuracy and intercomparison studies are even rarer. A survey of the last two volumes of 12 journals in occupational health and toxicology, including four journals with an additional four volumes from 1981 on, showed the following data:

1. *Effects on heme synthesis.* For 5-ALA-D, a European standardized method (ESM) exists (Berlin and Schaller 1974). Strangely enough, this method is not always used. Despaux-Pages et al. (1986) developed their own method and compared it with the ESM. For 5-ALA in urine, two papers were found: Tomokuni and Hirai (1985) described the depressing effect of urea on the 5-ALA concentration determination. A very rare example of good quality control is given in the paper on erythrocyte protoporphyrin (EP) by Rabinowitz et al. (1986): "In monthly interlaboratory blind trials with 111 samples sponsored by the Center for Disease Control, our methods produced values with an average absolute difference from the reference values of 8 (SE = 1) μg/dl, a difference of 6 for the 53 samples with EP less than 100, and a difference of 3 for the 8 samples with EP under 50, the range encountered in our sample".
2. *Effects on kidney function.* In the period mentioned, only one paper was found dealing with analytical problems in the determination of kidney function parameters. The paper by Mosczcynski and Lisiewicz (1985) mentioned the precision of NAG, calculated as relative standard deviation (RSD), to be 10.1%.
3. *Effects on cholinesterase.* Here too, only one reference was found. Hackathorn et al. (1983) calculated the precision of the method, presented as RSD = 10% for 12 groups, day-today RSD = 1.6%, and interindividual RSD = 6%. From the baseline value, RSD = 7.8%.

3.4 Matrix Variability

Only some clinical examples of matrix variability are known for blood. Lipoproteins and anaemia may cause problems in the determination of the effect parameter. For urine, the matrix variability is far more problematic. In addition to the above-mentioned dilution factor, nearly all major elements and compounds can vary dramatically, thus leading to interference problems for the determinationn of the compound of interest. An example would be the above-mentioned interference of urea in the determination of 5-ALA. One possible general recommendation may be improved separation with the goal of avoiding interfering substances.

3.5 Interpretation and Conclusion

Effect parameters can be used in different ways. One way is to use the effect parameter itself to assess health risk. Another way is to assess the dose via the dose-effect relation. For both ways, some important conclusions can be drawn:

1. For health assessment, the most sensitive parameter should be used.
2. For dose assessment on the basis of an effect parameter, the criteria should be a rather linear or log-linear relationship and, if possible, no time-lag. The assessment of the dose in this way gives a large scatter (Herber 1980). An improvement is offered by the approach of Brockmann et al. (1981), who suggested determination of two effect parameters, in this case EP and 5-ALA-U. This leads to an improved assessment of the dose or dose class. Another possibility is the use of the method of Goldstein et al. (1984), which uses early reversible indicators and with the aid of discriminant analysis presents the level of exposure to the toxic agent in relation to the index of biological damage.
3. Intercomparison surveys are just as necessary for effect parameters as for dose parameters. This also includes physical measurement parameters such as blood pressure and electromyography.
4. Insensitive methods may lead to faulty no-effect levels.
5. Different effect levels may be due to inaccurate methods.
6. Standardization is necessary for all enzyme methods, just as in the case of 5-ALA-D.
7. Repeated determination of effect parameters is strongly advised.
8. In journals, no papers without accuracy and precision data should be accepted, with the exception of new methods when no intercomparison is possible.

In fact, as the determination of an effect parameter is more related to health than the determination of an EM or BM parameter, even more care should be taken with respect to accuracy.

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Theme III
The Impact of Other Conditions at Work and off Work on Exposure and Response

The Impact of Aspects of Time and Duration of Exposure on Toxicokinetics and Toxicodynamics of Workplace Chemicals

H. M. Bolt and J. Rutenfranz

1 Introduction

The policy for defining a maximal concentration value in the workplace (MAK) for specific substances is different in different countries (Zielhuis 1974). In most countries, MAK values are set for 8 working hours per day and 40 h per week. Often, however, this does not correspond with reality since the organization of working hours, including shift work, implies substantial variations, depending on national regulations and social contracts in certain or even in the same industries; different shift systems are involved (Rutenfranz et al. 1976). The regular daily working hours in the German chemical industry vary between 8 and 12 h, the weekly working hours in special parts of shift systems between 36 and 60 h.

It is obvious from recent reviews (Rutenfranz et al. 1977, 1981) that shift systems should not be constructed arbitrarily, but should meet special physiological and psychological criteria. To sum up the most widely accepted criteria for continous systems with four crews, a shift system should be rapidly rotated, should include shifts of either 8 or 12 h, depending on the load of the task, and include 2 free days at weekends (at least one weekend per month); compressed weekly working hours should be avoided (Knauth and Rutenfranz 1982).

In constrast to these proposals, the current practice in the most important chemical plants in the Federal Republic of Germany is (a) rapidly rotated 12-h shift systems, with 48 h free after night shifts; (b) shift systems with five to seven identical shifts (morning, afternoon, night) in succession; or (c) shift systems in which the working hours of 4 weeks are compressed into 3 weeks, with weekly working hours up to 60 h (Fig. 1).

These variations in working hours and shift systems reflect a great variation of time, duration and sequence of exposure, which may lead, under special conditions, not only to problems of accumulation of toxic agents but also to influences on toxicokinetics and -dynamics.

The organizers of the workshop, therefore, addressed to the authors the problem of whether MACs/TLVs should be adapted to different work schedules. They also asked us to discuss the limitations of present MACs/TLVs on the basis of concepts arising in the new subdiscipline of chronopharmacology.

This paper considers both practical and theoretical aspects of this topic. The practical considerations are based on the current regulations in the Federal Republic of Germany concerning environmental monitoring (MAK values) and biological monitoring (BAT values) at work.

Day		Mo	Tu	We	Th	Fr	Sa	Su
Crew	1		N	N	N	N	N	N
	2	N				M	M	M
	3	M	M	M	M			
	4	A	A	A	A	A	A	A

Day		Mo	Tu	We	Th	Fr	Sa	Su
Crew	1	$\bar{D}$	$\bar{N}$			$\bar{D}$	$\bar{N}$	
	2		$\bar{D}$	$\bar{N}$			$\bar{D}$	$\bar{N}$
	3			$\bar{D}$	$\bar{N}$			$\bar{D}$
	4	$\bar{N}$			$\bar{D}$	$\bar{N}$		

Day		Mo	Tu	We	Th	Fr	Sa	Su
Crew	1	M	M	M	M	M	M	$\bar{M}$
	2	A	A	A	A	A	A	
	3	N	N	N	N	N	N	$\bar{N}$
	4							

$\bar{D}$ = day shift (12 hours)
M = morning shift
$\bar{M}$ = morning shift (12 hours)
A = afternoon shift
N = night shift
$\bar{N}$ = night shift (12 hours)
▒ = day off

Fig. 1. Shift systems for continuous production used in different plants in the chemical industry

2 Regulatory Situations in the Federal Republic of Germany

Details of this chapter refer to the current list of "Maximum concentrations at the workplace and biological tolerance for working materials" (Deutsche Forschungsgemeinschaft 1985).

2.1 Environmental Monitoring

The MAK is defined as "the maximum permissible concentration of a chemical compound present in the air within a working area (as gas, vapor, particulate matter) which, according to current knowledge, generally does not impair the health of the employee nor cause undue annoyance" (Deutsche Forschungsgemeinschaft 1985). This official general definition is followed by the modifying statement: "Under these conditions, exposure can be repeated and of long duration over a daily period of eight hours, constituting an average work week of 40 h (42 hours per week as averaged over four successive weeks for firms having four work shifts)". The main reasons for this condition were matters of legislation, and the question arises how far it is based on scientific grounds. In fact, this sentence changed in 1979. Before this date, the MAK values had been fixed for an average working week of up to 45 h. This nominal change was introduced without changing the concentration values of the MAK.

The question whether MAK values theoretically should depend upon time of exposure and work schedules cannot uniformly be answered for all compounds listed. A necessary differentiation may be based on the categories already established for limitation of peak exposures. This concept of regulating short-term exposure limits in the

Federal Republic of Germany has been explained in detail elsewhere (Bolt 1985). Most compounds mentioned in the MAK list are separated into "peak limitation categories", according to their toxicological and pharmacokinetic properties.

No problems with different work schedules may arise in exposure to *local irritants* (category I), where the MAK is set with the intention of avoiding irritation. The same holds true for *substances having intensive odor* (category V), comprised mostly of thiols and aliphatic amines. Also, *substances eliciting very weak effects* (category IV; MAK $\geqslant$ 500 ppm) are not at all problematic.

The remainder – *substances with systemic effects* – are separated according to their pharmacokinetic behaviour (categories II and III). Highly cumulating compounds, such as many heavy metals and organochlorine pesticides, are grouped under category III. In practice, the long period in which cumulation of these compounds occurs renders the MAK independent of a distinct exposure profile. After long periods of exposure, the accumulation in the body reaches a plateau, where the average effective uptake per unit time is equivalent to the eliminated dose. The possible uptake, under a given MAK, is theoretically determined by the average weekly exposure hours.

Compounds of category II (also exhibiting systemic effects, but with shorter half-lives) are more difficult to assess. The MAK list distinguishes between two subcategories: II, 1 (compounds with a short half-life, up to 2 h and II, 2 (compounds with a longer half-life, between 2 h and shift length). The MAK of category II, 2 compounds may be considered dependent on the maximal daily exposure time (shift length). However, this may not hold true for some of the short-lived compounds (falling into category II, 1), which are eliminated very rapidly. In this context, the importance of the elimination rate from the organism for the setting of occupational standards must be stressed (Henschler 1984).

The practice of standard setting is characterized by the necessity for a variety of compromises, e.g. lack of knowledge of basic data, lack of long-term experience, lack of human data (Henschler 1984). This – along with the considerable interindividual variations in response to, and metabolism of, toxicants – leads to uncertainty in standard setting. A careful review of some 150 occupational chemicals in the German list of MAK values has revealed that less than 10% of their exposure limits were based on appropriate and sufficient animal testing and/or human field experience (Henschler 1984). A similar conclusion was recently drawn on the Dutch MAC list of 686 agents (Zielhuis 1986, personal communication). Accordingly, MAK values of volatile chemicals are usually fixed at graduations of 1, 2, 5, 10 (etc.) ppm (ml/m^3). A noteworthy exception is CO (MAK = 30 ppm), where sufficient knowledge was available to set the MAK at this particular level. This also implies that, in general, minute influences exerted by possible alterations of work schedules were or could not be taken into account.

2.2 Biological Monitoring

The biological tolerance value for a working material (BAT value) is defined as the maximum permissible quantity of a chemical compound, its metabolites, or any deviation from the norm of biological parameters induced by these substances in exposed humans (Deutsche Forschungsgemeinschaft 1985). It is explicity stated: "As with

Table 1. Alphabetical list of substances on the BAT list in 1985

Substance	BAT parameter and commentary
Acetylcholine esterase inhibitors	30% inhibition (see text). This parameter is generally valid.
Aluminium	Al in urine. The justification of this BAT value is very provisional because only limited data are available. Because of a presumably long half-life, a dependance on exposure schedules, at first glance, is not likely.
Aniline	The analysis on aniline released from its haemoglobin conjugate renders the monitoring of this compound independent of exposure schedules.
Cadmium	Cd in whole blood and urine. Because of the long biological half-life, no dependence of BAT on exposure schedules.
Carbon monoxide	The toxic effect (binding to haemoglobin) can be directly monitored. The BAT of 5% carboxyhaemoglobin (CO-Hb) is therefore a true ceiling value, which is independent of exposure schedules.
Carbon tetrachloride	CCl_4 in expired alveolar air. Because of the only fragmentary date on human exposure and kinetics, no evaluation of different exposure schedules is possible.
Dichloromethane	The toxic effect (binding of CO to haemoglobin) can be directly monitored (see above, carbon monoxide). This BAT is independent of exposure schedules. When the concentration of dichloromethane itself in biological media is monitored, dependence of the biological limit on shift length is predictable.
Fluorine: Hydrogen fluoride and Fluorides	Two BAT values for F^- in urine (pre- and postshift). Upon application of both parameters, BM can be applied to any shift regime.
Halothane	Trifluoroacetic acid in whole blood. The evaluation is only provisional. Because of the long half-life of this metabolite, a significant dependence on exposure schedules is not likely.
Hexachlorobenzene	Compound in plasma. Because of the long biological half-life, the BAT is independent of exposure schedules.
Lead	Pb in blood; ALA in urine. Long biological half-life and persistance in the organism. Therefore, no dependence of BAT on exposure schedules.
Mercury, inorganic	Hg in blood and urine. Long biological half-life. Therefore, no dependence of BAT on exposure schedules.
Mercury, organic	Hg in blood. Long biological half-life. Therefore, no dependence of BAT on exposure schedules.
Styrene	Metabolites in urine. The biological half-life of styrene in adipose tissue ($t_{1/2}$ = 2.2 to 4 days) suggests a potential cumulation, which might be dependent on exposure schedules. However, it is presently thought that BAT (determination at end of the shift) will generally protect against health hazards.

Table 1 (continued)

Substance	BAT parameter and commentary
Tetrachloroethene	Compound in blood and exhaled air. Because the compound is active by itself (central nervous system), the BAT refers to determination of the active principle. Therefore, the BAT is valid for any exposure schedule.
Toluene	Compound in blood and exhaled air. The same applies as for tetrachloroethene.
1,1,1-Trichloroethane	Compound in blood and exhaled air. The same applies as for tetrachloroethene.
Trichloroethene	Trichloroethanol in blood. As this is the biologically active metabolite, the BAT is independent of exposure schedule.
Xylene	Xylene in blood, metabolite (toluric acid) in urine. Determinations should be done at the end of exposure. For interpretation of results, the Justification (Henschler and Lehnert 1983) must be consulted.

MAK values, the maximum period of exposure to a working material is generally given as eight hours daily and 40 hours weekly". However, this very general statement needs to be modified. The reasoning on the basic approach for BAT values is explained in detail in a justification volume (Henschler and Lehnert 1983). There are two different kinds of BAT parameters, namely (a) those referring to the concentration of the chemical or a relevant metabolite in a biological medium and (b) those referring to biological effect parameters of which deviations are induced by the chemical. The latter possibility has been used so far for lead [δ-aminolaevulinic acid (ALA) in urine] and for parathion and other acetylcholine esterase inhibitors (30% inhibition of the individual baseline value in whole blood). Such parameters are tightly connected with the toxic action which is to be avoided. Hence, it follows immediately that the validity of a biological effect parameter is independent of exposure schedules.

There is not such a general solution for compounds which are monitored by chemical determination. The justifications of BAT values (Henschler and Lehnert 1983) are, as far as possible, based on the idea that the parameter to be determined is selected according to the mechanism of action of the compound. This means that determination of the "parent" compound (to which exposure occurs) is given priority if the compound itself (not a metabolite) is the ultimate toxic principle. Conversely, in the case of a metabolite exerting the key effects, the determination of that metabolite is preferred, but this basic concept also has to undergo practical compromises. However, insofar as we chemically monitor the ultimate active principle, if the BAT value is determined at the correct point in time, it should also be independent of the prevailing exposure system. Such an interpretation, however, requires detailed knowledge both of the mechanisms of action and of the pharmacokinetic properties of the chemicals.

As of 1985, the BAT list had 21 entries. Each of these is briefly discussed in Table 1 on the basis of the foregoing arguments. (The numerical quantities of the BAT values are generally not included).

In summary, the result of the short compilation in Table 1 is that the BATs of nearly all compounds currently included in the BAT list are independent of the exposure schedule, as far as different times of exposure and different shift systems are concerned. However, these considerations did not take into account possible chronopharmacological differences in individual susceptibility to chemical toxicants. As practical experience in this field is lacking, such a question can at present only be approached from a theoretical point of view, as is done below.

3 Aspects of Chronopharmacology[1]

The toxicity of many foreign compounds is known to be dependent on the moment of application, and chronopharmacological influences have been described (see Lemmer 1984). This refers to many drugs acting on the CNS, such as barbiturates, benzodiazepines, lithium and anaesthetic gases. Similar effects have been seen with poisons acting on the autonomous nervous system (e.g. paraoxon, nicotine), and with other compounds (antimycin A, cardiac glycosides). As an example, the mortality for a single dose of 190 mg/kg phenobarbital in light-dark synchronized rats varies between 0% (in the phase of maximal motor activity) and 100% (at the end of the resting phase) (von Mayersbach 1976).

Such diurnal variations in susceptibility may be triggered directly by the light-dark cycle (which may be likely for compounds acting on the central or autonomous nervous system) or maybe indirectly, due to diurnal variations in the metabolism of foreign compounds. The occurrence of diurnal rhythms in hepatic metabolism of drugs has been classically demonstrated in humans by Vessel's group (Poley et al. 1978), using aminopyrine. In animal experiments, similar observations have been made using aminopyrine, *p*-nitro-anisol, hexobarbital, 4-dimethylaminoazobenzene, and other xenobiotics (see Lemmer 1984). However, in further investigations by Vessel's group (Shively et al. 1981), it turned out that the diurnal variations of (oxidative aminopyrine) metabolism were triggered by the food intake. Changes in eating times influenced the diurnal cycle of aminopyrine half-life, but not that of plasma 11-hydroxycorticoids.

The importance of the time of food intake for hepatic function and for toxicity towards the liver has been highlighted in a series of animal experiments by Schulte-Hermann (Schulte-Hermann 1976, 1977; Hoffmann and Schulte-Hermann 1979). It is well known that α-hexachlorocyclohexane (HCH) induces liver growth and cell replication in rats. This process requires stimuli by food intake (amino acids, and a carbohydrate, e.g. glucose). Food consumption is needed (a) before or at the time of HCH administration and (b) 12–15 h later, i.e. 5–8 h before the initiation of DNA synthesis. Therefore, it is experimentally well established that hepatic rhythms are likely to be a

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[1] Editorial note: During the Workshop, the not yet existing term "chronotoxicology" was proposed for use in industrial toxicology.

consequence of the daily distribution of food intake. The importance of such phenomena for action of chemical toxicants in man at the workplace is very difficult to evaluate, expecially as in shift work highly different eating schedules must be considered.

Finally, an interesting observation (the only one dealing with a particulate matter) should be discussed. In experimental studies on the pulmonary clearance of asbestos fibres, Bolton et al. (1983) compared rats with a normal light-dark cycle with those under "reverse daylight" conditions, where the activity phase was shifted towards daytime. It turned out that inhaled amosite, at two different concentration levels, was cleared much better than normal when reverse daylight conditions were applied. It has not been possible to give an explanation for this phenomenon so far, but the example demonstrates that diurnal rhythms may in fact be of considerable importance in occupational toxicology.

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The Impact of Physical and Mental Activity on Toxicokinetics and Toxicodynamics of Workplace Chemicals

J. Rutenfranz and H. M. Bolt

1 Introduction

The influence of physical activity on the disposition of chemical agents, mainly solvents, in blood and tissues of man has been studied by Zenz and Berg (1970), Åstrand et al. (1972, 1973) and Monster et al. (1979a, b) and was discussed in regard to physiological and practical aspects by Zielhuis (1971) and Åstrand (1975). Using physiological principles, the uptake of gaseous solvents, via the lungs, with a given concentration in ambient air (C_i) depends on (a) the pulmonary ventilation (intake = C_i x respiratory volume per unit time), (b) the diffusion of the solvent through the alveolar capillary membrane (uptake = intake x fraction resorption), (c) the solubility of the solvent in blood, (d) the circulation of blood through the lungs and other organs, (e) the diffusion of the solvent through tissue membrane, and (f) the solubility of the solvent in fatty tissues (Åstrand 1975).

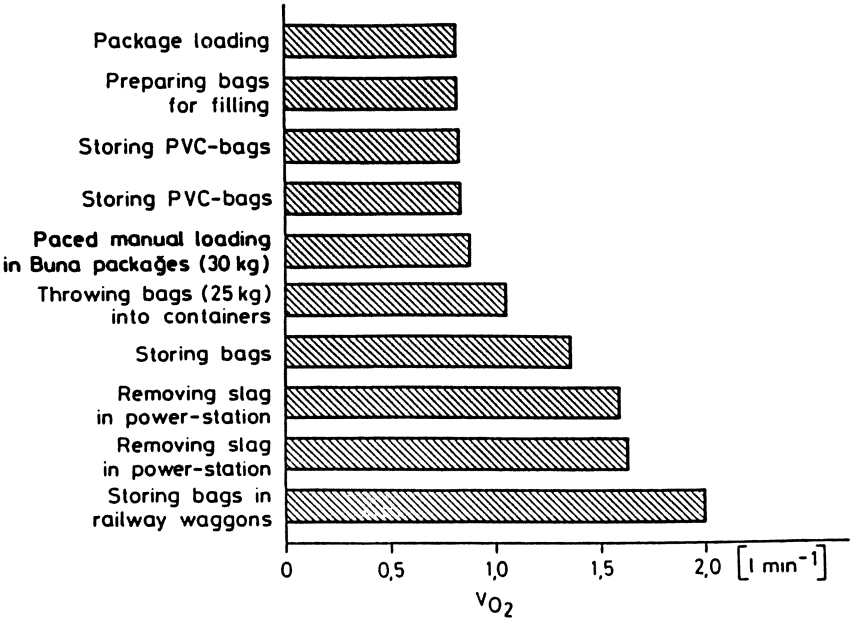

Fig. 1. Energy expenditure for different tasks in the chemical industry (from Ilmarinen 1978)

Since the pulmonary ventilation is linearly related to the submaximal workload (to oxygen consumption till up to 80% of the individual maximal aerobic power), the uptake of volatile compounds should be clearly influenced by the energy expenditure of a given task.

For different tasks, the pulmonary ventialtion may vary in chemical plants between 20 litres/min (operator in sitting position; oxygen consumption = 0.5 litres/min) and 50 litres/min (material handling; oxygen consumption = 2 litres/min) (Ilmarinen 1978; Ilmarinen and Rutenfranz 1980; Fig. 1). In addition to energy expenditure, the retention is influenced by a coefficient "M", proper to each substance, containing the blood solubility, properties of the tissues where the solvent is biotransformed and characteristics of the enzymatic systems (Droz and Fernandez 1977).

It is also well documented that physical activity may alter the toxicokinetics of workplace chemicals. As the inhalatory route of intake of chemicals at the workplace is the most important one, interest is mostly focused on the fate of volatile compounds in the organism, particularly organic solvents.

2 Kinetic Modelling (Toxicokinetics)

Two general approaches for a quantitative description of the fate of chemicals in the living organism are feasible, by using "compartmental" and "physiological" models. Whereas compartmental models view the organism as being composed of one or more compartments and (where possible) use first-order kinetics to quantitate the mass exchange of compounds between these, the physiological descriptions consider perfusion of different organ systems and parameters of distribution and extraction of the compound. Although, in principle, a consideration of physiological changes induced by workload is possible with both kinetic approaches, the use of physiological models (see Fiserova-Bergerova et al. 1984) offers considerable advantages for this purpose.

The workload increases both the ventilation rate and the cardiac output. An increase of cardiac output leads to changes in the perfusion of tissues. If the hepatic perfusion in particular is changed, metabolism of chemicals (of the "perfusion-limited type", see Bolt 1987) may be altered. However, much more important are changes in the ventilation rate induced by the workload. This has been theoretically deduced by Droz and Fernandez (1977) and practically confirmed by others (e.g. Monster et al. 1979a, b).

The influence of the physical workload on retention and metabolism of volatile chemicals is maximal for those compounds which are most soluble in blood and/or are metabolized most significantly. Thus, this effect of workload is different for different chemicals. Some solvents have been ranked in ascending order of metabolic clearance, as follows: benzene → trichloroethylene → toluene ≈ methylene chloride → styrene → ethyl acetate (Droz and Fernandez 1977).

In practice, the influence of the workload is believed to be one of the major factors responsible for differences in metabolism of workplace chemicals between laboratory experiments and field observations. This problem has been addressed in the evaluation of BAT values for several organic solvents, e.g. trichloroethylene, tetrachloroethylene

and 1,1,1-trichloroethane (Henschler and Lehner 1983). Influences of mental activity on toxicokinetics of workplace chemicals are not known.

3 Toxicodynamics

As far as the authors know, almost nothing is known about the influence of physical and/or mental activity on the toxicodynamics of workplace chemicals.

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Assessing the Health Impact of Total Exposure at and off Work: Methodological Problems in Occupational Epidemiology

S. Hernberg

1 Combined Exposure and Interaction

In occupational epidemiology, a central task is to establish connections between exposures to chemical, physical or biological factors on the one hand and health effects on the other. The vast majority of studies published so far have dealt with exposure to one single factor; other concomitant exposures have been controlled as potential confounders. However, man is usually exposed to several occupational and nonoccupational chemical agents. In spite of this, possible combined effects have received comparatively little attention, probably because of the formidable difficulties involved in studying concomitant actions of several exposing agents or energies.

Interactions of mixed exposure can be one of the explanations for seeming interindividual variation in sensitivity, others being, for example, variations in exposure intensity and host factors. This paper addresses only problems related to the epidemiological study of interactions.

2 Total Exposure

Man's total exposure burden is made up by the following different categories:

1. Exposures at work to one or more chemicals, their impurities and mixtures, and different physical factors such as noise, vibration and radiation
2. Exposure to similar agents or energies during leisure time, e.g. when driving the car, listening to disco music, shooting, painting, gardening and home repairing
3. Air and water pollution, especially in big cities, or domestic exposures in homes due to use of chemicals for cleaning and polishing
4. Food residues and additives
5. Smoking, alcohol, coffee, tea and possibly drugs
6. Medicinal preparations
7. Infective agents

In addition, different dietary habits (high/low fat, high/low vitamins and spices) have an influence upon the effects of toxic exposures.

3 A Priori Conditions

Study of the combined effects of different exposures requires several conditions. The most important ones are:

1. Knowledge of the mode of action of each single chemical, physical or biological exposure
2. Knowledge of the type of interaction
3. Accurate enough exposure data
4. Suitable exposed populations
5. A reference category showing large enough exposure contrasts

4 Mode of Action and Type of Interaction

The mode of action is known for many exposing agents. We know, for example, that some agents are carcinogenic, some neurotoxic and some irritating. However, there are many chemicals and some physical exposures for which sufficient data are lacking. Among these are a number of newly introduced chemicals and nonionizing radiation.

The type of interaction is known fragmentarily and for only a few combinations of chemicals. In principle, there are five main types of interaction (Ballantyne 1984, 1985)[1]:

1. *Independent action:* the toxic effects produced by separate exposures also occur in a similar qualitative and quantitative manner when the exposure is mixed.
2. *Additive effects:* when two or more chemicals produce the same effect, a mixed exposure produces an effect which is equal to the sum of the independent effects.
3. *Antagonistic effects:* exposure to two or more chemicals reduces the toxic effects of each single component. They can be of different types:
   a) *Potentiating effects:* a relatively inert chemical may quantitatively enhance the effects of a more toxic one.
   b) *Synergistic effects:* two or more chemicals interact to produce a toxic effect that is significantly greater than would result from an additive effect.

All types of interaction (apart from independent action) can either be pharmacokinetic, i.e. one chemical affects the metabolism of another, or biochemical, i.e. two or more chemicals act on the same target tissue.

5 Feasibility of Epidemiological Studies of Interaction

Needless to say, any study aiming at the evaluation of the effects of combined exposures should take into account what *type of interaction* is to be expected. The more exposures involved, the more complicated the issue. Lack of basic knowledge is an obstacle in the

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[1] The definitions differ slightly from those in the paper by de Mik et al. (this volume).

design of an adequate study. The acquisition of accurate *exposure data* is almost always a difficult problem in epidemiological studies, especially in retrospective ones. The more exposures to be considered, the more difficult the problem.

If several exposures are to be considered, and if the assessment is to be based on measurements, the costs will soon become formidable. Hence, it is necessary to lower the demands for quality of the exposure data, the more agents there are to be assessed. One alternative is then reliance on anamnestic data; another (they are not mutually exclusive) is to use the experience of industrial hygienists for approximate exposure assessments.

Whenever a well-defined disease entity is concerned (e.g. cancer, bronchitis, asthma), the *case-referent design* can be applied. Although this design does not solve the difficulties created by insufficient retrospective exposure data, it saves resources; therefore, it allows a more thorough penetration of each individual's background. There are several methods of securing data on occupational exposures in a case-referent study. One is application of the job-exposure matrix (JEM) method, which gives a crude estimate of actual exposures, based on job titles. Further refinement can be obtained by structured interviews; however, these are not feasible when many subjects are involved.

Elucidation of *nonoccupational exposures* usually requires questioning, sometimes also other methods. Some information is readily available and can be obtained by means of structured questionnaires, e.g. smoking habits, use of medicines and exposures from leisure activities. Alcohol use is more difficult; according to the Finnish Institute for Research on Alcohol, anamnestic data tend to underestimate true consumption by two-thirds. Drug abuse is certainly even more difficult to assess. The xenobiotic burdens coming from air, water and food pollution and from food additives and residues cannot at all be assessed by means of questioning. Some single cumulative agents, such as Pb, Cd or DDT, can be measured from biological samples, if deemed necessary, although practical reasons such as cost and availability of samples restrict the use of chemical measuring methods. Altogether, the unavailability (for one reason or another) of exposure data very often renders the epidemiological study of combined effects unfeasible.

Suitable *exposed populations* can, at least in theory, be found, provided the topic for investigation is not too complicated. Scientifically, it is irrelevant whether some chemical exposure takes place at or off work; its biological effects are the same, and this applies also for combined effects. From a particularistic viewpoint, it may, at least superficially, seem important to separate the sources of exposure; however, prevention of harmful effects by removing exposures does not necessarily require detailed knowledge of the niceties of interaction. Hence, in studying combined effects, one must try to sharpen the study design so that (a) relatively few exposures are studied simultaneously, (b) the study population exhibits large enough contrasts, (c) exposure data can be gathered and (d) the effects of interest are well defined and common enough in the study population.

Including too many combinations not only blurs the topic, it also increases the demands for study material, probably beyond the resources of the researcher. One study can never solve all problems, hence a *realistic* and *humble approach* is necessary. It is also important to be able to create subgroups with only one exposure, as well as different combinations of all exposures under study. The more combinations there are, the greater the demand for study material. Quite evidently, many exposures cause dif-

fuse, nonspecific symptoms. However, from an operational viewpoint, such effects are more difficult to study than well-defined disease entities. Nonspecificity of the effects also increases the demand for study material. Therefore, the study becomes more effective the better defined and the more specific the effects are. However, it must be recognized that this demand drastically restricts the spectrum of study.

Reference populations who are unexposed to all factors under study may be difficult or impossible to find and even more difficult to motivate to participate. This is one of the reasons why differently exposed subgroups of the population must be compared. However, when such subgroups cannot be defined, the only way to study the effects of combined exposure is to contrast the exposed groups with an "almost completely" unexposed one.

Provided data can be obtained, *statistical analysis* of the findings is possible, although complicated. It requires modelling and, of course, a skilled statistician equipped with a computer.

6 Conclusion

In conclusion, there are few multiple-exposure situations which can be studied epidemiologically. In the vast majority of situations, lack of data, economic resources or study material render the epidemiological study of combined exposures unfeasible. Better knowledge of modes of interactions, derived from experimental studies, may help the epidemiologist to form meaningful hypotheses and then focus on methodologically feasible and scientifically relevant problems.

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Feasibility of Composite Workplace Standards for Chemical and/or Physical Workplace Factors

J. H. B. M. Willems

1 Standards

Standards are instruments of government policy on occupational health and hygiene. The aim of this policy is to safeguard the good quality of the working environment and the health and wellbeing of people at work. This description implies that a standard is a relative concept (Zielhuis 1984a). After all, in practice what is meant by "good quality" and "health and wellbeing" is not solely dependent on objective, achievable quality aims: they are relative concepts.

Relating these concepts to each other and, on the basis of assumed causal relationships, arriving at numerical values (standards) above which the health of exposed persons is in jeopardy is in itself an oversimplification of a complex problem. In practice, this complexity emerges from the following facts:

1. Almost a century of international occupational health research has resulted in the establishment of about 800 standards worldwide; however, no standards have been drawn up yet for many tens of thousands of other injurious factors in the workplace.
2. The established standards mainly relate to single exposure to chemical substances, but in all workplaces more than one substance or other injurious factors usually occur simultaneously.
3. More than 90% of these established single-substance standards have been found to be inadequately underpinned by health criteria, animal experiments and/or epidemiological research (Zielhuis 1985).

This does not automatically mean that the standards offer inadequate protection. However, it should be pointed out that even in cases where there are well-described dose-effect (response) relationships, a standard may take a long time in coming, for political and economic reasons. Once established, the standard may be a compromise, or it may even fail to be ratified at all. One need only think of the period which elapsed before a compromise on an internationally feasible standard for exposure to noise in the workplace was brought about, even though the facts were available.

The evident conclusion from all this must be that the establishment of standards for exposure to (single) factors in the workplace that are adequately scientifically underpinned is so complicated that a policy-making authority should not assess the quality of a workplace solely or even largely by means of checking it against standards.

2 Are Standards Necessary?

One might question whether the statutory setting of standards has any greater value than, for example, issuing of guidelines or recommendations. In answering this question, the following considerations are important:

1. Experience has demonstrated that a government without enforceable standards is not fully able to impose mandatory improvements in the workplace.
2. Workers are frequently not in a position to judge the health risks attached to their own situation at work, nor are they in a strong enough position to be able to insist on improvements on their own. Despite all the drawbacks to standards, their statutory status will assist in assessing the quality of individual working situations and in negotiations on working conditions in labour organizations. In addition, they provide legal security to both employer and employee.
3. Employers are responsible for providing a safe and healthy workplace. The need for detailed directions, for example in the form of standards, is great. Experience has demonstrated that, despite the fact that these concepts are relative ones, employers are closely guided by governmental standards.
4. Experts (occupational health and hygiene experts and safety experts) who act as advisors to employees and employers know more about risks in the workplace than anyone else. Although standards can be of assistance to experts, they – more than anyone else – should be expected to evaluate them in the fragile context in which they frequently belong. Unfortunately, this happens too infrequently, and these experts, too, are inclined to attribute an overly absolute significance to numerical standards. The answer to the question of whether standards are necessary is therefore: standards are necessary for all parties, but they need to be seen more in perspective than is the case at present. Experts in the field of industrial safety and industrial health care should play a greater role than they do at the moment.

3 Composite Standards

The subject of composite standards in the context of multiple exposure is a topical one. A growing number of authors and organizations are pointing to the desirability of making this problem the subject of study and policy, although it is one that is even more complex than single standards (Cowles 1979; WHO 1981, Andrzejewski and Tarkowski 1983; Zielhuis 1985). Generally, it is assumed that numerous (often unknown) injurious factors occur in the workplace simultaneously, sometimes at relatively low levels. This is an entirely different situation to that which is frequently encountered in medicine, where patients may be clinically exposed to relatively few, well-known substances (medicines) in high doses. Even in this controlled situation, fairly little is known about the effects of this combined exposure on health – certainly not when more than two substances are involved simultaneously. A possible explanation for this lack of knowledge is perhaps that it is little sought after. The number of potential combinations is high, and side effects are readily accepted, so that the incentive to carry out research is indeed lacking. Employees are frequently exposed, often without their

consent, to even more possible combinations, albeit often in (much) lower concentrations. How should this problem, which is in principle one of occupational hygiene, be tackled? In principle, three different approaches are possible: a factor-oriented, a process-oriented, and a job-oriented approach.

3.1 The Factor-Oriented Approach

This approach has been the one most frequently adopted and the subject of many studies (including Menshov and Schleifman 1980; WHO 1981, 1983; Gibbons and Adams 1984; Hancock and Pierce 1985). Exposure is usually to two or more injurious factors of a chemical, physical or psychological/perceptive-mental kind. Ocassionally, there is exposure to one agent manifest in several forms (Zielhuis 1984b, 1985; Zielhuis and Wibowo 1984) or absorbed through different portals of entry. In a few cases, account is also taken of exposure outside the workplace: hobby, food, medicines, alcohol and smoking (Hills and Venable 1982; Damber and Larsson 1985; Boogaard et al. 1986). Problems of addition, subtraction and interaction (potentiating, inhibition) are referred to, but seldom worked out. The scientific problems are so complex that very few combined exposure standards could be drawn up. The climate indexes (WBGT), which are much used, constitute an exception, alongside perhaps attempts to incorporate certain chemicals (solvents) with the same target organ in a combined standard, on the assumption that addition occurs (Scheffers et al. 1985).

Consequently, the conclusion must be as follows: although the factor-oriented approach is of use in some cases, the great number of possible combinations implies that combined exposure standards which are based on this approch cannot be expected to offer a solution for widespread application in practice.

3.2 The Process-Oriented Approach

Process-oriented standards, which are almost always combined exposure standards, are based on health risks which are largely determined by the process. Just as with the single standard, no explicit account is taken of the influence which the employee may have on exposure. However, in many situations regulatory policies do determine actual exposure, and probably to no small degree. For these reasons, the approach is rather theoretical. In practice, however, it offers the opportunity of arriving at process profiles for large groups of workers simultaneously in a relatively simple way. Moreover, a description of acceptable basic conditions can be given, especially for processes which in themselves are not subject to major changes. It has to be accepted that a scientific underpinning will not always be possible and is often not necessary. One can bring about a considerable improvement in working conditions without knowing the distribution of exposure over time, the variance in methods of measuring, the variance in uptake in individual persons and between different persons. The ideal cab of a good vehicle can be described in detail in terms of comfort, vibrating properties of the seat, noise insulation properties, air-conditioning features and safety aspects, taking into account addition and interaction of these factors. This is an occupational health-oriented

approach: the potential risks are systematically listed and are weighed against health criteria in order to establish acceptable conditions.

An important addition to this is the fact that, using this process-oriented approach, one can also include the provisions which are important for an optimal way of working. Examples are the distribution of requisite personal protective devices, the mounting of extractor installations and the availability of sanitary facilities; however, immaterial provisions, such as training opportunities, are also important. The outcome of these profiles cannot be expressed in a single figure. Checking against a profile is of course possible, but subjective elements continue to play a greater role than with the factor-oriented approach. Moreover, every process, however similar to others, is nevertheless sufficiently different for on-site evaluation to continue to be needed. A statutorily established standard is therefore not self-evident. This approach would seem to be ideal for the government to encourage and develop. If basic profiles thus become available for a number of work processes (in the broadest sense of the word), this will be a major contribution to optimizing the workplace, provided that employees are well informed.

A problem in this connection is how to determine where one should start. Although the Dutch government is at present subsidizing research which should ultimately provide insight into the priorities for research and policy in the coming years, one cannot rely on the outcome of this alone. Employers and employees themselves will have to be sufficiently motivated to make an effort to solve the problems. For example, they will have to give the industrial health services and research workers the scope to actually achieve their good intentions.

3.3 The Job-Oriented Approach

A job-oriented approach goes a step further than the process-oriented one. A job is defined as the set of tasks that a particular worker has to carry out. The aim is to draw up job profiles from the activities involved in carrying out these tasks in a certain working environment. An essential difference between the job- and the process-oriented approach is that the job-oriented approach gives priority to the individual alongside the process (the working environment). The occurrence of a certain exposure at work is largely determined by the opportunity which the worker himself has of acting in a regulatory way. To be able to do something about the exposure, the worker has to be able to identify, to cope with it and to want to cope with it. These factors are unfortunately often neglected in discussions on standards. For the driver, it is not only important that his cab meets the job profile or that his vehicle is classified as safe, it is also essential that he can exert some influence on his working hours and rest times and is allowed a certain individual responsibility with regard to the purchase and maintenance of his equipment. This is what is meant by "regulatory possibilities" for the worker. Therefore, in drawing up a job profile, one should not only pay attention to the combination of exposure factors and the provisions necessary to carry out the activities. One has also to examine explicitly whether the worker has enough room for manoeuvre (regulatory possibilities, in terms of organizing his time, responsibilities, allocation of

duties and opportunities for discussion with colleagues) to be able to carry out his job optimally.

This "room for manoeuvre" cannot be defined in such a way that a standard can be established. Job profiles in the sense discussed here are less general and more specifically related to an individual or group of individuals and a specific workplace. Consequently, the contribution of the government is only a very limited one. This is a task for the employer, the first authority responsible for ensuring that working conditions are optimal. However, the drawing up of job profiles should not be carried out without workers themselves being involved; in fact, this should be regarded as essential.

An important role must also be accorded to the experts in occupational safety, hygiene and health at work. They should undertake the first step towards developing these profiles at company level. Unfortunately, this seldom happens, although initiatives in this direction are emerging (e.g. Draaisma et al. 1985; Brouwers and den Held 1985). The exposure profiles for specific jobs in the construction industry which have been drawn up at the initiative of the Dutch Stichting Bedrijfsgezondheidsdienst voor de Bouwnijverheid (Industrial Health Service for the Building Industry) in recent years must also be seen as a valuable contribution in this context. Perhaps attention should be paid to regulatory opportunities on a much greater scale than is done at present. It is also crucial that such profiles should be available to the workers themselves. It is true to state that in general the feedback of research results to the worker ought to be given much higher priority. Neither research workers nor the government and not even employers have the final say in the degree to which improvements can be achieved in the workplace.

4 Conclusion and Discussion

In conclusion, the following can be stated:

1. The development of process-oriented profiles may make a major contribution to optimizing working conditions. It is an instrument that can be deployed at the industrial branch level so that large groups of workers can benefit from it. Although we are not dealing here with statutorily established standards, the government has a major task in promoting the drawing up of such profiles.
2. The development of job-oriented profiles is a major responsibility of employers, employees and their expert advisors. If such profiles are used well – this includes a sound contributions from and feedback to employees – they provide the best instrument in the endeavour to optimize conditions in the workplace.

Finally, in developing instruments to safeguard and protect the quality of work, the road from a factor-oriented to a job-oriented approach can be seen as a line of development.

Standards, whether they are based on single or multiple exposure, offer no guarantee to the individual worker. Process profiles and job profiles, too, are based in principle solely on factors relating to the working environment and the person working in it.

But health and wellbeing of workers also depend to a high degree on factors outside the working environment (Zielhuis 1985). Without going into detail, this applies to

host factors (smoking behaviour, age, sex, race, general state of health and socioeconomic status) and environmental factors (housing, distance from work and journey from home to work). The personal nature of these factors makes it impossible to take account of them in government policy making (except perhaps by making allowances for them in a safety factor when setting standards). However, there are probably many situations in which the functioning or dysfunctioning of workers is determined to some degree by such factors. There is a major responsibility here for the company doctor. The frequent attempts to distinguish factors specific to work and factors not specific to work at the individual level do have some sense, as they may be important for any intervention which is regarded as necessary. The sound functioning of employees requires a wide scope, and pleas for managing health instead of managing occupational health derive from this view (Collings 1984). The significance of the standard, and certainly of the single standard, is overrated in this context.

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Priority Setting for Health Surveys of Workers

W. J. Hunter

1 Introduction

Wathever form it takes and in whatever sector of the economy it is performed, work, like any other human activity, entails a certain number of risks and dangers that may lead to an impairment of the physical and mental health of workers.

In spite of the technical progress that has been made to date, the risks of accidents at work and of work-related diseases remain high. These risks are associated with many different factors, which include (a) the organization of work; (b) production methods; (c) the agents, substances and techniques used; and (d) the pattern and pace of work.

Furthermore, accidents at work and occupational disease can be ascribed to technical shortcomings, use of toxic products and substances, methods of organizing work and production incompatible with health and safety requirements, inadequacy of preventive and protective measures, and failure to analyze the effects of new products or processes on health and safety before they are introduced. Such accidents and disease may also be the result of human shortcomings and reflect insufficient training and information about the techniques and materials used, about their effects on health and safety at work and about the regulations applicable in this sphere. This lack of information is particularly dangerous for certain categories of workers, such as migrant workers, who may have difficulties in fully understanding information that is supplied to them in a language other than their mother tongue.

The available data on accidents at work for the countries of the European Community demonstrate very clearly the disparity of these data. They suggest that the data collected are not only incomplete but also difficult to compare because of the different methods used for the establishment of the data. The lack of homogeneity in the collection of information on accidents at work stems from a number of factors: for example, the data collected in some countries also cover accidents on the way to work; in others, the statistics cover only accidents at work entailing at least 3 days' absence from work, contrary to the situation in yet other countries, where accidents at work are recorded as from the first day of absence. Table 1 for the year 1980 clearly illustrates this.

The data on work-related diseases are even more divergent. One reason for this is the disparity of the rules on notification of work-related diseases. Nevertheless, it is evident that occupational accidents and diseases are still occurring at a high rate.

The prevention of occupational accidents and diseases is thus the primary objective of any policy designed to improve safety and health at work. This objective can only be achieved with the full involvement of the social partners. In this context,

Table 1. Accidents at work in countries of the European Community

Country	Workers employed	Accidents at work entailing absence from work	Fatal accidents at work
Ireland	868000	4330	30
Luxembourg	137400	16530	17
Belgium	3230000	210000	250
Greece	1668000	47500	250
Denmark	2091000	33900	75
Italy	15239000	1600000	2200
United Kingdom	22834000	400000	700
Netherlands	4548000	90000	80
France	18133000	971301	1423
Federal Republic of Germany	22296000	2158000	3998

employers are responsible for ensuring the highest level of health and safety that is reasonably practicable in their enterprises and undertakings. Workers must participate fully not only as individuals but also in safety and health committees and/or as safety and health delegates. Governments have to establish and enforce the necessary laws, regulations and administrative practices. While the primary role of prevention remains the responsibility of employers, it is important to remember that specialists in safety and health, such as those in occupational health services, can contribute significantly to prevention.

Some countries have had legislation in force for many years on occupational health services, whereas others have left it to individual employers or groups of employers. For many years now, occupational health services have been a major preoccupation of international organizations such as the Council of Europe [Committee of Ministers Resolution (72) 5 of 18 February 1982 on the harmonization of measures to protect the health of workers in places of employment], the International Labour Organization (ILO) [Recommendation 112 of 1959 and the Recommendation 171 and Convention 161 of 1985], the Commission of the European Community (CEC) ifself [EEC Commission Recommendation of 20 July 1962 on occupational medicine within the enterprise (Official Journal of 31. 8. 1962)] and the Economic and Social Committee, which on 27 September 1984 adopted on its own initiative an opinion on occupational medicine.

2 Occupational Health Services

The primary aim of occupational health services is to contribute to the prevention of occupational accidents and diseases. Their principal role is to advise the employer, the workers and/or the workers' representatitives in the enterprise or undertaking on (a) the requirements for establishing and maintaining safe and healthy working and (b) the adaptation of individual worker's jobs to their physical and mental state.

The preventive task means that occupational health services may carry out health surveillance which can be of different kinds: (a) health surveys on recruitment, (b) annual or other periodic health surveys, (c) complete medical check-ups, (d) examinations of persons returning to work after an absence due to illness and (e) examinations as part of special monitoring.

Health surveillance is not obligatory in all Member States. In the Federal Republic of Germany, workers are not compelled to undergo medical examinations. In Belgium, medical examinations are compulsory only for the following: (a) workers exposed to a risk of work-related disease due to specific causes or agents, (b) workers holding safety posts, (c) workers in direct contact with foodstuffs, (d) handicapped persons and (e) workers under 21 years of age.

At all events, periodic health surveys and examinations are justified only if they are organized as part of a preventive campaign. They serve a useful purpose when they form a backup to the preventive role of occupational medicine. This explains why in certain countries periodic health surveys and examinations are confined to undertakings with special hazards.

Professional and medical secrecy has to be observed in connection with such surveys and examinations. Confidentiality must not, however, impede the circulation of information about the occurrence of work-related dieseases for the purposes of epidemiological and statistical studies. Although the notification of various work-related diseases is compulsory in certain countries and cannot be impeded by medical secrecy, these same priciples of confidentiality can still pose problems when it comes to learning about the causes of sickness and mortality for the purposes of epidemiological studies.

The organization and practice of occupational medicine are generally geared to the importance of the risk (e.g. handling of toxic substances). Nevertheless, some high-risk sectors of employment would not seem to have the occupational health services warranted by the seriousness of the risk (e.g. health services, agriculture).

In the Federal Republic of Germany, about 11 million of the 22 million workers in employment were actually covered at the end of 1981, with most of those not covered working in small and medium-sized enterprises. In Denmark, occupational health services are not obligatory in all branches of the economy, nor for all workers. (on 1 July 1982, 368000 workers were in fact covered.) In the Netherlands, occupational health services are only obligatory in enterprises employing more than 500 workers. In Ireland, medical supervision at work has not been put on a permanent footing, but is something decided on by the Ministry of Labour on a case-by-case basis and in the light of accident risks, the likelihood of occupational disease and health hazards. In Greece, the law does not impose mandatory occupational health services, nor are they compulsory in the United Kingdom. In some countries, such as Italy, Ireland, Luxembourg and the United Kingdom, occupational medicine either goes beyond the scope prescribed by the law or, in the absence of legal provisions, is available in many big or medium-sized firms.

The organization of occupational medicine is generally geared to the size of the enterprise in question. The biggest ones generally have their own occupational health services, whereas medium-sized and small enterprises are often not covered and are sometimes affiliated to group services covering several firms.

Table 2. Occupational physicians in countries of the European Community

Country	Year	Full-time occupational physicians	Part-time occupational physicians
Belgium	1977	215	667
Denmark	1978	5	95
Federal Republic of Germany	1979	2100	6700
France	1978	2297	3229
Italy	1977		2500 altogether
Netherlands	1979	320	70
United Kingdom	1979	800	1200

In France, occupational health services are required by legislation and cover enterprises of all sizes. They can legally take the following forms: (a) an occupational health service for an individual firm or establishment, where the occupational physician has to devote at least 169 h/month to this duties and (b) a group occupational health service, where the occupational physician does not need to devote more than 20 h/month to his duties; if a group health service can be set up between more than one establishment of the same enterprise, the physician must devote at least 20 h/month to his duties.

Prevention in occupational medicine presupposes regular inspection of the workplace. It implies that occupational health specialists have the necessary time to carry out their preventive work at the workplace and also have the necessary equipment. In France, the occupational physician has to be present for a minimum of 1 h/month per 20 salaried staff, 15 manual workers and 10 wage earners, including temporary workers subject to special supervision. This minimum therefore varies between 3 and 6 min/month per worker. This law also specifies that the occupational physician must be able to devote a third of his working time to the working environment, i.e. the supervision of working conditions, the rest of the time being devoted to other activities (e.g. clinical work).

In Belgium, the law stipulates that an enterprise must be visited by an occupational physician at least once a year. The number of physicians attached to an occupational health service is determined by the requirement that each year an occupational physician must, in each enterprise or establishment, devote an average of at least 1 hour of his time to each worker subject to compulsory medical examination. This time falls to 8 min for each worker not subject to compulsory medical examination.

The obligation to be present at the workplace poses the question of occupational health service staff numbers. It appears that there is a gap between the objectives laid down in the legislative provisions of certain countries and the achievements in practice because of the inadequacy of financial, technical and human resources. A Commission report on occupational medicine in the Member States gives the figures for occupational physicians in 1977–1979 (Table 2).

3 Occupational Health Monitoring

In recent years, an increased awareness has developed of occupational health, hygiene and safety requirements, which has led in turn to improvements in working conditions and to reductions of worker exposure to some toxic agents. However, substantial hazards still remain; the number of cases of occupational illness resulting from these hazardous exposures is still high. In addition, new cases will continue to occur if there are no improvements. Furthermore, new hazards have appeared with changes related to energy development, biotechnology, electronics and chemicals.

In response to this situation, there has been an increasing tendency to develop ambient limit values and in some cases biological limits, as well as methods to ensure their implementation. This has forced all those concerned to pay more attention to the significance of these limits, to their application and to the problem of achieving a common terminology at international level.

In 1980, the CEC, National Institute of Occupational Safety and Health, (NIOSH) and Occupational Safety and Health Administration (OSHA) organized a seminar on "Assessment of Toxic Agents at the Workplace". This seminar agreed on the following:

Monitoring can be defined as a systematic continuous or repetitive health-related activity designed to lead if necessary to corrective actions. Three types of monitoring can be defined: ambient, biological and health surveillance.

- *Ambient monitoring* is the measurement and assessment of agents at the workplace and it evaluates ambient exposure and health risk compared to an appropriate reference.
- *Biological monitoring* is the measurement and assessment of workplace agents or their metabolites either in tissues, secreta, excreta, expired air or any combination of these to evaluate exposure and health risk compared to an appropriate reference.
- *Health surveillance* is the periodic medico-physiological examinations of exposed workers with the objective of protecting health and preventing occupationally related disease. The detection of established disease is outside the scope of this definition.

The definitions of biological monitoring and health surveillance constitute separate components of a continuum which can range from the measurement of agents in the body through measurements of metabolites to signs of early disease. A problem left unresolved concerns the precise place within these definitions of certain biochemical tests such as zinc protoporphyrin (ZPP), delta aminolaevulinic acid dehydrase (ALA-D), delta aminolaevulinic acid (ALA) in the blood and urine, etc. which are in fact indicators of metabolic effects which have occurred as a consequence of exposure.

4 Priorities for Health Surveys

Several international organizations have proposed that occupational health services should cover all workers in every sector of employment. While this may be a long-term aim, the diversity of the existing arrangements in the various countries and the inadequate numbers of trained and qualified staff means that this is not possible at the present time. As a result, priorities need to be established in relation to health surveys.

In setting priorities for such surveys, several factors need to be taken into account, including (a) the identification of an agent as hazardous, (b) the potential value of the surveys and (c) existing legislation. In addition to these factors, it has to be recognized that others may also need to be taken into account in certain circumstances, such as the personal interest of the workers concerned, as well as social and economic issues.

4.1 Identification of Hazards

The *European Communities Inventory of Existing Chemical Substances* contains about 100000 chemical substances to which workers may be exposed. For the majority of these agents, little or no toxicological data are available. Estimates of the number of agents to which workers are commonly exposed vary, but it seems that some 3000–4000 chemical substances may give rise to frequent exposure. Of these, exposure limit values have been established for a total of about 1000 in the Member States of the European Communities.

Several reviews have been made and published of the available data on toxic agents, including those published by the European Commission, as well as NIOSH/OSHA, who have also published *Occupational Health Guidelines for Chemical Hazards* (Mackinson et al. 1981). When toxicological data are available, they can be used to determine the risk to workers by examining the magnitude, level of significance and consistency of the data. This should result in higher priority being given to those agents producing higher risks to health.

The establishment of priorities also depends on other factors, such as the degree to which such evidence is supported by other studies, including data from occupations with similar exposures, positive findings in routine statistics, case control studies, cohort studies and other surveillance studies. Evidence that an agent produces serious effects in experimental studies in animals should raise the level of priority. Quantitative ratings of toxicity may prove useful in the effort to prioritize chemicals for study. Other factors which may be taken into account include experimental evidence such as clastogenicity, mutagenicity and structure-function relationships.

4.2 Potential Value

Once an agent has been identified as potentially hazardous, the potential value of health surveys can ideally be assessed by estimating the number of cases of ill effects or overt disease that could be prevented. The elements that need to be considered in such an assessment include:

1. *Number of workers exposed.* The number of workers with exposure to a suspect agent may vary considerably, depending upon the level at which the survey is carried out. This may be local, e.g. a single enterprise, regional, e.g. several enterprises or at a national level. Clearly, if the agent proves deleterious to humans, the number of workers adversely affected would be directly related to the number of workers exposed to levels which produce effects. Some data bases are available that can assist in estimating the numbers of workers exposed at regional and national level. Since many of these data bases are based on surveys of samples of industry, care must be exercised in their use, as they may reflect erroneously the potential numbers of workers exposed to unusual but hazardous chemicals.
2. *Exposure of workers.* Some chemical substances are being used in larger quantities or in more ways. In general, agents which are used increasingly need to be given a higher priority than those whose use is stable or diminishing. Although a chemical agent may be commonplace in industry, this does not automatically mean that the workers' exposure will be substantial. Ideally, the level of exposure of workers to the chemical agent of interest should be used as a criterion for prioritization, but such data are often limited, necessitating surveys in industry of the extent of exposure. Additional information may come from reviews of the frequency of exposure in a given occupation and from data on materials, processes and work practices, as well as quantities of the chemical agents manufactured.
3. *Exposure data.* The response to a hazardous agent in a given population can only be determined if there has been a dose sufficient to produce effects and thus a response. Dose depends on the level and duration of exposure, but in addition there must be sufficient latency, i.e. time since exposure for the response to develop. Data on exposure may sometimes be obtained from personnel records, which are often necessary aids in such a survey.
4. *Confounding factors.* The validity of a health survey may well depend on the control of confounding factors in the group of workers concerned. There are several acceptable means available for such control. Suspect agents for which surveys permit the control of confounding factors should receive a higher priority; for example, surveys relating to a suspect lung carcinogen should receive a higher priority ranking if data on smoking are available. There are differences in the local, regional and national incidences of disease, which can make the control of these confounding factors difficult when comparisons are made between different areas, regions or countries.
5. *Attributable cases.* The response in a given population, and therefore the number of cases potentially attributable to exposure, is a function of several factors, including the toxicity of the agent, level of exposure and number of workers exposed. In epidemiological terms, the number of attributable cases is a function not only of the rate of disease in the population but also of the relative rate in the population and of the size of the exposed population. Agents that will potentially result in a greater number of attributable cases should receive higher priority.
6. *Environmental exposure.* On occasion, there may be exposure of residents of the community to an agent that is not currently a health concern in the workplace. This may result in the recognition of new health hazards for workers, e.g. zeolite, thus requiring higher priority to be given to such an agent.

7. *Reproducibility and intercomparability.* These two elements are interdependent. They depend upon the fact that valid surveys have already been carried out, and the methods fully described. Where validated methods exist, these should permit a higher priority to be given to surveys using such methods. To ensure intercomparability of these methods, studies are required to determine and thus to remove the causes of variation. A higher priority should be given to methods which have been standardized by means of intercomparison studies.
8. *Analysis of results.* There now exist many mathematical methods for analyzing with confidence the results of such surveys. The existence of mathematical models or the applicability of existing forms of mathematical analysis which can be used to analyze the results of health surveys are of importance for the establishment of statistical significance and meaningful results. Higher priority should be given to those surveys which permit the use of these mathematical techniques.

4.3 Existing Legislation

Reference has already been made to the existence of legislation on occupational health services in various countries. It is now generally accepted that the employer is responsible for all aspects of safety and health in his enterprise, including the prevention of occupational accidents and diseases.

All Member States of the European Communities have lists of recognized occupational diseases for which social security benefits are paid. This means that as a general rule, the employer should ensure that health surveys are available for all workers who are exposed to a risk of developing such a disease. In this context, the ILO in 1980 amended its list of occupational diseases, which was first published in 1964. The European Communities schedule of occupational diseases, which was first published in the 1960s, is also being updated, and a revised list will be published by 1988.

In the European Communities, several Council Directives have been adopted which contain measures relating to health surveillance for workers exposed to vinyl chloride monomer, lead, asbestos and noise. Discussions are currently taking place on benzene, and proposals dealing with other agents are currently being prepared. It is therefore evident that health surveillance is required in a certain number of cases because of existing legislation.

5 Individual Variability

The use of statistical analyses for the diagnosis and treatment of disease dates back to the work of the French physicians Pinel and Louis, in the late eighteenth and early nineteenth century. Since that time, epidemiological studies have used statistical analyses to determine the probability of a given event occurring in the group under study. Thus, epidemiology has been used in occupational medicine to determine, for example, the likelihood of disease from a given exposure or to evaluate the effectiveness of a certain treatment. However, it has only been possible to determine the probable cause of a disease by studying its incidence in sufficient numbers of indivi-

duals in a group or in sufficient groups of individuals. Epidemiology has therefore considerably advanced our knowledge on the causation of disease and its treatment. However, these techniques tend to ignore the reasons for negative findings in a group.

It is therefore difficult to explain why one worker develops disease while another worker apparently similarly exposed does not develop disease. This variability is almost certainly multifactorial and probably includes such factors as genetic disposition and differing multiple exposures resulting from diverse living and working conditions. Because of our lack of knowledge, it is not possible today to establish priorities for health surveys of individual workers as opposed to groups of workers.

Nevertheless, the discovery of an occupational disease in any worker should act as a warning that there may be other workers who have been similarly exposed suffering from the same disease. Therefore, investigations of such groups of workers using modern scientific techniques should permit the determination of the various factors which make up inter- and intraindividual variability, such that priorities can be established more clearly in the future.

6 Summary

In determining the priorities for health surveys of workers, several factors need to be assessed, including (a) existing legislation, (b) the identification of an agent as hazardous and (c) the potential value of the surveys. Each of these factors has been examined in more detail with a view to determining the various elements that need to be taken into account in establishing priorities. In addition, a review has been made of occupational health services and of occupational health monitoring in the European Community.

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Towards a Dynamic Model of Exposure, Susceptibility and Effect

F. J. H. van Dijk, T. F. Meijman and P. Ulenbelt

1 Introduction

The ultimate goal of occupational health practice and research with respect to the use of chemical substances at work is the prevention of adverse effects (Samuels 1986). Contrary to well-controlled experimental dose-effect studies, one is confronted in practice with a multitude of effect-modifying variables, influencing not only the dose but also the dose-effect relation ifself. Several interrelated phases can be distinguished in the process from source to final effects. These phases can be schematically modelled (Fig. 1). Referring to Zielhuis and Henderson (1986), we use "internal exposure" to refer to biological monitoring procedures and "biological effect" to refer to biological effect monitoring.

In this contribution, we describe the transitions between the various phases. The modifying factors that are relevant in these transitions can be considered as tools for prevention. Moreover, a schematic review of these factors may direct our attention to gaps in the present state of knowledge.

2 From Structure to Environmental Exposure

Given a certain cource, the environmental exposure may vary. This transition is largely determined by three sets of factors, related to (a) the technology and the

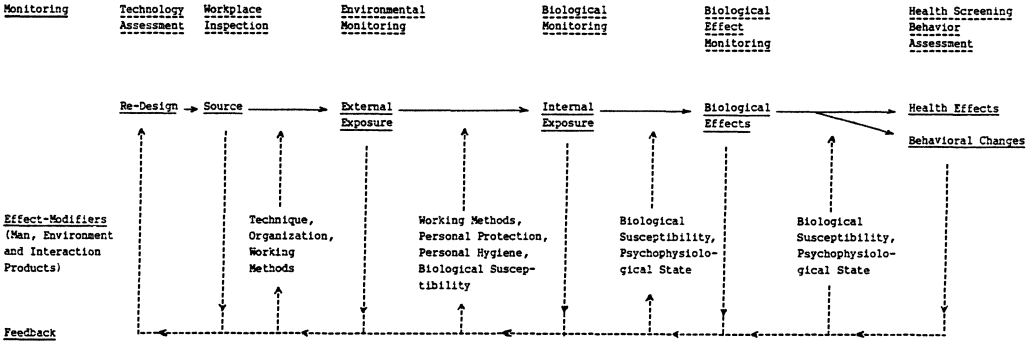

Fig. 1. Dynamic model of exposure, susceptibility and effect, including monitoring and feedback

layout of the production process, (b) the organizational structure and (c) the actual working methods.

Factors in the first set are, of course, the technical characteristics of the production units, but also their number and their place among other units in the production area. Moreover, one should consider the position of the various units relative to each other and to windows and doors (air flow), as well as the presence and the state of exhaust and protection devices (Worwood 1984). The ergonomic layout is important because it may prevent or enable the employee to keep a safe distance from the source (Cralley and Cralley 1984).

In the organizational structure, the demands of each job are prescribed. These prescriptions restrict employees in their work with more or less stringency both in time and in place, thus fixing exposure times and influencing exposure levels (Hoyos 1980). In these prescriptions, the formal working methods are formulated. These may directly change the environmental exposure. Amounts of chemical substances, for example, can be weighed, packed and transported in very different ways, contaminating the employees and the environment a lot or hardly at all. Prescriptions concerning the cleaning of spillages or safety procedures with respect to breakdowns are other examples.

It should be noted that the various departments within the industrial organization have their own aims, which may result in the formulation of working conditions that are good for production, but bad for health. The relevance of some prescriptions is another point. Recommendations such as "good housekeeping" may be necessary from the viewpoint of the safety department. However, what seems to be good in one situation may be bad in another. Thus, sweeping dirt is generally regarded as good housekeeping. It may be, however, an important secondary source of contamination in industry. Under such circumstances, the cleaners or the sweepers are the most-exposed group of workers (McCammon et al. 1985).

The importance of the aforementioned technical and organizational conditions must be recognized, as they determine the upper and lower limits of the intensity, frequency and duration of environmental exposure. The impact of the actual working methods of individual employees is less well recognized. This is a serious omission, both in field research and in occupational health practice, because these concrete activities of employees determine the *actual* level of their exposure. The actual working methods, including the working strategies of the individual, result from the interaction between structural factors, such as layout of machinery, equipment at hand and prescribed working methods on the one hand and personal factors, such as anthropometrical characteristics, cognitive abilities, perceptual-motor skills and motivations on the other hand. Fundamental to this interaction is the concept of "degrees of freedom" with respect to the choice between the various safety strategies which employees have at their disposal in the working situation. These degrees of freedom largely depend on the task structure and on the organizational rules. Stringent task demands, strictly prescribed working methods, inadequate ergonomic layout of the machinery and the working environment limit the degrees of freedom (Karasek 1979). They may thus prevent the use of adequate strategies in the actual working situation (Bernhardt et al. 1984). As the strategies may vary both in availability and in effectiveness depending on the situation and on the employee's qualifications, the involvement of em-

ployees is crucial with respect to the decisions concerning their tasks, the layout of the workplace and the equipment used (Matilla 1985). This involvement enables employees to change the situational aspects in order to minimize the risk factors.

However, the degrees of freedom per se do not guarantee safe behaviour. Thus insight into the reasons why employees use apparently unsafe methods, sometimes even deliberately, is crucial. Of course, without sufficient knowledge, one cannot expect employees to follow the appropriate working methods (Oosterom 1986). In addition, on-the-job training and supervision are necessary to improve the specific skills needed to cope with more complicated processes (Hale and Else 1984). Apart from these educational measures, one should note the possibility of interference strategies to avoid discomfort and risks. A conflict between strategies is often observed in situations of *combined exposure.* For example, when controlling the air conditioning, an employee may change the ventilation, thus interfering with the local exhaust. Or, noisy exhaust equipment is easily turned off, particularly when the operator is fatigued. Finally, factors related to the culture of the working place must not be overlooked, as they favour certain strategies at the expense of others – "earmuffs are for donkeys". Younger workers are often stimulated or stimulate each other to do the physical and the more dangerous things. On the other hand, younger workers, perhaps due to education, are more conscious of invisible threats such as those from chemical substances.

We know about of the above-mentioned factors concerning the production process, the organization and the actual working methods, considered separately. Knowledge of the interactions between them is needed.

3 From Environmental Exposure to Internal Exposure

Given a certain environmental exposure level at work, the internal exposure level may vary. Interindividual differences in biological susceptibility may play a role. Factors from the behavioural domain, however, seem to be the most relevant ones in this transition. We can distinguish between the acutal working methods and other task-related activities (McQuiston et al. 1986), the use of personal protection devices (Morgan 1983) and hygienic behaviour.

Some aspects of these factors are known. For example, task-related physical exercise adds to the intake. Also, intense perceptual activity, which may be required in the task performance, may interfere with the wish to keep a safe distance from the source. The effectiveness and, to a lesser extent, the comfort of personal protection devices is a popular object of study. Whereas hygienic behaviour is a major problem in practice, hardly any research has been developed in this field.

The actual use of protection devices and hygienic behaviour depends on the presence, effectiveness and comfort of the various provisions. The presence of these facilities, i.e. personal protection devices and provisions, is one thing, their useability another. The latter depends on the characteristics of the facilities themselves, e.g. comfort. The useability can be further restricted by the task demands and by the working environment. Under high ambient temperatures, the motivation to wear protective clothes decreases. Incompatible task demands and time pressure reduce the use of protec-

tion devices that are not immediately at hand. Moreover, time pressure inclines the employee to set aside safety measures simply because they take time. An inadequate ergonomic design of the workplace and stocked materials may also restrict the use of protection devices. Finally, the useability – and by implication the use – depends on the characteristics of the employee in two ways. First, we should consider the fit of the device to the person. Protection devices are often far from optimal on anthropometrical grounds. Secondly, we should consider the psychophysiological state of the operator or his fatigue, which may play an important role in the use of protection devices. Special attention both in research and in practice should be given to the problem of fatigue. It is well known that under fatigue the operator will limit his field of perception and attention (Bartlett 1943). Fatigue impairs judgement and may thus stimulate risk-taking behaviour. It is also known that under fatigue the performance of complex skills deteriorates, e.g. doing the right things at the wrong time. Otherwise, slight physical discomfort may under fatigue become a severe annoyance, with consequences for the comfort of protection devices. Finally, a fatigued operator is emotionally more easily irritated and will resist activities that are not strictly needed in the task performance at the moment. This may influence his willingness to keep to the safety measures.

4 From Internal Exposure to Biological, Behavioural and Health Effects

Given a certain internal exposure level, the biological, behavioural and/or health effects may vary. Much research has been done on the problem of differences in biological susceptibility between individuals. Biological susceptibility can be considered as consisting of two components, a permanent and a transient component. Among the *permanent* components, genetically determined characteristics are gender and race, and in some sense age. Reactivity patterns are also partly genetically determined, as can be seen in the atopic syndrome. Moreover, among the permanent components we may include acquired organ deficits and morphological differences. With respect to these components, environmental causal factors such as diseases, sensitization, accidents, leisure activities and home and living environment must be considered, both for prevention and for special care of susceptible individuals. Apart from the well-known problem of the susceptibility of the unborn child, more attention should be given to paraoccupational health effects on children and other relatives of occupationally exposed workers due to transport of toxic substances from the workplace into the home (Knishkowy and Baker 1986). The scope of industrial hygiene does not end at the factory gate.

Transient changes of the reactions of various functional systems, such as the immune system, the cardiovascular system and the respiratory system, are also considered as components of susceptibility. These changes are partly determined by biologically based patterns such as diurnal rhythmicity and menstrual cycle. There is a growing awareness in research and in practice of the impact of environmental conditions that affect these transient components. Although of a completely different order, shift work and pregnancy are among the more frequently studied. The exploration of the influence of stress and acute diseases, such as virus infections, is still in its infancy.

From life stress studies, and to a lesser degree from work stress studies, it is known that psychosocial stress may induce immune and cardiovascular system reactions (Tecoma and Heuy 1985). To our knowledge, no human studies have been done on the impact of work stress on the transient components of susceptibility to toxic agents.

Particularly in research on solvents and trace metals, the performance in perceptual-motor and mental tests is studied, in the search for behavioural effects and alterations in the mental state due to intoxication (Xintaras 1974; Williams and Teo 1986).

5 Feedback

Each stage in the model can be considered as a sign for the employee and for the organization, indicating the risks of working in an environment with toxic substances. In the model, as in reality, the logical sequence goes from left to right. At first there may be a fault in the design before a source exists, next comes external exposure, followed by internal exposure. Bearing in mind the ultimate goal of prevention, we may consider the model as a sequence of situations that can be monitored in order to provide signals necessary in feedback procedures. When, for instance, the internal exposure is monitored, indicating that the level is too high, feedback procedures may be started, this time going from right to left in the model in order to affect the preceding transitions. Thus, working methods, personal protection and hygiene, but also biological susceptibility, technology and organization may be chosen as points of attack. To prevent future sources, better designs are needed.

Coping behaviour of the employee may be provoked when early health effects or behavioural impairments are noticed, e.g. headache or eczeme in an early phase, or attentional deficits. In many cases, however, employees must be instructed by formal educational programme to notice and interpret these "body signs". Special education programme, on-the-job training and supervision are needed, according to the principle that information enabling employees to cope with early health effects is basic in the maintenance of health and safety at the workplace. Many toxic agents, however, cause biological and early health effects which cannot be noticed by the employees themselves. Information stemming from occupational monitoring programmes must be given to the employees. Skills needed to interpret this information should be acquired in special education programmes and on-the-job training.

Recently, Miller (1986) proposed a model of the relationship between multiple causes, host and effects. Our model and the Miller model differ in some minor, but still very important, details. The Miller model focuses on the total life exposure and does not recognise the major contribution of occupational exposure. A more fundamental distinction between the models pertains to the final question of the actions that should be taken in prevention. The Miller model is too limited in this respect, as it recommends the removal of the worker from exposure, the use of preplacement medical examinations including genetic screening and medical treatment as the primary tools of prevention. In our opinion, occuptional health care has a broader scope,

including the removal or at least diminution of the primary sources. To accomplish these aims, occupational health practice must embody a multidisciplinary approach, including engineering and social sciences.

6 Consequences for Occupational Health Practice

In most situations of occupational health practice, an improvement of design leading to the removal of the source is the most effective and the most desirable strategy. This strategy, however, cannot be followed in most cases for political and so-called economical reasons. Sometimes the presence of toxic chemical substances is even generally accepted, for example in laboratories. Also, it is not always easy to decide which chemicals should be abandoned, simply because definite knowledge of the adverse effects is still missing. Even if standards are established, it must be noted that agreement upon an operational standard is the outcome of political negotiations, both on the national level and *also in everyday practice on the shop floor* (Grundberg 1980). Under these circumstances, occupational health professionals are committed to alternative strategies. Until now, most attention has been given to technological measures, personal protection devices and preselection and screening of susceptible individuals. The impact of organizational structure, formal work methods, worker strategies and hygienic behaviour is underestimated. Information, knowledge and tools enabling employees to cope with risk factors and early effects are basic in the maintenance of health and safety at the workplace. Thus, more attention has to be paid to organizational conditions and prescribed working methods, improving the conditions for coping with risk factors on the shop floor. The importance of the choice between various strategies and coping activites of employees must be recognized, as there is in many cases no "one best way" pertaining to all employees at the same time.

In large areas of industry and agriculture, neither management nor employees have even the basic information about the toxicity and hazards of the chemical compounds at their disposal. Therefore, systematic education and re-education programmes have to be developed and applied (Cohen 1985).

Government and social partners could have an essential role in occupational health politics. The trade unions can contribute to occupational health care using their formal and informal organizational structure. Checklists on working conditions, administered and discussed with respect to the results by union groups, and information campaigns are important instruments, which may be more effective than prescriptive information given by experts and nonexpert governmental and business authorities. A job - or sector-oriented approach should be stimulated. In consultation with experts, the social partners have to establish standards and guidelines with respect to, inter alia, provisions, working methods, workplace layout, educational programmes, occupational health monitoring programmes, and formal participation and information procedures.

In conclusion, in occupational health practice the employees should not be regarded as objects of prevention programmes or study, but as subjects who must be enabled to prevent adverse effects of toxic agents.

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Structural Properties of Economic Systems and Health Risks

W. H. C. Kerkhoff

1 Introduction

Increasing amounts of money and manpower are spent to set standards for toxic substances that may endanger the health of workers. Numerous publications refer to areas where facts and insights are increasing. Notwithstanding this, however, only a relatively small number of scientific findings turn out to belong unrestrictedly to the area of health policy within labour organizations. Among the number of suspect substances, only a few are subjected to undisputed norms and/or are accepted as hazardous and really undesirable. On the other hand, the number of new substances, constantly introduced into our lives, that we know little or nothing about is overwhelming.

This state of affairs could discourage the continuation of serious research such as is carried out in the field of physical and mental health. To safeguard valuable research investments and traditions and at the same time to reflect critically on their course of development, it seems appropriate to pay some attention to dynamics that govern relations between science and practice. What can be said about strategies to introduce results of scientific research into practice? To stimulate the debate on this relevant topic, this paper offers some ideas about the background to health policies in labour organizations.

Of course, this is a dangerous area: borderlines between science and policy may easily be crossed. It is by no means the intention of this paper to defend the view that there is no boundary between the two areas of responsibility to be respected. On the other hand, practice-oriented researchers can hardly be supposed to accept a situation where science does not have a substantial bearing on the way things work out in practice.

In labour organizations, the difference of responsibility between science and policy is recognizable in professional and managerial functions. An organization's management is responsible for the way an organization runs. Professional functionaries essentially do not share this responsibility: they are responsible for advice concerning possible anternative options that management may follow to reach its goals. In their advisory role, professionals normally rely on the state of the art of scientific procedures and knowledge in their professional field.

An intriguing new title in this area, covering essentially old policy habits, is *Technology Assessment* (Dijkstra et al. 1986). Technology assessment implies the introduction into policy decisions of science-based, generally technicoeconomical predictions about future effects of investments. Its social counterpart would mean the introduction of social considerations into decision making, for example, not introducing

a substance into the work environment because of its suspected effects on health in the future. But it seems that there is no equivalence in technology assessment between technoeconomical and social considerations.

2 The Making of Reality

In our days, one can be pretty sure that the topics of scientific research are of an artificial nature. This holds true not only for the chemicals which are studied for their possible negative influence on the human body (and mind) and for the countless new substances that are constantly introduced into our lives. Equally artificially based are the organizational structures, the labour organizations and the factories that often represent the birthplace for potentially hazardous environments. And even the knowledge and capacity to erect such structures are man-made and often of scientific origin.

So scientists may study lead, cadmium and mercury in their isolated or combined effects on the human body and not necessarily bother with the reasons why they are present in the work environment. Even the questions about how to eliminate such chemicals or how to reduce their influence do not necessarily have to be part of a research worker's programme. But this does not mean that these are irrelevant questions and by implication of an unscientific nature.

However one should aware that there are different questions at stake. Questions of the second kind do not deal with the nature and the effects of existing chemicals, but rather concern the reasons for their existence. The questions bear directly on human behaviour, individual or organized, and have to do with human rationality, human goals, power, conflicts of interest and – at a certain level – with human culture, including its scientific conventions and knowledge.

Taking this standpoint does not imply that every piece of health research should necessarily have to embody such considerations. But at a certain place or moment in time, these contextual problems will inescapably confront the research worker.

Toxic substances are hardly ever produced as such. Normally, the term refers to unwanted or unexpected side effects of goal-directed, mostly profit-oriented production devices. So if there is lead in the air, one should not only investigate its effects on the human body but also be aware of the reasons why it is there. If research uncovers hazardous effects of mercury on the human body, one cannot just leave the field with this knowledge, leaving those concerned behind unattended. But then immediately other questions rise, for example, regarding the circumstances that cause the situation and that may obstruct a change. However, our knowledge in this area is very limited, not only because it is a difficult area from a research point of view but also because it is politically burdened and therefore less accessible. Nevertheless, one should realize that science has to attack such problems, if only to underpin its societal function.

It is not the aim of this paper to comment extensively on this problem area. Given its complexity, the goal of the paper is just to highlight some topics that pertain to the question of social criteria in economic policy making. An analysis of the effects of the economy on environmental factors may serve as an illustrative case in this respect.

3 Production Policy and the Natural Environment

In order to operate, profit centres use different means of production. Generally speaking, they organize capital goods together with so-called natural means of production into a dynamic system. In terms of legal ownership, there is an essential difference between capital goods, which are formally owned by the organization, and the natural means of production, e.g. air, water and also a human labour force. The latter are borrowed from the environment without costs or, in case of shortage, against prices set by the market. In an organization's financial records, natural resources are headed under the complementary costs (Gill 1974).

Now let us imagine a production organization in the 1950s, a profitable investment period as we nowadays know, producing residual waste in making its products. Assuming that we are dealing with a responsible entrepreneur, we presume that he spends a certain amount of money to protect the environment from unnecessary pollution.

For reasons of economic dynamics, times then change in due course. We know that during the 1960s, industrial overcapacity developed, or that markets grew saturated, which essentialy leads to the same effect: increasing difficulties in maintaining profitability by way of sales. Under these circumstances, it is a matter of economic rationality to watch production costs carefully. It is then not unthinkable that our entrepreneur reconsiders his spending related to residual waste. The money spent will not be remunerative within this economic system, and so he might decide to just put his waste somewhere where it can be left without costs. This kind of behaviour is not really subversive; on the one hand, it is a logical outcome of internal rationality, whilst on the other hand, the general environmental consciousness is still low, and the environmental absorption potential is hardly touched. Improving profitability in a tight market may easily provoke the same reaction in other organizations within the business area concerned.

With this point of departure, some irreversible developments may be set in motion. Neglect of environmental care may first become a looping habit and may finally, under strong competition, develop as an inescapable institutionalized element of economic policy. The environment may of course show increasing saturation with waste elements, environmental movements being the first to react. Quite naturally, more and more work arises for researchers studying the hazards of ever-increasing numbers of pollutants. Of particular and logical importance is the fact that under such circumstances industries do not develop means of proper waste treatment. They combine this with increasing resistance against any appeal to accept responsiblity for environmental pollution. For some time, these two phenomena may develop together: increasing pollution and resistance against taking responsibility for it. Bad maintenance of the environment and a lack of knowledge and of resources for environmental recuperation may finally act as positively correlated semiautonomous variables, leaving in the end no other outcome than an outburst of disease. Taking responsiblity during the later phases of the process would imply enormous, probably intolerable demands on industrial systems. For this reason, denial and reference of the problem to governmental institutions develop as the usual and self-evident reaction: after all, the employment situation and international competition exclude any other approach. Undeniable proof of suspected risks is demanded from researchers working on toxic hazards, while

measures to prevent risks can only be considered if they do not imply economic costs. Only evident, and in later phases absolutely obvious, hazards will give rise to measures. Less obvious cases present the conventional research worker with a paradise of scientific exploration. Although the law of diminishing returns may govern their research, the search for increased partial correlations may very well satisfy investigational needs and publicational ambitions. Meanwhile, reality goes on untouched by research results, subjected to ever-increasing numbers of new chemicals that will show off their unwanted or unexpected effects to later generations and that will undoubtedly engage later research workers.

Gradually, it is only common sense to refer to a crisis-like situation confronting our society and scientific conventions as well. The vicious circle described before may contain some clues that can explain its dynamic background. This cyclic phenomenon may just as well be fatal to science as a possible new challenge. But the foregoing example contains specific illustrative power for the research area concerning the nature and the fate of human labour as one of the natural resources upon which the economy still heavily relies.

4 Manpower as a Natural Means of Production

Economic systems seem to be more and more restricted in dealing with environmental factors. The counterpart of this seems to be that society at large is confronted with an increasing influence of autonomous, but more and more interwoven, economic profit centres (Emery and Trist 1974: turbulent field). Responsibility for the general environment, i.e. the care for the so-called externalities, is restricted by decreasing degrees of freedom. One can witness the consequences thereof in the state of natural resources and in the general reactions to them.

An important variable for health research is the fact that in the industrial economic system, manpower is dealt with very much the same way as other natural resources. Manpower in general can be considered as a means to produce an income, as well as being a means of livelihood for the working population. But from the industrial point of view, manpower is mainly a natural means of production; it is derived from the market against the lowest possible costs, to be employed in the most profitable way.

There is no need to comment on numerous specific consequences of this situation; at wish, one can verify this point of view in the general socioeconomic map of our country, showing unprecedented numbers of unemployment and disablement (Sociaal Cultureel Planbureau 1984). The point to be underlined here is that if one carries out research on pollutants, this research as a rule concerns the labour population; i.e. natural means of production means manpower. Much of what has been said before about natural means of production also applies to the labour force. So research on toxic matters influencing the human body is equally embedded in structural constraints that prevent the translation of research assignments into practice.

There is one similarity between manpower and other natural resources that is of particular importance. Previously, attention was drawn to the fact that the broadly practised dumping of waste prevented the development of procedures more proper from the

environmental point of view. Ever since the end of the 1960s, comparable structural features seem to have determined the way we deal with the labour force. An abundant labour market, together with excellent social security provisions, allowed an impressive reduction of the effective working life, resulting in high degrees of youth unemployment, unprecedented numbers of disabled and a steadily decreasing age of retirement (Sociaal Cultureel Planbureau 1985). As a result of this development, the currently dominant reaction of economic institutions faced with economic problems still seems to be a reduction of labour costs. We are not very effective, or creative, in dealing with working lives.

Whereas in the former case, environmental pressures may steadily develop to countervail enduring traditions of internal rationality, comparable signals from the social environment of not seem to evoke sorrow as yet. In spite of an alarming disturbance of the balance between the level of income premiums and the amount of money needed for social security, we still seem to believe that shortening of the effective working life can be continued. Notwithstanding the greying of our population and of our workforce, we seem to accept unpaid work and a considerable reduction of the public workforce as a proper and workable outcome of modern technoeconomical developments (Scenario Commissie Vergrijzing 1985).

During the 1970s, work problems following industrial policy were partly masked by the very well paying social security system. Furthermore, a temporary solution followed from rising employment possibilities in the private and public services. Now, during the 1980s, private and public institutions seem to be forced to follow the same manpower policy as started earlier in the industrial area. Reduction of social costs has apparently now reached an institutional status, acting as an inescapable semiautonomous force, thereby restricting employment prospects and possibilities to improve the work environment according to scientific understanding. The burden for the social environment following this mode of behaviour will without any doubt manifest itself in an intensified way in the near future and will then be further aggravated by the consequences of the greying of our nation.

It seems appropriate to suppose that we are here facing learned behaviour form the past, which, looking at it from the perspective of the future socioeconomic environment, may turn out to be less tenable than we may now think or hope it is.

5 Ageing Institutions and Policies

Within the framework of the workshop, this paper pertains to structural conditions that determine the actual exposure to chemicals at work, the capacity to cope with the workload and also the possibilities to introduce programmes for protection of workers' health. The foregoing examples embody some less good looking perspectives on this subject. But in themselves, the throughts presented may offer some clues in considering the reasons why, with so much applicable knowledge in the field of health conditions developed during the last decennia, one only observes so little improvement following health research efforts. The line of thought may even offer some explanation for the fact that health research so often has to bother about the degree to which research results contain proof – undeniable proof – before it is accepted as a point

of departure for policy concerning health at the workplace. Barriers to finding a way into practice for health-related research results as described above may additionally be understood as a possible soil for a scientific convention that persists on pure scientific research without bothering what is going on in reality.

In the past, our Institute carried out a lot of research on obsolescence of skills and capabilities of ageing workers (Kerkhoff 1981). The subject of obsolete workers is nowadays a generally understood problem. At the same time however, little effort has been observed to meet this problem through measures that preserve the individual working life. Quite generally, the problem is met by replacing obsolete workers by better-educated, often cheaper ones, or, more recently, by replacing an obsolete workforce by modern technology. The possibilities to study obsolescence and its consequences have increased to more numerous examples than ever thought of before. However, rather than to continue on this paved road, it seems appropriate to alter the subject on purely practical considerations. Considering obsolescence as a very evident phenomenon caused by a social change, one could assume that the evidence of its consequences may not be restricted to workers on the shop floor; social change can very well evoke resistance to change at higher, more institutional levels. At these levels, however, there are fewer possibilities to solve the problem through replacement. Power positions occupied at this level may effectively resist change and preserve or even augment conservatism. Of course, preservation of gained insights cannot be regarded as negative per se, but positions taken toward this phenomenon are not insensitive to questions of power. At some places, notably the lower loci of control, obsolescence seems to diminish; at other levels, however, it seems to persist or even to expand (Kimberly and Miles 1980).

Within this area of interest – the field of industrial gerontology – it could be worthwhile to shift attention from workers' obsolescence towards conservatism in management styles and institutions (Kaufman 1974). In times of relative stability, growing conventional experience contains accumulated knowledge, which may be very valuable for directing future behaviour. If the future, however, shows fundamental change and calls for different behaviour, obsolescence occurs. The crucial question is then whether one is able to preserve valuable experience from the past whilst combining this with a creative, unprecedented approach towards the future (Boulding 1978). The level at which societies preserve a potential for creative behaviour is decisive for the kind of development to be expected. If the creative act is restricted to the individual level because of a high degree of institutional conservatism, one may expect individual actions to be described as deviations. As a consequence, continued conservatism at the structural level will be observable. However, if a society does allow degrees of freedom to explore new directions, to create new modes of behaviour, this openness will probably act as a soil for new developments into the unknown future.

For many years, specific disciplines evolved around the problem of working conditions. Each of these has now developed considerable interest in preserving the domain concerned. Lots of territorial conflicts are now fought regarding the burden that specific specialties are confronted with. Instead of wasting energy in trying to preserve the gained identity, one could imagine that the future demands rather a state of scientific experimentation. For most probably, the future will not be merely a replica of the past. There are reasons to believe that the increasing burden of environmental

factors will set constraints on the freedom of economic operations. Signals stemming from pollution and from misuse of human resources will inescapably influence economic policy making in the future. As a consequence, policy makers will address to the social and health sciences questions similar to the requests usually made of the technical and economical sciences, i.e. to introduce scientific knowledge into the process of industrial planning and decision making. This mode of social technology assessment will require cooperation between distinct social disciplines in order to foresee social consequences of investments, rather than to test them empirically afterwards. This cooperation, now developing within the programme on Work and Health at the University of Amsterdam (Van Dijk and Meijman 1987) may act as an example of this kind of scientific behaviour, one that contains an open mind towards the future.

There are too many problems in the work environment and too much is left open for new experiments to allow ourselves the conclusion that standards of science as developed until now could meet the needs of times ahead. Pulling together the strengths of several disciplines could mirror reality in a better way and could at the same time offer a platform for the role that science may be expected to play in our society: to study and eventually to assist mankind on its insecure road to the future.

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Subject Index