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European Centre for Ecotoxicology
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SUMMARY

A practical approach to risk assessment for occupational exposure standard setting and practical guidance on requirements for animal and human data are given in this report. The various types of OEL, the way in which health may be affected by exposure and the processes used by authorities and company specialists when setting OELs are explained. A step-wise process of data acquisition is described for deciding which substances may require an OEL, for developing OELs and for modifying these in the light of knowledge and experience to produce more definitive limits. In this document OELs initially set are termed 'provisional' while those which have been subject to review are termed 'revised' OELs. Development of OELs is a dynamic process; no OEL can be said to be a final, definitive standard.

While health risks need to be assessed from available animal and human data for each substance and preparation used in the workplace, an OEL will need to be set for a relatively small proportion of these, since many will not become airborne and adequate control of others will be achieved by control of the more major workplace contaminants. Chemical and physical properties are listed which, together with knowledge of the way substances are likely to be handled, stored, transported and disposed of, are of value in deciding if an OEL should be set.

Before studies are planned, any industrial experience with the substance or similar substances should be examined, as should structure-activity relationships for new substances. Information on the acute toxicity, irritancy, sensitising ability, genotoxic activity and short-term, repeated dose toxicity is required before setting a provisional OEL. This information may demonstrate that further toxicological studies are required before a provisional OEL can be set.

Since animal and other experimental studies can never guarantee freedom from adverse effects on health, workplace atmospheric monitoring and health monitoring are recommended when new materials are introduced into the workplace. The design of such studies would need to be determined on a case-by-case basis. Information so gained may confirm the adequacy of the provisional OEL or may indicate the need to set a revised OEL. The need for a revised OEL may also become apparent from data sought by competent EC authorities, from advances in medical knowledge and from workplace experience. Major changes in the use of a substance may also necessitate the setting of a revised OEL. This may necessitate the performance of further studies in animals and man.

The setting of OELs should be carried out on a case-by-case basis by professionally competent groups. Unnecessary standardisation of the process should be resisted. When completed, the data on which an OEL has been based and the considerations which have led to the actual figures should be made freely available.

INTRODUCTION

A rapid expansion of the chemical industry over the past century, particularly in the production and use of organic materials, has been accompanied by increasing recognition of the potential health hazards to workers from exposure to substances during the development, manufacture, use, storage, transport and disposal of chemical products.

Measures to protect the health of workers and others who may be exposed to the toxic hazards of substances occurring in a wide variety of workplaces have been developed in many countries and also internationally, since much of the trade in chemicals is international. In the EEC, measures to provide such protection are being harmonised.

In providing protection, a primary requirement is identification of those properties which will constitute a toxic risk under conditions of exposure in the workplace. This was recognised for new chemical substances by the EEC requirement to notify specific production, use, physico-chemical properties and toxicity and ecotoxicity data to national competent authorities prior to marketing. EEC Regulations have more recently been promulgated requiring the reporting to authorities of toxicity and other data on existing chemicals (chemicals appearing on the EINECS list), initially those produced in large volumes.

It is neither necessary, nor practicable, to develop a full range of toxicological data (e.g. long-term inhalation toxicity, carcinogenicity or reproductive toxicity data) on the vast number of chemicals produced, used or occurring in the workplace (e.g. as contaminants, by-products or waste products). The only data required should be those essential to the identification of toxic hazards, to the assessment of the risks from those types of exposure likely to occur in the workplace and to the setting of OELs, should they be required.

With this in mind, ECETOC set up a task force to consider the need for a practical base set of data for occupational risk assessment and OEL setting with the following terms of reference :

- To determine the toxicological information requirements necessary for risk assessment and exposure standard setting to achieve health protection in relation to chemical exposure in the workplace;

- To determine the extent to which this information is, or can be made available, from existing physico-chemical and toxicological testing and other sources and to make recommendations, if necessary, for protocol amendments;

- If necessary, to recommend the type of additional studies and the circumstances in which they should be undertaken with due regard to humanitarian and logistic considerations.

It was envisaged that the report would be of value in rationalising demands for additional data under the Existing Chemicals Regulation and would assist industry in providing the data necessary for setting 'in-house' OELs.

The report outlines the various types of occupational exposure limit (OEL) (chapter 2) and discusses exposure to substances in industry and the ways in which health may be affected by exposure (chapter 3), subsequently the processes used by authorities and by specialists within individual companies, when setting OELs are described; the step-wise process of data aquisition used when developing provisional OELs and when modifying these in the light of knowledge and experience to produce more revised limits are provided (chapter 4).

Recommendations are made for the minimum toxicological testing needed to set a provisional OEL designed to control atmospheric exposure; in many cases no additional data or studies will be required. The need to confirm or modify the provisional OEL and the data required must be decided on a case-by-case basis (chapter 5).

Data required to set standards for biological monitoring or biological effects monitoring are not considered here.

2. THE ROLE OF OCCUPATIONAL EXPOSURE LIMITS (OELs) IN HEALTH PROTECTION

2.1 BACKGROUND

Employers are obliged to manage activities so that they do not adversely affect the health and well-being of their workers. This moral requirement is reflected in the regulatory requirements of EC Directives and the legislation of member states. Occupational exposure limits (OELs) have been developed to assist employers to achieve this goal. While OELs are now developed by regulatory authorities, standards have for a considerable time been similarly derived within individual companies for the control of substances. This still continues where no regulatory OELs exist and should be encouraged.

OELs are designed to assist in protecting the health of exposed individuals so that, provided exposure is kept below the OEL, the likelihood of an individual developing an occupational disease or suffering from ill-health will be low. However, because of the limitations surrounding the degree of health protection any OEL affords, the interpretation of what constitutes compliance with such a standard is complex, (Leidel *et al*, 1977; CEFIC, 1984; CEN, 1991); this important subject, which is essential to the proper use of OELs, is outlined in Appendix A.

2.2 TYPES OF EXPOSURE AND EFFECTS MONITORING

There are four main ways in which workplace exposures or their effects may be surveyed or monitored. These are described below.

2.2.1 Environmental Monitoring

Environmental monitoring requires measurement of contamination of the proximate environment (atmosphere, skin, work surfaces or clothing) by analysis for the chemical concerned. Comparison is made between the measured concentration and an OEL in order to assess the health risk. For example, the air in a PVC plant may be monitored for vinyl chloride to ensure that it remains below the level likely to increase significantly the risk of occurrence of angiosarcomas.

2.2.2 Biological Monitoring

Biological monitoring requires estimation of uptake into the body (absorbed dose) by measurement of the chemical or one of its metabolites in blood, urine, exhaled air, hair etc. Comparison is made between the amount of substance in blood etc. and the biological monitoring standard. For example, urine samples may be analysed periodically to ensure exposure to mercury remains below that likely to affect health.

2.2.3 Biological Effects Monitoring

This requires quantification of a biological effect (not of itself detrimental to health) which is dependent on uptake and may sensitively reflect reversible effects on body functions which, if sufficiently great, could result in adverse health effects. For example, blood may be analysed for cholinesterase levels to ensure that exposure to certain organophosphorus pesticides is minimised. ECETOC (1989a) evaluated the use of DNA and protein adducts in exposure monitoring.

2.2.4 Health Effects Monitoring

This implies detection or quantification of an indicator of ill health which is present or tending towards an indication of impaired health. For example, pulmonary function tests may be carried out at intervals in order to detect at an early stage any effect on the lungs of individual workers exposed to fibrogenic dusts.

Of these standards OELs are the most numerous. A smaller number of biological exposure limits and biological effects limits have been set.

2.3 TYPES OF OCCUPATIONAL EXPOSURE LIMITS (OEL)

There are two main categories of atmospheric OEL. 'Health-based' OELs are set on the basis that adequate evidence is available to ensure that exposure at levels less than the standard will be free from adverse health effects for nearly all workers. 'Technical' OELs (see section 2.3.2), while representing an exposure which is not believed to be associated with adverse health effects, cannot be considered to be entirely free from that risk.

In addition to these two main categories, most OEL systems distinguish between longer-term (usually 8 hour) "time-weighted average" (TWA) limits and "short-term exposure limits" (5-30 min. but usually 10 or 15 minutes) TLV-STEL (ACGIH, 1991).

The 8 hour TWA limit is intended to be used for the protection of health in those who may be exposed to a substance throughout the working day.

The STEL is intended to be used for the protection of health where excursions in the atmospheric concentration of a substance may be so high as to produce (usually acute) adverse health effects, even though the 8 hour TWA limit is being respected. Since short, high exposure might be particularly injurious if repeated frequently, criteria to limit their incidence may be specified, e.g.

> "Excursions in worker exposure levels may exceed three times the TLV TWA for no more than a total of 30 minutes during a work-day, and under no circumstances should they exceed 5 times the TLV-TWA, provided that the TLV-TWA is not exceeded" (ACGIH 1991).

STELs, as originally defined by the ACGIH, were values which should not be exceeded even

instantaneously because acute irritant, corrosive or narcotic effects may occur above such levels, while different chronic or subchronic toxic effects occurred with lower, longer-term exposures. However, it was recognised that most measurements cannot be made instantaneously and that, in practice, most measurement techniques average the exposure over a finite collection period. Accordingly, STELs are now intended to deal with time-weighted average exposures determined over a 15 minute period.

Where the primary toxic effect is irritation, corrosion or narcosis, two approaches have been adopted. Either the TWA value has been designated a "ceiling" value, in which case excursions above it are not permitted (ACGIH), or only a STEL is published (UK-HSE, 1992).

2.3.1 'Health-based' OELs

The longest-established health-based OELs are the Threshold Limit Values (TLVs) published by the American Conference of Governmental Industrial Hygienists (ACGIH). The 8-hour standard is defined as:

> The 'time-weighted average concentration for a normal 8-hour work day and a 40-hour work week to which nearly all workers may be repeatedly exposed, day after day, without adverse effect' (ACGIH, 1991).

The corresponding definitions of European health-based OELs are essentially similar. The MAK values published by the Deutsche Forschungsgemeinschaft (DFG) on the recommendation of the MAK Kommission are:

> the "maximum permissible concentrations of a chemical compound present in the air within a working area... which, according to current knowledge, generally does not impair the health of the employee nor cause undue annoyance". The definition continues to explain that effectively it is to be compared with an 8-hour, time-weighted average value (DFG, 1992).

The MAC values published by the Dutch Directorate General of Labour (DGA) are:

> "the Maximum Acceptable Concentrations of a gas, vapour, mist or dust in the air of the workplace which, according to current knowledge, in repeated long term exposure, even up to a whole working life, does not in general lead to health impairment of either workers or their offspring" (DGA, 1992).

The Occupational Exposure Standards (OES) values published by the UK Health and Safety Commission (UK-HSE) refer to:

> "the concentration of an airborne substance, averaged over a reference period, at which, according to current knowledge, there is no evidence that it is likely to be injurious to employees if they are exposed by inhalation, day after day to that concentration..." (UK-HSE, 1992).

Most other European countries also have health-based occupational exposure limits which, like those of Germany, the Netherlands and the United Kingdom, were originally derived from the ACGIH TLVs. The definitions of the limits differ slightly but there is considerable correspondence between the figures.

In relation to the recent criticisms of TLVs by Castleman and Ziem (1988) and Roach and Rappaport (1990), one fact of probable significance is that while the German and British systems have recognised the need for technical limits where health based limits cannot be established, such a facility was not established by the ACGIH TLV Committee. Thus, some of the limits which have been promulgated by ACGIH as health-based might have been designated as technical limits, had this option been available to them.

The question of what constitutes compliance with health-based exposure standards is complex and much debated. There is a tendency for statistical methods to be applied to determine from the measurements taken (which are a sample of the population of all possible measurements) the probability that all values would be below the OEL. A popular criterion is that there would be compliance if 95% of all measurements are likely to be less than the OEL.

Many companies and regulatory bodies take action when exposures exceed certain fractions of a health-based OEL. Any individual exposure measurement which exceeds a defined 'action level' might trigger an investigation into the operational condition of the plant, work practices and exposure control measures. The relationship of such an action level to the OEL may depend on, amongst other things, the historical exposure levels, the variability of the exposure levels and the closeness of the historical exposure levels to the health-based OEL.

In addition, an individual company may set 'target exposure levels' well below the OELs to assist in the maintenance of exposures in a particular plant at the low levels experience as shown possible when using best available technology.

2.3.2 Technical OELs

In Germany, the Committee for Hazardous Working Materials of the Ministry of Labour and Social Affairs may assign 'Technical Guideline Concentrations' (Technische Richtkonzentrationen - TRKs) for carcinogenic substances for which health-based MAK values cannot be set. The values chosen take into account analytical capabilities, current exposure control technology and the absence at these exposure levels of adverse medical reports.

In the UK, the Health and Safety Commission adopts Maximum Exposure Limits (MELs) which represent "the maximum concentration of an airborne substance, averaged over a reference period, to which employees may be exposed under any circumstances". MELs are set when data are inadequate to set an health based OES (Occupational Exposure Standard) which can be met by all industries or where exposures above an OES are likely to lead to serious ill health.

In general, technical OELs are set where no threshold can be defined for adverse health effects in all or some of the persons exposed. This is the case with some carcinogenic substances and respiratory sensitisers where the induction of disease is a stochastic response which might occur at any level of exposure but where the probability of disease becoming manifest increases with the increasing levels of exposure.

In some cases, technical OELs have been set at levels which are technically attainable and at which there is no clinical evidence of an adverse health effect, but where there are other data, for example from animal experiments, that suggest a degree of uncertainty about the safety of such exposures.

Because of the uncertainties surrounding their effectiveness in protecting health there is normally a requirement to reduce exposures as far as practicable below the standard(s).

3. THE NATURE, FORM AND EFFECTS OF WORKER EXPOSURE TO SUBSTANCES IN THE WORKPLACE

The type of information required to set OELs is dependent upon the likely routes of exposure occurring in industry and upon the range of adverse health effects known to occur.

3.1 ROUTES OF EXPOSURE

Chemical substances in the workplace may affect the human body following their inhalation, ingestion and skin (and eye) contact. All tissues and organs along these exposure pathways (respiratory tract, gastrointestinal tract and skin) and organs and tissue to which the substances or their metabolites may be carried by the circulatory system are possible targets. Exposures can lead to a wide variety of effects. The routes of exposure and the range of effects against which OELs are designed to protect are described here.

3.1.1 Inhalation

Inhalation is an important route of exposure to substances in the workplace. Substances may be inhaled in the form of gases and vapours, fumes and mists or particulates. Water soluble gases are taken up mainly into the mucus covering the epithelia of the nose and upper respiratory tract into which they are then absorbed. Absorption may occur also through the gastrointestinal tract when the mucus is swallowed.

Gases and vapours tend to pass down the airways as far as the alveoli where gas exchange is normally so fast so that uptake into the blood depends essentially on the ratio of the concentrations of substance in air and blood. The total intake of such substances is thus decided by this ratio, the pulmonary ventilation rate (which depends on the work load of individuals), the concentration of the substance in the inhaled air and the time spent in the contaminated zone.

If no, or only slow excretion or metabolism of the substance occurs, pulmonary elimination (at a rate depending on the air-blood partition) becomes the main route of excretion when exposure ceases. Analysis of exhaled air can be used as a biomonitoring tool for such substances.

Solid particles are deposited in different parts of the respiratory tract (extrathoracic, tracheobronchial and alveolar regions), depending on their physical properties, particularly the aerodynamic particle size. Absorption of the deposited particulates may occur in any part of the respiratory tract, depending on the solubility of the substance and the physiological activity of the parts of the respiratory tract. Particles which are deposited in but not absorbed from the upper part of the respiratory tract (extrathoracic and bronchial region) are transported in mucus towards the throat by the ciliated epithelium and swallowed. Insoluble particles deposited in the alveolar region are enveloped by macrophages and some, e.g. asbestos and silica can enter the tissue and remain in the lung. Substances bound to particulates will be transported and deposited with them in the respiratory tract.

The influence of the size of particulates on the site of deposition makes it necessary, when setting OELs for particulates, to define the particle size to which the OEL relates. In practice, different OELs may be set for the control of inhalable particles (deposited mainly in the upper respiratory tract) and respirable particles (deposited also in the alveoli). It has also to be kept in mind that absorption of particulates is governed by their chemical properties and that less soluble particles may be transported to the gastro-intestinal tract from which they may be absorbed.

3.1.2 Ingestion

Ingestion is not a major route of entry of hazardous substances into the body since the consumption of food and beverages (which could become contaminated by workplace substances) is normally strictly prohibited in the work force. Involuntary ingestion of hazardous chemicals, e.g. from contaminated hands, gloves or apparatus should be prevented by standard hygiene measures. Nevertheless, should ingestion occur, the amounts absorbed may be considerable (Woollen *et al*, 1992, Wilks *et al*, 1994. Chemicals which are accidentally swallowed can lead to high intakes in a short time. Breathing through the mouth as a result of nasal obstruction or a high work-load may result in deposition or dissolution of substances in oral or pharyngeal mucus which is then swallowed. Inhaled particulates which are deposited in mucus in the upper respiratory tract may also be swallowed.

3.1.3 Skin penetration

Intact skin provides relatively good protection against most substances. Nevertheless some substances can travel through skin rapidly and in great amounts and, for some of these, skin permeation may be the major route of exposure. Some national lists supplement OELs (ACGIH, DFG, etc) with a special notation where significant absorption through the skin must be expected with a substance. So far, no limit values specifically designed for control of skin absorption have been established, although biological exposure limit (BEL) values (ACGIH and DFG) are used to control the total uptake of substances, including the uptake through skin absorption. The strategy for assigning a skin penetration notation to substances has been considered by ECETOC (1993a).

The rates of skin penetration are unknown for most liquid, solid and gaseous substances. Even the rates at which substances permeate the various protection materials used for gloves etc. are often not known. Because permeation of protective materials does occur, high concentrations may arise inside the protective clothes. Furthermore, penetration through the skin may be enhanced by the conditions inside protective clothes, e.g. by humidity or heat. While intact skin generally provides good protection against substances, injured skin can provide an entry for almost any chemical. Some substances may also act as carriers, assisting entry through the skin of other substances.

3.1.4 Other Routes of Exposure

Subcutaneous injection of substances may occur by accident, e.g. by misuse of high

air-pressure driven devices such as grease guns. Exposure by innoculation is also possible, e.g. in laboratories in which substances are handled along with hypodermic needles or other sharp instruments. These routes of entry do not influence the setting of an OEL.

3.2 EFFECTS OF EXPOSURE ON HUMAN HEALTH: PREDICTION FROM ANIMAL STUDIES

For most substances there is a recognisable threshold of exposure below which no adverse effects on health will occur; at some point above that threshold the toxic effects of exposure will become manifest. In general, the higher the degree of exposure and the longer the period of exposure, the greater the probability that adverse effects on health will occur and the greater the severity of those effects.

Adverse health effects may be acute, that is, they may develop soon after exposure, rapidly reach their peak and then decline in severity, usually to resolve completely. Acute effects on health usually arise from one or a few high exposures taking place within one work shift. Acute effects may, in some cases, not become apparent immediately following exposure but may develop later, often when the initial symptoms of toxicity have abated. Such "delayed" effects are important, since they can, if not recognised, prove fatal at a time when there is apparent recovery. For example, exposure to methyl bromide can produce pulmonary oedema and death many hours after the initial symptoms of poisoning have disappeared.

Adverse effects on health may also develop gradually, usually following prolonged or repeated exposures over periods of weeks or months (often termed sub-acute or sub-chronic toxicity) or many years (often termed chronic toxicity). While such effects may resolve (quickly or slowly) when exposure ceases, some or these effects may persist or even gradually worsen.

The information required to set OELs must encompass each of the forms of toxicity, all of the pathological processes which produce the toxic effects and all the types of adverse effects which can occur in body organs and systems following exposure to chemical substances. Many types of adverse effects can occur following exposure to substances in the workplace, as described in Table 1, some of which can regularly be detected in "base set" studies (e.g. VII Amendment), some of which are detectable or indicated by experimental, follow-up studies and some of which are unlikely to be identified in such studies.

Thus, while experimental "base set" studies are capable of detecting many of the abnormalities which may follow chemical exposure, or of pointing to the need for further studies to clarify the toxic potential, these studies can not completely guarantee detection of adverse effects. Basing OELs on exposure levels found to be without detectable adverse effect in animals and use of an appropriate safety factor does overcome this defect in most cases but complete certainty that use of an OEL will ensure freedom from disease can only come from follow-up studies on those who are being exposed, i.e. by health monitoring of the workforce in association with determinations of exposure.

Table 1: Examples of Adverse Effects

	Demonstrable in "base set" studies	Detectable in appropriate "follow-up studies"	Unlikely to be indicated by experimental studies
EYES	Conjunctival irritation and burns; corneal oedema and burns	Corneal keratitis: conjunctival discolouration cataracts	Myopia, retinal disturbances (e.g. loss of colour vision)
NOSE	Rhinitis, epistaxis	Perforated septum; carcinoma	Persistent sneezing
MOUTH	Salivation; ginivitis; pharyngitis	Chronic ulceration; carcinoma	Loss of taste
NERVOUS SYSTEM	Convulsions; ataxia; rapidly developing motor nerve damage	Slowly developing motor nerve damage; Neuronal damage; nerve transmission defects	Headache; drowsiness; mild weakness; mood and intellectual changes; sensory changes
RESPIRATORY SYSTEM	Tracheobronchitis; Irritant alveolitis; rapidly developing pulmonary fibrosis	Slowly developing fibrosis and granulomas; carcinomas and mesotheliomas	Asthma, allergic alveolitis; mild changes in pulmonary function
CARDIOVASCULAR SYSTEM AND BLOOD	Myocardial damage; vascular defects; rapidly developing anaemia and clotting disorders	Cardiac function and pressure; slowing developing anaemia and clotting disorders; leukaemia	
ALIMENTARY SYSTEM	Diarrhoea; acute hepatic damage; gastric and intestinal irritation and erosion	Subacute and chronic gastric, pancreatic, intestinal and hepatic damage; hepatic cancer	Nausea, vomitting, colic, constipation
MUSCULOSKELETAL SYSTEM		Bone and muscular necrosis; adverse effects on joints; Osteomalacia; Osteosclerosis	Acroosteolysis
SKIN	Irritant dermatitis; ulceration; folliculitis	Photosensitisation; Acne and chloracne Skin and mammary granuloma and cancer	Pigmentation abnormalities; Hair abnormalities
RENAL SYSTEM	Acute renal damage	Subacute renal damage; renal and gonadal cancer; Urinary tract irritation	Renal stone formation
REPRODUCTIVE AND DEVELOPMENT SYSTEM	Gonadal changes	Impairment of fertility (male or female); congenital abnormalities	
ENDOCRINE SYSTEM	Thyroid and adrenal changes	Blood hormone levels; Pancreatic charges; islet	Mild variation in blood/tissue hormone levels

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4. LIMIT SETTING

4.1 GENERAL CONSIDERATIONS

The data required for setting an OEL and the types of study that will supply them are influenced by the processes used in setting an OEL. The processes vary somewhat from authority to authority but, in general, follow those outlined in Figure 1. While health risks need to be assessed from available animal and human data for each substance and preparation used in the workplace, an OEL will need to be set for a relatively small proportion of these, since many will not become airborne and adequate control of others will be achieved by control of the more major workplace contaminants. Chemical and physical properties are listed which, together with knowledge of the way substances are likely to be handled, stored, transported and disposed of, are of value in deciding if an OEL should be set. In essence a provisional OEL is set by evaluating the findings of experimental toxicological studies which define the range of toxic effects and the dose/effect characteristics of the substance, under exposure conditions likely to occur in industry. A safety factor is used when judging the probable safe exposure level for man from the 'no observable adverse effect level' (NOAEL), or the 'lowest observable adverse effect level' (LOAEL), as determined in animal studies (for definition, see on 4.2.3: experimental studies). The safety factor varies with the nature and severity of toxic effects, the degree of uncertainty arising from insufficiencies in toxicological data and the degree of protection deemed necessary to prevent adverse effects. Historically the factor has been between one and ten (Lewis *et al*, 1990; Galer *et al*, 1992).

The provisional OEL also depends on industrial experience in the use of the particular substance, chemically similar substances and substances used for the same purposes, and on any findings in studies performed on human volunteers. Setting a provisional (health based) limit also depends on the availability of a suitable analytical method for determining the concentration of the substances in air or biological media (Biological Monitoring). Where uncertainty associated with the data make it impossible to set a health based limit, a technical limit may be set.

In most cases the principal concern in setting the limit is to protect health but in some cases atmospheric OELs are set at the air concentration which provides a comfortable environment by ensuring freedom from nuisance properties of the substance; this concentration may be well below that set to avoid pathological abnormalities in the exposed population.

As it is the case with all health protection limits the provisional OEL and technical limits are always open to modification. This may be because practical experience of the limit or new toxicological, human experimental or epidemiological data show that a limit is inadequate to protect health or produce a comfortable working environment, or is unnecessarily stringent. This process of modification, which may be repeated, will eventually lead to adoption of a more definitive (revised) limit. It is equally important to recognise that even if exposure is controlled at the revised OEL, a small proportion of those exposed may experience discomfort, a few may suffer aggravation of existing disabilities, and some may become ill; for this reason, whatever the OEL, atmospheric concentrations of contaminating substances

should always be maintained at as low a level as technically reasonable.

4.2 DATA REQUIRED FOR SETTING AN OEL

The acquisition of data for setting an OEL is conducted in a step-wise manner, with gradual accumulation of data on exposure and biological activity until sufficient is known to allow assessment of the health risks of exposure. The type and extent of the investigations in each step, the factors which trigger subsequent phases of investigation and the point at which data are considered adequate vary considerably from substance to substance and may depend on, for example factors such as:

- the physical and chemical properties and the toxicity of the substance;
- the probable number of people exposed, the population characteristics (e.g. healthy workers or the general population) and the past experience of those who have handled the substance and similar substances at work;
- the probability that exposure will occur and the likely extent, frequency and length of exposure;
- the possibility of minimising or eliminating exposure - where exposure can be eliminated or readily reduced, this may be a better control strategy than extensive testing with the aim of setting an OEL;
- the potential health risks as judged from exposures and toxicity of the substance and substances of similar structure and/or physico-chemical properties;
- the ability to monitor exposure of populations and the development of impaired health;
- the ability to end exposure should unexpected adverse health effects occur.

It is possible to generalise to a limited extent, but the need for various types of data is largely dependent on the probable or actual exposure pattern and on knowledge which accumulates gradually from the basic toxicological studies and the studies shown to be necessary to follow up these findings (Figure 2). This is discussed in more detail below.

Three types of information are needed to establish a provisional OEL or technical limit for a substance:

i) Chemical structure and data on the physico-chemical properties of the substance.

ii) The range and patterns of use and consequent extent and patterns of exposure at the workplace. For many chemicals the uses to which they may be put is unknown, so that it may not be possible to define the extents and patterns of exposure. Where this is so, authorities which set standards generally assume that long-term exposures will occur and OELs are set to protect against exposure for 8 hours a day, 5 days a week for a full working life (40 years) and against any acute effects caused by the inevitable fluctuations in concentration above the norm.

In other cases the use of a chemical and the extents and patterns of exposure are limited and readily defined. This is particularly so for substances used for specific

purposes at one site or within one industry. Where this leads, for example, to only sporadic or acute exposures, it may be possible to set an 'in-house' limit to control against the effects which result from these types of exposure only.

iii) The toxic activity as shown by experimental systems and studies on human subjects who have been exposed to the substance and experience gained from the use in the workplace of the substance, substances of similar composition and of other substances used for similar purposes.

Figure 1. Steps in the Development of OELs

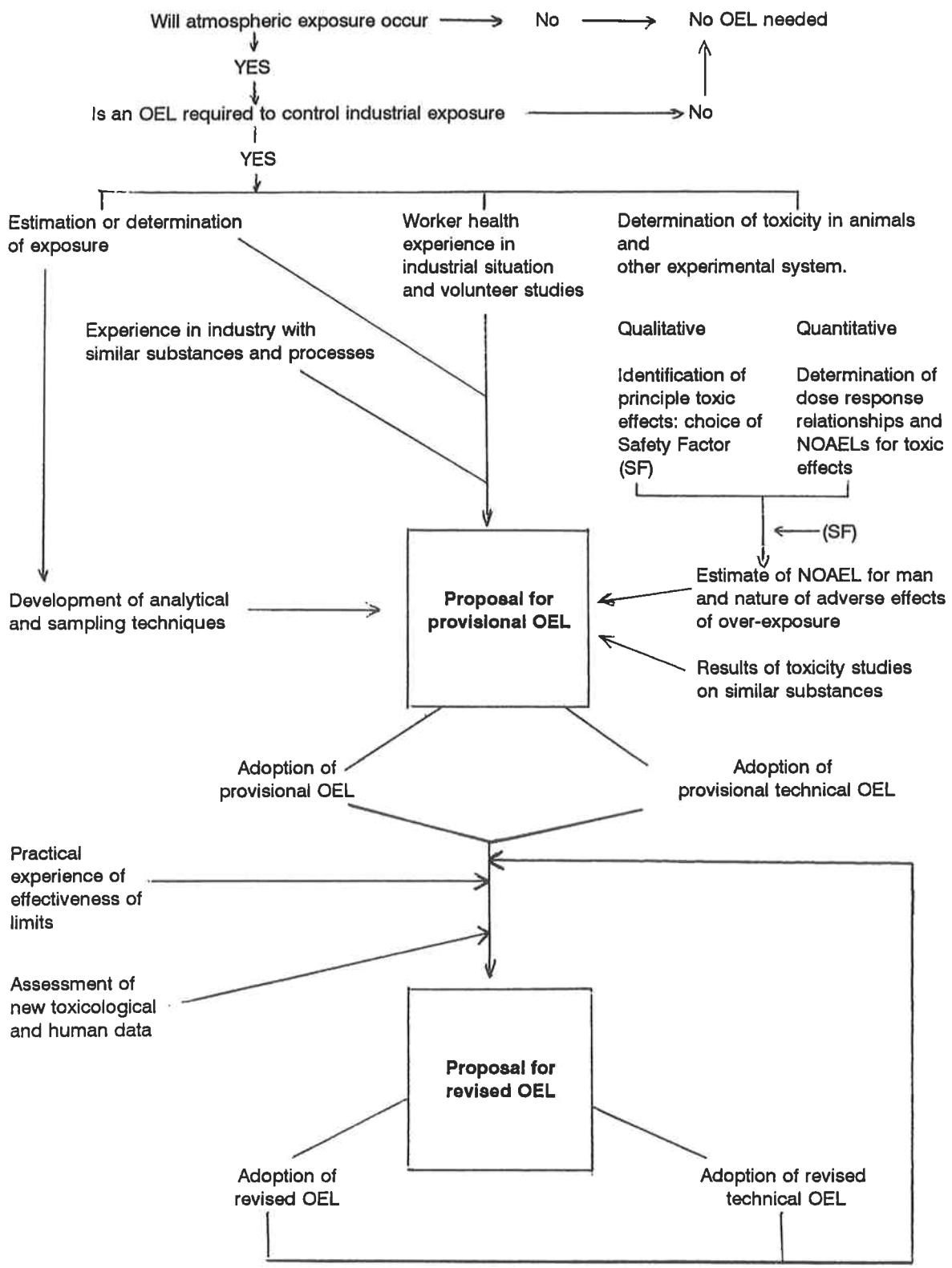
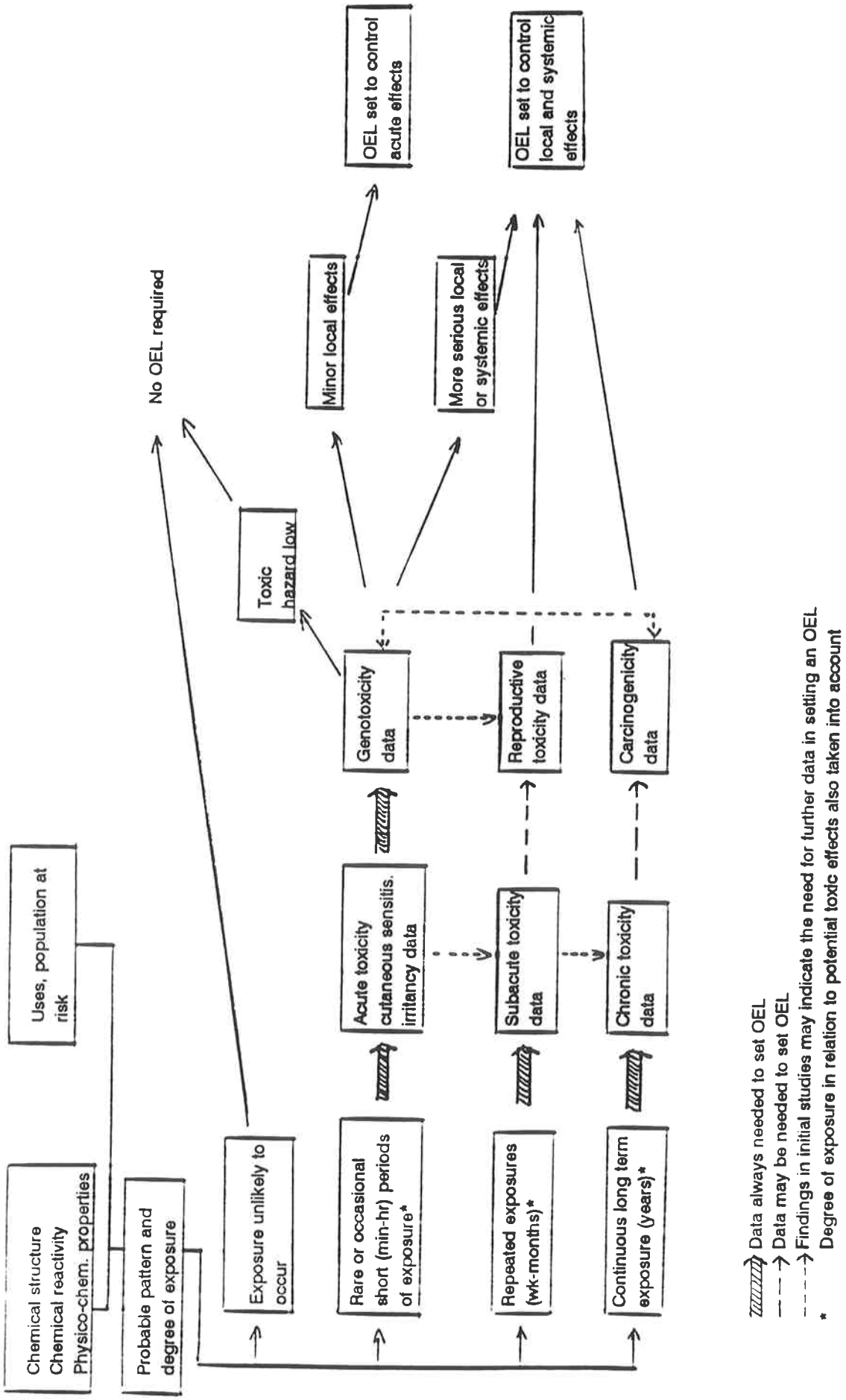


Figure 2: Factors Governing Toxicological Data Required in Setting an OEL



4.2.1 Chemical Structure and Relevant Physico-chemical Data

The following chemical and physico-chemical data are of value in identifying a substance and in evaluating its risk to health:

Identification

- Chemical name (IUPAC nomenclature)
- C.A.S., E.E.C., E.I.N.E.C.S. numbers
- Synonyms and trade name
- Molecular and structural formula
- Molecular weight
- Purity, reported as technical product; a list of known impurities and their percentages should be known.

Chemical - Physical Characterisation

- Physical state and appearance
- Organoleptic properties: odour and odour thresholds
- Boiling point (°C)
- Melting point (°C)
- Density (g/ml at 20°C)
- Vapour pressure and saturation concentration in air at 20-25°C.
- Vapour density (air = 1)
- Solubility in water and/or other relevant solvents (i.e. generally used at workplace)
- Flash point (°C)
- Flammability limits (LEL, UEL)
- Conversion factor (1 mg/m^3 = ... ppm / 1 ppm = ... mg/m^3)
- Octanol/Water partition coefficient (Log Po/w)

Furthermore, it is important to understand the chemical reactivity of the substance and to be equipped with reliable methods of sampling and analysis.

4.2.2 Use Pattern and Estimation of Exposure at the Workplace

Knowledge of the processes in which the substance will be used and the manner in which it will be handled, transported, stored and disposed of will, when evaluated in the light of the physico-chemical properties of the substance, indicate the probability and extent of exposure at the workplace and hence the types of toxicological studies which may be required.

The nature and depth of toxicological tests may also depend on the production volume, the number of people liable to be exposed and the nature of the intended use.

The important question to be answered is whether the anticipated exposures might have adverse effects on workers. If there is no evidence on this from prolonged handling of the substance (including medical surveillance and recording of the exposure levels of workers)

an expert judgement has to be made from experimental toxicological data.

4.2.3 Toxic Activity in and Effects on Biological Systems

In general, all available information on human and animal toxicity, toxico-kinetics, and metabolism should be evaluated and toxic activity should be compared with that of structurally similar compounds. All sources of information should be examined; the scientific literature, computerised data-banks, documents produced by Expert Committees or profit and non- profit making research organisations and unpublished data (e.g. industry reports) are important sources. It is helpful if such reports cite guidelines used and the degree of compliance with Good Laboratory Practice (GLP).

Where similar chemical structures exhibit a common pattern of effects, the need for detailed testing may be substantially reduced. The relationship of toxic activity to chemical structure has been discussed by ECETOC (1986). Where there is considerable variability in the toxicity of chemically similar substances there will be a higher degree of uncertainty in deducing effects in man from toxicity studies or from the use of structure/activity relationships.

Epidemiology and Industrial Experience

Where a substance has been used in industry for a number of years, industrial experience and epidemiological data may provide sufficient information from which to set an OEL, or may point to the types of test required for the setting of an appropriate standard. Epidemiological investigations correlate exposure to a substance with the state of health of exposed populations. The selection of the workplaces in which epidemiology studies can be conducted is complicated by a number of factors. The most important is that exposure to a single substance is relatively uncommon; it is most usual to find exposure to multiple substances in the workplace and to many stresses both at work and in the non-occupational environment. Focusing only on the substance of interest as the cause of ill health effects may therefore lead to an overestimate of the seriousness of the hazard.

In the design of epidemiological investigations the following criteria will help to provide data of value in setting an OEL:

- the toxic substance to be studied should be the only or the predominant chemical agent to which exposure occurs;
- other substances to which exposure occurs should be identified and quantified and their possible influence on the investigation assessed;
- the concentration of the substances in the working atmosphere should be known;
- uptake of the substance by other routes should be taken into account;
- the exposed population should be sufficiently large for a statistically valid correlation to be obtained;
- if possible, two or more exposed populations of the same type but with different degrees of exposures should be studied;
- the data should be compared with adequate control groups;

Demonstration of a correlation does not necessarily prove that exposure has caused the health effect; an association may be spurious or arise from an association of exposure and the effect with a common variable. While epidemiology cannot prove exposure has caused ill-health, it can lend considerable support for or against. Any epidemiological investigation, whether indicating a positive or negative association, should therefore be systematically reviewed using accepted criteria (Bradford-Hill, 1965).

In the past, some exposure limits have been set on the basis that good industrial practices and procedures have produced particular exposure levels without evidence of adverse effects on health. Such experience is of value only if it can be shown that the industry had adopted procedures which could have detected adverse health effects, had they occurred. Positive evidence of the absence of health effects at particular exposure levels is of more value in setting OELs; unfortunately, information on health and exposure is often derived from retrospective analysis of data obtained without any set protocols or even documentation of methods.

In the future, authorities which set standards may well come to acccept as the basis for an OEL only quality-assured, protocol directed studies on worker exposure and health; such studies should be considered, particularly in the early phases of use of a new chemical, or where an existing chemical is scheduled for review or establishment of an OEL.

Experimental Studies

The initial evaluation of the information may show that some data for setting provisional OELs are missing.

The type of testing required for setting a provisional limit and the nature of any further experimental work will depend on the type and extent of exposure; where exposure data and the physico-chemical properties of the substance show an OEL is necessary, a minimum set of basic information should be available. This will be obtained from acute toxicity tests by oral, dermal or inhalation routes, as appropriate to the mode of possible exposure, and from tests for skin and eye irritation and mutagenicity. Where exposure will be repeated or continuous or, where the patterns of exposure cannot be predicted, information from a repeat-dose study will also be needed in setting a provisional OEL.

In carrying out experimental studies some general factors should be kept in mind. Data from animal species whose metabolism is closest to that of man are of greatest value even though, for reasons of integrity of the toxicological review, findings in all the animal species investigated are reported. Since the majority of studies on chemical substances have been carried out in rats and mice, data on at least one of these species is essential. The most relevant route of exposure should be used for the studies. For gases, highly volatile liquids and liquids under pressure which produce liquid aerosols, studies using the inhalation route are essential. Similar studies may need to be carried out on powders which generate respirable dusts particularly when these are water insoluble. Studies by the dermal route are necessary for chemicals whose penetration through the skin can be foreseen. The oral route is also important since ingestion of chemicals could occur during industrial handling; in

addition valuable information can be produced on systemic toxicity and target organs.

For acute studies carried out by the inhalation route the exposure period should be at least as long as 4 hours. For repeated dose toxicity studies, the experimental design should be as close as possible to working environmental condition; generally exposure for 6h/day, 5 days/week, for several weeks is used. At the end of the treatment it is useful to maintain a proportion of treated animals for a period of several days without further treatment, for the evaluation of the reversibility of any toxic effect.

In acute studies the mortality rate at each dose (concentration) tested should be determined; in particular the lowest dose causing adverse effects, including mortality and the highest dose at which no animal dies should be noted. The clinical signs of toxicity should be observed to help in the prediction of the target system (e.g. CNS, cardiovascular) affected by the substance. The time of the onset and duration of toxic signs should be recorded. The post-mortem examination of animals that die during a test or survive to its completion should be carried out and the target organs identified.

In repeated dose studies, the experimental design should include evaluation of clinical signs, body weight gain and food and water consumption. Appropriate haematological and clinical chemistry examination should be performed, at least at the end of the treatment period.

The parameters of health to be checked should be in line with official guidelines. These may include biochemical indicators of damage to specific target organs (e.g. serum ASAT and ALAT for liver damage and serum creatinine for kidney damage). Historical data from untreated animals may be valuable in identifying a treatment-related alteration. Macroscopic and histopathological examination should be carried out on all the major organs to obtain detailed picture of both gross and microscopic lesions; historical data are also of value in interpreting these findings.

Ideally, repeated dose toxicity studies should be constructed so as to determine both LOAEL and NOAEL for each toxic effect since these provide an effective basis for setting OELs for the workplace.

The NOAEL has been defined as that dose of a chemical at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate "control" (Dourson and Stara, 1983). The LOAEL is defined as the lowest dose of a chemical in a study or group of studies which produces statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate "control" (Dourson and Stara, 1983). Clearly the NOAEL and the LOAEL are not synonymous since an "adverse effect" has been defined (US-EPA, 1980) as "functional impairment or pathological lesions which may affect the performance of the whole organism or which reduces an organism's ability to respond to an additional challenge" (Lewis *et al*, 1990). Nevertheless, figures for the NOAEL and LOAEL may be quite close.

Nature of Experimental Studies

Acute systemic toxicity

These studies are described in OECD (1993) Guidelines No 401-403. Information of greater value for risk assessment can be obtained from dose-, time-response studies (Zwart *et al*, 1992). The chemical should be tested in the form in which it is used in practice (e.g. pure, technical grade or formulation). In oral or parenteral acute toxicity tests a single dose of the chemical is administered while for dermal or inhalation toxicity tests an exposure period of up to 24 hours is usually used. Since the respiratory tract and the skin represent the main routes of exposure to industrial chemicals in the workplace, knowledge of the local and systemic acute toxic effects resulting from skin contact and inhalation is of greatest importance.

Data from oral or parenteral toxicity tests should not be neglected because comparison of toxic activity occurring with different exposure routes may provide clues about the fate of the chemical in the organism and may help to identify target organs.

Acute toxicity studies will provide an indication of the likely lethal dose or concentration and of the dose-response relationships for lethal or other toxic effects.

In practice a rough estimate of the lethal dose is adequate because of the considerable intrinsic variability of LD_{50} and LC_{50} values obtained from acute studies. Far more important is information on the signs of intoxication, the possible cause of death, the latency period between the onset of toxic signs and recovery, the slope of dose-response curves and the pathologic organ changes seen on macro - or microscopic examination.

The degree of confidence which can be placed upon the results of acute toxicity studies may be increased if they are carried out in more than one species. However, where major differences in toxic activity occur in different species the cause of these may need to be investigated, e.g. by pharmacokinetic studies.

Irritation

Information on the irritant ability of a substance and, in particular, its ability to irritate the respiratory tract, eyes and skin when present in the atmosphere is essential in setting an OEL.

The irritant potential of chemicals on the eye and skin is normally tested in albino rabbits using techniques described in OECD (1993) Guidelines Nos. 404 and 405. If a compound is clearly a corrosive agent to the skin or its potential irritancy can be foreseen by chemical-physical analogy or SAR with compounds of known activity, eye irritation should not be further studied on the concentrated substance; in some cases studies on dilute substance may be of value in demonstrating the irritant threshold and in judging the effectiveness of washing the eye to prevent adverse effect resulting from accidental eye contamination.

In vitro tests for both skin and eye irritation are being developed. For skin irritation several cellular types (keratinocytes, mast cells, machrophages etc.) or tissues have been used in studies (ECETOC, 1990). For eye irritation cells (liver fibroblasts, corneal cells etc) or organ cultures (enucleated eyes, isolated cornea, rabbit isolated rabbit ileum etc) have been evaluated (ECETOC 1988). At the present time, however, no official Guidelines nor validated methods are available. Results from such *in vitro* studies must be used with care in setting limits.

Information on pulmonary irritation can be obtained from a single exposure study by the inhalation route. The method in OECD (1993) Guideline No.403 for determining the LC_{50} value is commonly used. The modified Alarie-Test (Barrow *et al*, 1977) assists in providing an indication of the atmospheric concentrations likely to be perceived as irritant by man.

In the case of strongly irritant substances the basis for setting an initial OEL may be the highest non-irritating concentration, provided this does not exceed the no-observable effect level (NOEL) for other effects. In some cases an provisional OEL may be set from knowledge that a chemical is strongly acidic or strongly alkaline and will inevitably produce a local irritant reaction. Where repeated exposures are possible, long-term effects will need to be examined since, as in the case of HF, it must be confirmed that chronic toxic effects will not arise when exposure is maintained below the irritant threshold.

Sensitisation

Skin sensitisation should be studied where there are structural similarities to known sensitisers, where results from animal tests or case reports of skin allergy in man suggest an effect on the immune system, or where no information whatsoever exists on sensitisation potential. OECD (1993)Guideline No. 406 describes the methods of value. A particular aspect is photosensitisation which results from the combined action of solar rays and the chemical compound. There are neither official Guidelines nor internationally unified test methods but several models for assessing photosensitisation after topical application of a chemical and exposure to U.V. radiation are available. These will be helpful with those particular classes of chemical known to be associated with photosensitisation.

Other toxic effects, such as corrosiveness, may require a handling procedure which will automatically prevent intensive skin contact and consequently reduce the probability of being sensitised. In such cases, sensitisation testing may not be required.

No official Guidelines are available on respiratory sensitisation. Development of a validated experimental model is still under way and current progress has been reviewed (ECETOC, 1993b). Similarity of chemical structure to that of a compound known to be respiratory sensitiser may suggest that such a risk should be included when evaluating risks for setting an OEL.

Repeated Exposure

Where repeated or continuous exposure is likely to occur or where the pattern of exposure

is uncertain, a reliable OEL for a substance with unknown reactivity can only be set on the basis of repeated exposure studies. This is particularly so when other toxicological data or analogy to closely related products are not available. If exposure to a non-irritant substance is extremely low it may be possible to predict subacute effects by analogy to chemicals of similar structure.

Data from subacute, subchronic and chronic toxicity studies carried out according to OECD (1993) Guidelines Nos. 407-413 and 452 should indicate organ(s) and system(s) adversely effected, the NOAEL and the LOAEL, dose-response relationships, the extent and rate of reversibility of the lesions and the likelihood of accumulation of substance in tissues. The longer the period of treatment, the more useful will be the data for risk assessment; as life-time exposure studies on all chemicals could be impracticable, a subchronic study (up to 3 months but more normally of 28 day of treatment) may be adequate for setting a provisional OEL for substances to which repeated exposure is likely.

The exposure routes in experimental studies should be those which are predominant in the workplace. For setting an OEL the most appropriate exposure route is inhalation. However, when oral or dermal studies only are available, data from these should be evaluated with respect to type of effects demonstrated and with an understanding of the limitation of these studies. When no serious or irreversible effects are reported following high levels of exposure, a provisional limit may be deduced using information from similar substances or by extrapolating data from one route to another. This process can be used in only a limited number of cases where the analogy to other substances allows such prediction.

Such extrapolation will lead to uncertainties with respect to the validity of the OEL. This short-coming may be compensated for by using higher safety factors and by recognising that any OEL set provisionally will need to be reviewed as soon as possible. In specific cases, it may be of practical value to set an OEL based on limited data rather than to await results of time-consuming testing.

Increased demands for valid and reliable OELs on substances to which there may be exposure over several years, and existence of uncertainties in the existing data pool due to lack of data, low quality of data, incomplete documentation of data resulting in weak conclusions etc., may be partially met by results from inhalation toxicity studies of 4 weeks to 3 months exposure duration with appropriate design, performance, and interpretation of the study.

However, where exposure of workers may occur over periods of years, long-term testing to evaluate chronic toxic effects and carcinogenicity may become necessary. Chronic toxic effects should not normally be investigated in a lifetime exposure study since there can be high variability of morphological and functional parameters in this type of study; 6 to 12 months studies should be adequate. Chronic toxicity tests may also be necessary if there are conflicting results from shorter-term studies with respect to type of effects and their dose dependence. Where there is delayed development of toxic signs or lesions in short-term tests, where lesions may progress with longer exposure or where organ specific accumulation may occur, chronic studies may also be needed.

A repeated exposure toxicity study may show certain effects (e.g. pathological changes in one or more organs or tissues which are irreversible or only slowly reversible) which will require further study using subchronic or even prolonged toxicity tests. This will be particularly so where human levels of exposure are expected to be high compared with levels shown experimentally to produce the adverse effects. The need for further studies may also be indicated by specific findings. For example damage to reproductive organs may suggest the need for specific studies on reproductive toxicity; morphological abnormalities of the lymphoreticular system may suggest the need for further examination for immunotoxic effects; behavioral, abnormalities may trigger morphological and functional studies of the central and peripheral nervous system.

Mutagenicity testing

Examination of the mutagenicity potential is essential in setting provisional OELs. Tests are described in OECD (1993) Guidelines Nos. 471-478 (EEC 1993). To evaluate the mutagenic potential, a number of tiered testing strategies using *in vitro* and *in vivo* models have been proposed (ECETOC, 1987a). *In vitro* studies should examine the ability to cause point mutations and chromosomal aberrations. Where the findings in *in vitro* studies indicate the need, *in vivo* studies should be carried out, using the most appropriate route of administration; a final assessment of the potential to produce heritable disease should be made on the basis of *in vitro* and *in vivo* findings and of metabolic and pharmacokinetic data, where available.

The results of mutagenicity studies should also be used as a basis for prediction of possible carcinogenicity and hence to select those substances which may require long-term carcinogenicity tests in order to set an OEL.

Carcinogenicity testing

The need for a carcinogenicity study in setting an OEL requires careful evaluation. A detailed examination of the toxicity findings in acute, short and long-term tests and mutagenicity tests should first be made. This should include a study of information about type of tissue lesions, occurrence of regenerative processes or any kind of proliferative process, irritative/necrotic effects, pharmacokinetics, the possible saturation or overload of toxification/detoxification mechanisms and the relationship of these to the degree and pattern of exposure. The mutagenic activity, chemical structure and reactivity and the toxic effects of known or expected metabolites should also be considered.

This review may point strongly to the likelihood that the substance is carcinogenic, in which case any provisional OEL should take account of this. Equally the data may strongly suggest no carcinogenic activity; in such a case carcinogenicity studies would not be warranted unless there is likely to be widespread and extensive exposure to the substance. In other cases the review of biological and physico-chemical data and of exposure may suggest that tests may be needed and point to the priority for the tests to be done. Tests are described in OECD (1993) Guidelines Nos. 451 and 453. When planning studies it is important to consider whether inhalation is the most appropriate exposure route. Highly volatile

compounds and gases will require inhalation testing but for many other materials the high concentration to be administered in tests can be generated in the atmosphere only as an aerosol; in these cases it is important to consider whether aerosol exposure reflects the situation at the workplace. Studies should always mimic closely the practical situation in the workplace, although in many cases the oral route will be perfectly satisfactory since the substance can be shown to be absorbed and distributed systemically in the same way whatever the exposure route. Where the inhalation route is selected, care should be taken to ensure the maximum tolerated exposure levels is not exceeded and that, with dusts, the particle size allows penetration of particles into the alveoli without producing lung overload.

The need to include more than one animal species in carcinogenicity testing is a critical matter in only some cases where an OEL must be set but should be considered when the available information, including that from a long-term study on one species, is inconclusive or implausible or when the species already used is considered to give false negative or false positive results, or is inappropriate in some other way for the chemical class tested. Extensive and life-long exposure in a wide range of industry may also indicate a need for second species testing, particularly when the conclusion based on existing data is weak or borderline. Carcinogenicity studies may not be necessary when the initial review provides strong evidence that there is no carcinogenic risk or that such risk is extremely unlikely because of low exposure.

Testing for Reproductive Toxicity

Repeated exposure toxicity tests provide only limited information on possible effects on reproductive function. Nevertheless, certain parameters measured in such tests may indicate a low or high priority for the initiation of studies on possible effects on male and female fertility, embryo-foetotoxicity and lactation. For example, if the gonads and accessory organs and hormone dependent organs are not affected by exposure and when other information support a lack of effect, the testing of reproductive function would not be of high priority.

Tests for reproductive and developmental toxicity are described in OECD (1993) Guidelines Nos. 414-416. Prediction of impairment of foetal developmental from tests other than specific teratology tests is discussed by ECETOC (1989b), EEC (1993). Alkylating agents or agents structurally related to known teratogens may be considered for early testing where woman of child-bearing age may be exposed to the substance. It is common practice to use the oral exposure route for these tests but gases and organic solvents of high vapour pressure would require an inhalation exposure teratology study. A second species may need to be tested where initial results are ambiguous or where there is suspicion from existing data or from the chemical structure that the species used initially may produce false negative results. Reproduction and teratology studies may also be indicated by findings in the so-called SIDS-(Standard Information Data Set) proposed by the OECD or in the HEDSET (Harmonised Electronic Data Set) from the EEC; this includes a screening test system for prediction of reproductive and developmental functions. Embryo-culture systems also may be a tool for setting priorities for reproductive toxicity testing. The predictive accuracy of these tests is, however, not yet validated.

Toxicokinetics

The principles of toxicokinetic investigations are outlined in OECD (1993) Guideline No. 417. The toxicokinetic studies examine the extent and rate at which a substance is absorbed, distributed, metabolised and excreted by the body, after administration by various routes.

In many cases the acute, short and long-term studies, particularly when carried out using more than one exposure route, will have indicated the rate and extent of absorption of the substance into the body and whether the substance or its metabolites are accumulated when exposure is prolonged. These data may be adequate for setting an OEL. In relatively few cases the extent of absorption into the body may need to be studied in more detail.

Absorption studies may be needed to examine the rate and extent of penetration of a substance by the various routes (pulmonary, dermal and intestinal). Distribution studies examine the transportation of the substance and its metabolites through the body, and the degree of binding to blood and other tissues and the extent to which tissues accumulate the substance. Metabolism studies may be required to examine qualitatively and quantitatively the biotransformation of the substance in the body. The possibility of saturation of a specific metabolic pathway with higher exposure levels should be kept in mind when performing such studies. Excretion studies may be needed to examine the elimination of the chemical or its metabolites in exhaled air, urine, bile, faeces, milk and skin. The half-life in body fluids and tissues and the biological half-life may provide information valuable in setting an OEL, particularly one used in biological monitoring (ECETOC, 1992a)

Other Studies

The need for special studies may be indicated by the physico-chemical properties, by structure-activity relationship with chemicals of known toxicity or by the results of earlier studies. The potential neurotoxicity, immunotoxicity or cardiac sensitisation properties of a substance, for example, may require further investigation. Screening for neurotoxic potential has been addressed by ECETOC (1992b) and strategy for assessing immunotoxicity has also been proposed (ECETOC, 1987b).

5. CONCLUSIONS

5.1 DETERMINANTS OF EXPOSURE

While an assessment should be carried out of risks to health arising from each substance and formulation used in the workplace, an OEL will need to be set for a relatively small proportion of them since many will not become airborne and adequate control of others may be achieved by controlling those most likely to become airborne contaminants. Substances requiring an OEL are likely to be:

- gases, liquids which are highly volatile at workplace temperatures or substances or preparations which produce vapours or aerosols of inhalable size when used,
- solids which volatilise at workplace temperature or which form fumes or dusts with particles of inhalable size when in use,
- gases, aerosols, fumes etc. formed by the decomposition of substances or their reaction with components of air or other substances commonly found in the workplace.

Conclusion

The chemical and physical properties of a substance and its probable manner of use in the workplace and the way it is likely to be handled, stored, transported and disposed of should be examined initially. If inhalation exposure is likely the setting of an OEL should be considered. The following physico-chemical data are of assistance in making such a decision and for setting an OEL:

- physical state, appearance, odour;
- boiling point, melting point, sublimation point, vapour pressure, as appropriate;
- solubility in water and organic solvents;
- relative density;
- n-octanol/water partition coefficient;

5.2 INDUSTRIAL EXPERIENCE AND USE

Available human, animal and other experimental data and human experience gained during industrial use of a substance should be examined before further studies are contemplated. OELs set for substances of similar chemical structure and with similar physico-chemical properties and substances used for similar purposes should also be examined, together with information on the basis on which the OELs were set. Structure-activity relationships should also be examined.

Conclusion

Before studies are planned any industrial experience with the substance or similar substances should be examined. This information, together with an estimate of probable exposure, will assist in judging the priority for setting an OEL and identify any information to be obtained

from further studies.

5.3 DERIVATION OF PROVISIONAL OELs

OELs are set on best available data and for existing chemicals, workplace experience in handling can be valuable in setting a provisional limit. In most cases, a provisional OEL can be set for a new chemical on data obtained from base-set studies (see also section 4.1). However, in some cases, an initial assessment of these data may show that further toxicological and other studies are needed before a provisional OEL can be set.

Conclusion

For setting a provisional OEL, the following information is desirable:

- acute oral, dermal or inhalation toxicity;
- skin and eye irritancy;
- cutaneous sensitisation potential;
- skin penetration ability as indicated by structure-activity data, the octanol/water partition coefficient and other physico-chemical data and data on dermal and other acute toxicity;
- repeated exposure toxicity - where exposure may occur repeatedly or over prolonged periods or where the exposure pattern is unknown - a study should be carried out by the most relevant route over a 28-90 day period. In many cases this will be by the inhalation route;
- genotoxicity: a point mutation test *in vitro* plus a clastogenicity test are required, additional *in vitro* and *in vivo* tests may be required, depending on the findings in initial tests and on the nature of the substance.

The need for and the design of further studies should be judged on a case-by-case basis.

5.4 FURTHER TOXICOLOGY TEST REQUIREMENTS

All OELs, and in particular, provisional limits, need to be reviewed periodically and revised limits set when necessary. Toxicological data additional to that in the base set may be acquired when demanded by competent authorities of the EC when production volumes exceed certain thresholds. This and advances in medical knowledge or experience in the workplace may allow or necessitate the setting of a revised OEL.

Conclusion

To derive a revised OEL, information from studies on reproductive toxicity, long-term toxicity, carcinogenicity, mutagenicity, immunotoxicology, neurotoxicity and toxicokinetics and metabolism may be needed. Longer term toxicity studies and epidemiological studies on exposed populations are most likely to become necessary when exposures occur repeatedly or continuously over a period of years. The need for each individual study and its design should be decided on a case-by-case basis.

5.5 HEALTH SURVEILLANCE

Animal and other experimental studies can not guarantee freedom from adverse effects on health.

Conclusion

For each new material which may contaminate the workplace atmosphere, health monitoring of those exposed should be instituted along with determination of their exposure to the material. The design of such a study would need to be determined on a case-by-case basis.

5.6 OEL SETTING PROCESS

In-house OELs are generally set by groups experienced in the interpretation of animal and other experimental data and epidemiological studies, in medicine, in industrial hygiene practice and in the technology of the industry in which the substances are used. Similarly experienced groups should set national and international standards, usually in conjunction with regulatory officials and in some cases with worker representatives. Setting an OEL requires integration of scientific and medical facts and professional judgement. There is no set formula for setting a figure; analysis of the weight of evidence of the data and of its relevance to man are required.

Reliable data on NOAELs and LOAELs in animals are of value, particularly with new substances but the uncertainty (or safety) factor used in judging the safe level of exposure in man, while generally less than 10, is variable and depends on the nature and quality of data, the severity of the adverse effect the OEL is set to control (usually the most sensitive effect) and the seriousness and degree of reversibility of adverse effects which could result from over-exposure.

Conclusion

Setting of OELs should be carried out on a case-by-case basis by professionally competent groups. Unnecessary standardisation of the process should be resisted. When completed, the data on which an OEL has been based and the considerations that have led to the actual figure should be documented in detail.

APPENDIX A. STRATEGIES FOR EXPOSURE CONTROL

Introduction

Although OELs have been published for 1,000 or so chemicals, no such standards exist for a vast number of substances which have a potential to contaminate the workplace atmosphere. Since there are moral and legal requirements to protect health, other occupational health and hygiene strategies have had to be developed and implemented in the absence of OELs.

One absolute standard which applies throughout industry is a "performance" standard which requires employers to ensure that the risks to health resulting from their activities are controlled so that no adverse effects on health occur amongst their employees or any other persons who may be affected by their activities. While OELs assist employers in assessing whether they have achieved this standard, simple compliance with an OEL does not automatically mean that the performance standard has been attained. OELs are of varying quality and offer differing levels of health protection to exposed individuals. Moreover, they normally only take into account exposure through inhaling a material while, in practice, exposure by other routes (dermal or oral) may be occurring simultaneously. Efforts to improve the working environment should not therefore cease when all exposures to substances with OELs are compliant with those OELs. Priorities for further improvement will be dictated by results of an assessment of all principal routes of exposure (inhalation, skin contact, ingestion), and this will lead to the introduction of measures to control these exposures in an acceptable manner.

Strategy in the Absence of Exposure Standards

It should be recognised that an individual's exposure derives both from the tasks undertaken and the environment in which work is done. Both elements may be capable of improvement, although task governed exposures are generally the more important, particularly with substances possessing acute toxic effects. In such cases an individual's exposure should be reduced by determining where and how exposure arises during the course of a task and identifying those events which appear to produce excessive exposure.

The focus of exposure control tends to move away from task to environmental sources, e.g.in the case of fugitive emissions from process plant and equipment, or where materials produce health effects following chronic exposure or exhibit stochastic effects.

Control strategies for task and environmentally governed exposures can operate without OELs, the objective being to identify and control any significant exposures, regardless of whether the risk is perceived to be substantive or not. Continuously seeking to identify where improvements can be made to the working environment is consistent with the principles of, for example, the 'Responsible Care' programme adopted by the chemical industry in some countries.

Strategy using Generic Exposure Standards

The concept of Generic Exposure Standards (GES) has been introduced recently. It is essential to recognise that GESs are not derived using the normal techniques of risk assessment. A GES is assigned either on the basis of the principal hazardous properties of a substance (Gardner and Oldershaw, 1991) or the substance's relative position in a list of materials produced by ranking key toxicological indicators against one another (Crabtree *et al*, 1991; Henry and Schaper, 1990). Because of this, GESs tend to differ from each other in a stepwise fashion corresponding to marked changes in hazardous properties. For example, in the scheme suggested by Gardner and Oldershaw (1991) for volatile organic solvents each GES is an order of magnitude different from the next.

GESs have been criticised for not offering the same degree of health protection as OELs. For example, GESs derived from the risk and safety phrases assigned to a substance suffer from the limitation that the classification is often based on a limited range of toxic effects, most frequently acute toxic effects, and not on an appraisal of all acute and chronic toxicological properties. Whilst these are substantial criticisms, GESs should not be dismissed as having no role in the control of exposure to hazardous substances in the workplace. GESs would better be termed "guideline control values" (CIA, 1993) in that, while the quality of data underlying them is often insufficient to provide confidence that they will protect health, they can be used as the basis for the satisfactory control of particular types or groups of substance. The manner in which GESs are used must be more circumspect than for soundly health-based OELs. GESs may nevertheless provide an indication of how far improvement in exposure control has been or needs still to be made. They can also act as a baseline value against which to assess any significant deterioration of exposure control performance over periods of time.

Strategy where OELs are available

Many have examined what constitutes satisfactory compliance using OELs (WHO, 1984 BFAS, 1984; Herve-Bazin, 1989; Rappaport, 1990). The various approaches suffer from the assumption that exposure to atmospheric concentrations below the OEL will not adversely effect health; however, the OELs set by most authorities are not claimed to protect all workers and complete protection can clearly not be guaranteed for certain substances such as carcinogens or sensitisers. Some regulatory authorities have attempted to differentiate between OELs which should protect health if complied with and those for which there are doubts about the ability to protect the health of all those who are exposed.

For those OELs which may not provide complete health protection, a different control strategy is required and a more precautionary policy must be adopted to manage the risks to health which exposure may entail. The need for different strategies has been recognised in varying degrees by European Member States (UK-HSE, 1977). The control strategies required for these two types of OEL differ in one main respect. For 'health-based' OELs (OELs set on the basis of adequate knowledge of effects of over-exposure and of the levels of exposure at which these effects are no longer manifest), control of exposure to a level within the standard should protect nearly all individuals; for all other standards, no confidence can be invested

in such a strategy and exposures should therefore be reduced to as far below the standard as practicable.

Comparison of Control Strategies

There is actually little difference between the three approaches, providing the principles of quality management in the area of occupational health and safety are adhered to. A "health based" OEL provides the greatest confidence in ensuring the health of employees is adequately protected. However, even when such an OEL is complied with, there remains a small residual risk that some individuals may be adversely affected so that performance should not be judged satisfactory if further substantive reductions in workplace pollution levels can readily be made. Whilst many occupational health and hygiene strategies appear to rely on the existence of an OEL, employers should, in their absence, still be able to control the risks to health arising from their operations in a manner which is consistent with both regulatory and ethical requirements. A published OEL merely provides greater confidence that the desired endpoint, the protection of health, has been satisfactorily achieved. It does not excuse an employer from identifying where further reductions in exposure can and should be made; indeed concern about the quality of OELs, such as the recent debate on Threshold Limit Values (Castleman and Ziem, 1988; Roach and Rappaport, 1990), has led to a suggestion that such a strategy be wholly adopted and OELs discarded entirely (Tarlau, 1990). However, having no OELs would be a retrograde position; they are of assistance in pinpointing the highest priority for improvements and are useful (when supported by appropriate health surveillance) in determining and assessing the performance of exposure controls. Moreover, their mere existence encourages measurement of airborne exposures which, in turn, may provide baseline data against which it is possible to monitor control performance. Even so, provided that an occupational health strategy consistent with quality principles is embraced, risks to health can be managed as well, if not better than, by a strategy reliant upon the existence of a health-based OEL.

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