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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.