Social Europe

Methodology for the Derivation of Occupational Exposure Limits

Key Documentation (version 6)

European Commission

Preface

This document has been drafted by the "Scientific Committee on Occupational Exposure Limits" (SCOEL), which was established in 1995 by a European Commission Decision to provide the Commission with opinions relating to the toxicological examination of chemicals for the purposes of assessing their effects on workers' health.

SCOEL developed his own methodology to evaluate chemicals on a case by case basis. This approach was reflected in a document, which summarizes the outcome of the individual discussions and broad debate within the Committee, while doing this exercise. The document ("Methodology for the Derivation of Occupational Exposure Limits : Key Documentation") was presented to the representatives of the Member States, workers' organisations and employers' organisations at a **seminar held in Luxembourg on 16 June 1998.** The text was complemented by comments and discussions on that occasion, and finally published as Report EUR 19253 EN in 1999.

The 1999 report has been gradually updated to reflect the development of science in general and of the work procedures of the Committee. The latest update (version 6 of the Report "Methodology for the Derivation of Occupational Exposure Limits: Key Documentation") corresponds to December, 2009.

Members of the 1999 Committee

Dr Erich POSPISCHIL	A-2340 MÖDLING
Prof. Robert LAUWERYS	B-1200 BRUXELLES
Prof. Helmut GREIM	D-85758 OBERSCHLEISSHEIM
Prof. Hermann M. BOLT	D-44139 DORTMUND
Dr. A. SCHAICH FRIES	DK-2100 KOBENHAVN
Dr. Enrique GONZALEZ-FERNANDEZ	E-28027 MADRID
Dr. Alicia HUICI-MONTAGUD	E-08034 BARCELONA
Mr André PICOT	F-91198 GIF-SUR-YVETTE
Mr Benoît HERVE BAZIN	F-54500 VANDOEUVRE
Dr. Henrik NORDMAN	FIN-00250 HELSINKI
Dr. Emmanuel VELONAKIS	GR-10433 ATHENS
Dr Ken MACKEN	IRL-DUBLIN 4
Prof. Vito FOA	I-20122 MILANO
Prof. Pier Alberto BERTAZZI	I-20122 MILANO
Mr Marc KREMER	L-2010 LUXEMBOURG
Prof. Victor J. FERON	NL-3704 HE ZEIST
Prof. D.Salvador Massano CARDOSO	P-3000 COIMBRA
Prof. Francesco GAMBERALE	SE-171 84 SOLNA
Dr. Steven FAIRHURST	UK-MERSEYSIDE L20 3QZ
Dr. Leonard LEVY	UK-LEICESTER LE1 7DD

New Members of later mandates of the Committee (2005-2009)

Prof. Eleonora FABIANOVA	SK- Banska Bystrica
Prof. Andrea HARTWIG	D - Berlin
Prof. Alastair HAY	UK- Leeds
Dr. Aranka HUDAK	H- Budapest
Prof. Gunnar JOHANSON	SE- Stockholm
Prof. Dominique LISON	B- Brussels
Dr. Gunnar NIELSEN	DK-Kobenhavn
Dr. Iona PRATT	IRL-Dublin
Dr. Jolanta SKOWRON	PL- Warszawa
Prof. Isabelle STUCKER	F- Villejuif
Dr. Ruud WOUTERSEN	NL- AJ Zeist
Prof. Rafael MASSCHELEIN	B-Leuven

Table of content

1. INTRODUCTION AND LEGAL BACKGROUND

Council Directive 80/1107/EEC, as amended by Council Directive 88/642/EEC, on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work, introduced into EU legislation the objective of establishing occupational exposure limits (OELs) agreed by Member States. Under this Directive, two types of occupational exposure limit were brought in, Binding Limit Values and Indicative Limit Values (ILVs). It was envisaged that ILVs would be the more common type of limit and that their values "shall reflect expert evaluation based on scientific data".

In 1991 the first set of ILVs was introduced by Commission Directive 91/322/EEC. The ILVs for these 27 chemicals (or groups of chemicals) were proposed by the Commission and agreed by Member States on the basis of pre-existing national positions. However, at about the same time, the Commission assembled an advisory group of experts in the various disciplines (toxicology, epidemiology, occupational medicine, occupational hygiene, chemistry) concerned with the scientific and technical issues surrounding the derivation of occupational exposure limits. This group began its work as the Scientific Experts Group (SEG) in 1990. More recently the status and work of the group has been formalised by its maturation into the Scientific Committee on Occupational Exposure Limits (SCOEL), via Commission Decision 95/320/EC.

From the outset, the SEG (now the SCOEL) has had as its major remit the role of examining appropriate scientific documentation, usually in the form of Criteria Documents, on the toxicological and other relevant properties of chemicals and to recommend to the Commission values for substance-specific occupational exposure limits. SEG/SCOEL is asked to attempt to identify the highest level of exposure (with corresponding reference time period) at which, in its judgement, one could have confidence that there would be no adverse effects on health. SEG/SCOEL recommendations of this type have then been proposed to Member States by the Commission as prospective ILVs. Where a "no-effect" level of exposure cannot be reliably identified, SEG/SCOEL is asked to attempt to estimate the risk of adverse health effects at specified levels of exposure; the Commission takes account of such views in developing proposals for Binding Limit Values. In addition to recommendations related to airborne occupational exposure limits, SEG/SCOEL is also asked to express opinions on associated occupational risk management measures such as "skin" notation and biological limit values.

Since the beginning of the 1990s, SEG/SCOEL has been scrutinising Criteria Documents and advising the Commission on occupational risk assessment and risk management issues emerging from the documents. The Criteria Documents have been either those made available from national limit-setting systems in individual or groups of Member States (DECOS, MAK Commission, Nordic Expert Group, UK WATCH Committee) or documents specifically produced by European institutes under contract to the Commission.

Much of the work of SEG/SCOEL has entailed making recommendations to the Commission for "health-based" occupational exposure limits (see next chapter). These recommendations and the summarised basis for their derivation have been issued by the Commission as ILV proposals in SEG/SUM documents, which have been used as the basis for wider consultation with government officials, industry and workers representatives. By this procedure a second list of ILVs has been generated, consulted on and agreed by Member States in Commission Directive 96/94/EC and third and fourth lists are currently under consideration.

In 1998, the Council Directive 98/24/EC on the protection of the health and safety of workers from the risks relating to chemicals agents at work (the "Chemical Agents Directive") has been adopted by Member States. This Directive sets ILVs, Binding Limit

Values and biological limit values into a wider framework of risk management in relation to occupational exposure to chemicals.

Alongside its deliberations on specific chemicals, SEG/SCOEL has developed a series of Key Documents. These Key Documents attempt to set out the general principles and approaches taken by SEG/SCOEL in dealing with the general issues arising in relation to the committee's work. This publication represents a collection of most of the Key Documents produced by SEG/SCOEL. It is hoped that its publication and availability for scrutiny by outside bodies will enhance the understanding and appreciation of the manner in which SEG/SCOEL approaches its work.

2. AIMS AND OBJECTIVES OF OELS

Occupational Exposure Limits (OELs) have been a feature of the industrialised world for the last fifty years or so. They were first introduced at a time when the benefits of preventing occupational ill health (as opposed to compensating its victims) were beginning to be appreciated, and analytical methodology had advanced to a state in which it was possible to measure the level of contaminating substances in the workplace air. OELs began to be established in order to provide criteria on the basis of which decisions could be made as to whether the airborne concentrations of given substances were sufficiently low to prevent adverse effects on health.

For the purposes of this document, it is considered that the objective in establishing OELs is to set limits for exposure via the airborne route such that exposure, even when repeated on a regular basis throughout a working life, will not lead to adverse effects on the health of exposed persons and/or their progeny at any time (as far as can be predicted from the contemporary state of knowledge).
This Methodology-Document is concerned with the process of setting **'health based'** OELs, which is the main specific task of SCOEL. However, OELs may be broadly defined into one of two categories, depending on the scientific basis on which they are established:

- **'health based' OELs -** An OEL of this type may be established in those cases where a review of the total available scientific data base leads to the conclusion that it is possible to identify a clear threshold dose below which exposure to the substance in question is not expected to lead to adverse effects. Such OELs should meet the objective outlined above.

- **'risk-based' OELs** - For some adverse effects (in particular genotoxicity, carcinogenicity and respiratory sensitisation) it may not be possible on present knowledge to define a threshold of activity. In such cases it must be assumed that any level of exposure, however small, might carry some finite risk and OELs for substances possessing these properties must be established following a risk-based approach. The Commission sets, in such cases, OELs at levels considered to carry a sufficiently low level of risk. A series of exposure levels associated with estimated risks might need to be calculated by SCOEL. But it is not the remit of SCOEL to determine the acceptability of such risks. This is the responsibility of the Commission, and requires further consultation with pertinent groups (organisations/bodies).

  When data are insufficient to offer a quantitative risk assessment and there is a technical demand for SCOEL to give guidance, SCOEL will consider this possibility and explain clearly what the basis for this recommendation is (e.g. flour dust). In this case, no value will appear on the front page of the recommendation, which is reserved for health-based values, but a clear explanation of the proposal will be given in the document.

OELs may be used for a number of purposes. The principal intended use, as described above, is to provide standards or criteria against which measured exposure levels in existing workplaces may be compared in order to ensure that, as far as the current state of knowledge permits, control is adequate to protect health. They may also be used for design purposes, to ensure that new plants and processes are engineered in such a way that exposures can be controlled at levels which will not damage health. They should not be used as a basis for assessing the acceptability of non-occupational exposure or for simplistically comparing the 'toxicity' of one substance with that of another.

Correct and appropriate use of OELs in practice demands considerable knowledge and experience, particularly in cases where there is exposure to more than one substance (contemporaneously or sequentially), where routes of exposure other than inhalation may be significant or where the working patterns (e.g. shift system/exposure duration) are non-standard.

3. GENERAL PRINCIPLES

3.1 Definitions

The objective of Council Directive 80/1107/EC is "The protection of workers against **risks** to their **health** and safety from exposure to chemical, physical and biological agents considered **harmful**". Within the context of OEL setting, it is possible relate this objective to the description of a 'health based' OEL given in Chapter 2, and restate it as "The protection of workers against **adverse effects on health** arising from exposure to chemical agents".

The effects of increasing exposure to chemical substances may be viewed as a continuum:

(1) no effects observed

(2) compensatory effects or early effects of dubious significance without adverse health consequences

(3) early health impairment (clear adverse effects)

(4) overt disease, possibly death.

Effects may be considered to become 'adverse' during the transition from (2) to (3) above.

It is the intention of the SCOEL to identify firstly what effects can be produced by exposure to the substance in question and secondly, to decide (and explain in the documentation underpinning recommendations for OELs) which effects should be considered 'adverse'. This requires a full review of the available toxicity database, which will include any effects which may occur in the offspring of workers.

The broad definition of adverse effects on health given above is considered by the SCOEL to include the concept of '**nuisance**'. Development of criteria for 'nuisance' is often considered difficult because of the essentially subjective nature of perceived nuisance and the wide variation in individual perceptions. Many chemical substances do, however, have a local irritant effect on the eyes or the respiratory tract producing symptoms ranging from the trivial to the serious.

As with systemic health effects, responses to irritants may be viewed as a continuum:

(1) no effects observed; no awareness of exposure

(2) very slight effects; awareness of exposure

(3) slight irritant effects or nuisance (e.g. smell); easily tolerable

(4) significant irritation/nuisance, overt health effects; barely tolerable

(5) serious health effects (e.g. pulmonary oedema); intolerable

The SCOEL considers that symptoms such as ocular and/or nasopharyngeal discomfort, decreased performance and headache should be regarded as 'adverse' effects on health and well-being. Effects may be considered to satisfy the criteria for 'nuisance' at

somewhere between (2) and (3) on the above continuum. For the purposes of establishing OELs, no distinction should be made between irritation or 'nuisance' and the somatic adverse health effects described previously, although the SCOEL will attempt to distinguish between 'nuisance' and a mere perception or awareness of exposure (e.g. smell).

3.2 General procedure for setting OELs

The SCOEL will adopt a 'case by case' approach to the setting of OELs, considering each substance individually. Wherever possible the SCOEL will attempt to establish a 'health based' OEL, using the following general procedure:

(1) assemble all relevant data on the hazards of the substance. This will include human, animal and other experimental information, as well as background data (e.g. physical properties) relevant to the establishment of an OEL.

(2) determine whether the database is adequate for the setting of an OEL

(3) identify the adverse effects that may arise from exposure to the substance.

(4) establish which adverse effect(s) is(are) considered to be crucial in deriving the level of the OEL

(5) identify the relevant studies (in humans or animals) which characterise these key effects. Carefully review the quality of these studies.

(6) establish whether the substance acts via a non-threshold mechanism or whether a conventional (threshold) toxicological model can be used. Where non-threshold mechanisms are involved, the SCOEL considers that 'health based' OELs cannot be established and different considerations will apply (see Chapters 3, 8 and 9).

(7) assess the dose/response data for each key effect. Establish 'no observed adverse effect levels' (NO(A)ELs) wherever possible, otherwise establish 'lowest observed adverse effect levels' (LO(A)ELs) or benchmark doses.

(8) decide whether a short term exposure limit (STEL) is required in addition to an 8 h time weighted average (TWA) limit (see Chapters 4 and 5).

(9) decide whether a biological limit value might be established and, if so, what kind of limit value it will be (see Chapter 11).

(10) establish a numerical value for an 8 h TWA OEL at or below the NO(A)EL (or, if this is not possible, below the LO(A)EL), incorporating an appropriate Uncertainty Factor (UF) (see Chapter 6).

(11) establish a numerical value for a STEL (if required).

(12) establish a numerical value for a BLV (if required).

(13) document the entire process such that the rationale for the OEL is clear.

(14) assess the technical measurement feasibility of the air and biological values recommended.

3.3 Information relevant to the establishment of OELs

As indicated above, the first stage in the OEL setting process is to assemble all the information available on the hazards of the substance and decide whether this provides an adequate data base on which to proceed. Although in general the greater the amount of reliable information, the greater the confidence that can be placed in an OEL, this is not always the case; where several different studies give conflicting results the situation may be confused rather than clarified.

The key components of a relevant data set are likely to be:

(1) information on threshold effects
(2) information on non-threshold effects
(3) information on short term (acute) effects (effects of a single exposure)
(4) information on long term effects and the effects of repeated exposure by an appropriate route (including dose-response relationships)
(5) information on target organ(s) and the nature of the effect(s)
(6) information on the methodology of measurement of airborne levels

This information is needed to decide whether a conventional (threshold) toxicological model can be employed and whether or not reliable NOAEL(s) can be established. In addition, information on the kinetics of absorption, distribution, metabolism and elimination (with special attention to accumulation) is desirable but may not always be available.

Information may derive from observations in humans, experiments in animals or laboratory investigations.

3.3.1 Human data

In general, good quality human data are to be preferred to animal data, but may frequently either not be available or be inadequate scientifically. Human data falls into one of four broad categories, as follows;

(1) individual case reports

(2) studies in human volunteers

(3) cross-sectional studies

(4) cohort and case-control studies.

With the exception of (2) above, human studies generally suffer from poor characterisation of exposure and clear dose-response relationships are rarely demonstrated. The amount of weight given to human studies in establishing an OEL will depend on the nature of the adverse effect involved and the quality of the studies (in particular in relation to dose-response information).

Case reports can be useful in indicating relationships between exposure to given substances and specific adverse effects. Such reports will not provide a basis for establishing OELs, but the more reports there are indicating the same relationship, the greater is the need for further investigation.

Well conducted volunteer studies may be particularly useful where the key adverse effect has been identified as one associated with short term (acute) exposure (e.g. central nervous system depression or upper respiratory tract irritation).

Cross-sectional studies may also be useful in establishing exposure-effect relationships and may indicate the need for further investigations. In some cases, where the studies have been well conducted and reported (and in particular where exposure is well characterised) they may be useful in identifying NOAELs.

Case-control, historical cohort or longitudinal prospective studies may be of particular value where the adverse effect in question is associated with repeated or long term exposure. Such studies represent the only satisfactory way to study long term effects in humans and well conducted studies may provide powerful evidence, particularly where adverse effects are clearly defined, exposure is well characterised and potential bias and confounding factors are well controlled.

3.3.2 Animal data and laboratory studies

In many cases human data will either not be available or will be inadequate. In such instances it will be necessary to consider establishing an OEL on the basis of data derived from experiments in animals.

Animal studies clearly suffer from the disadvantage that the species under investigation is not the human. In addition, practical considerations limit the number of animals involved, leading to group sizes very much smaller than those involved in many human cohort studies. Nevertheless, animal studies possess some clear advantages, particularly in respect of good characterisation of exposure, adequate use of controls, extensive pathological investigations and the potential to give clear indications of dose/response. The SCOEL considers that well conducted animal studies provide an acceptable basis for the establishment of 'health based' OELs, where human data are either not available or are inadequate.

In order to establish a 'health based' OEL it is necessary to have sufficient information on both acute and chronic effects. Information available from animal studies falls into several categories, which can be related to different aspects of the OEL setting process.

(1) Single exposure data

Acute inhalation studies may be useful in cases where the principal concern is for short term effects. Studies which permit dose/response relationships to be characterised and NOAELs to be determined may be particularly useful where a STEL is required. LD_{50} or LC_{50} studies as such are unlikely to be of value.

(2) Repeated exposure data

Evidence from repeated exposure studies is required to provide information on possible adverse effects arising from long term exposure. Adequate study duration will depend on the nature of the effects; in some cases a 28 day study may be sufficient, but in most cases 3 to 6 months, or even longer, may be required. Studies using the inhalation route of exposure are clearly to be preferred (but see (3) below).

(3) Routes of exposure

Studies conducted by the inhalation route are clearly to be preferred, but in many cases the only repeated exposure information available will have been generated by the oral route. If an OEL is to be satisfactorily based on such data it is essential that the critical adverse effect should be systemic (and not local) and also that well-founded toxicokinetic data are available. In addition here must be reassurance that local effects on the respiratory tract (which will not be revealed by the oral route) are unlikely to occur. For the dermal route, see chapter 10.

(4) Toxicokinetic data

Information on the kinetics of absorption, distribution, metabolism and elimination may be useful in a number of respects. In particular data on dermal absorption will be useful in determining the need for a 'skin' notation (see Chapter 10) and kinetic data are essential if an OEL is to be established on the basis of repeated exposure data by the oral route (see (3) above).

(5) Other information

In some situations specially targeted investigative work may be useful in establishing OELs. For example, metabolic studies (including human *in vitro* work) may be of particular value in determining whether a specific effect seen in one species but not in another is relevant for humans.

The use of 'structure-activity relationships' is not generally regarded as a reliable method of predicting toxicological properties, except where there is a dominant common denominator of toxicological significance.

All animal studies will need to be assessed for adequacy both in respect of the conduct of the study and the reporting of the outcome. The degree to which they conform with internationally agreed guidelines should be assessed. The greater the degree of such conformance, the more confidence can be placed in the study. Studies not regarded as reaching minimum standards will be ignored.

3.4 Documentation

The SCOEL will normally work from criteria documents supplied by Member States, contractors or other expert groups. These documents will conform with the guidelines for criteria documents published by the EC (EUR 13776 EN). Any relevant additional data, which may be supplied by interested parties or otherwise obtained by the Commission, will also be taken into account in the evaluation.

The process of establishing a 'health based' OEL for any given substance will be documented by the SCOEL to the extent necessary to make the rationale underlying the process clearly understandable to health professionals. This should specifically include clear identification of the target organ(s) and critical effect(s), any NO(A)EL(s) established, the reference period chosen and the reasons for the numerical value of the OEL in relation to the NO(A)EL(s) (including a note on the choice of Uncertainty Factor).

3.5 Mixtures

In practice, exposure is frequently to mixtures, rather than to one substance in isolation. It is not practicable to make an evaluation of the effects of all possible combinations of exposure. However, when this is of particular significance at the workplace, it will be noted in the documentation summarising the recommendation.

3.6 Occupational exposure assessment

The sound use of an OIL to properly interpret the results of an occupational exposure assessment depends on the sampling strategy and technique as well as the analytical methodology and its quality control program.

The sampling strategy is a crucial aspect in assessing workers' exposure and is part of the core competencies of occupational hygiene.

The sampling technique is usually associated with the analytical methodology and its performance criteria are part of the overall general requirements for the performance of procedures for the measurement of chemical agents at the workplace as defined by the CEN *(Comité Européen de Normalisation, 2005, EN 482*).

Each aspect of exposure assessment should be conducted within an effective quality assurance (QA) programme. The analytical methodology used by the laboratory must

have accuracy, sensitivity and specificity needed to produce results consistent with the OEL. Appropriate quality control samples should be included in the analysis, and the laboratory must follow routine quality control rules. The laboratory should participate in the external quality control programme.

It is accepted that no measurement difficulties are foreseen when the limit of quantification of the method fit the requirement set by the EN 482 to be above a tenth of the OEL proposed.

4. 8 HOUR TIME WEIGHTED AVERAGE (TWA) EXPOSURE LIMITS

4.1 Introduction

For practical reasons, it is normal to establish OELs in relation to a reference period of 8 hours (a typical working day). They are also normally set on the basis of a nominal 40 hour working week and for a working lifetime. They will be expressed in units of ppm (volume/volume) or mg/m^3. Application of these OELs to working days of different length or to non-standard working patterns may not be straightforward and should not be undertaken except on expert advice.

This document does not deal with measurement strategies for the application of OELs in the workplace. However, when proposing OELs, the SCOEL will indicate whether measurement difficulties are likely at the levels recommended (see Chapter 12).

4.2 Criteria for SCOEL recommendations on OELs

The objective of the SCOEL is to make recommendations, based solely on current scientific evidence, leading to the establishment of OELs for exposure via the airborne route, such that exposure repeated for 8 hours per day, 5 days per week over a working lifetime will not result in adverse effects on the health of workers. In addition, it is the intention of the SCOEL to protect the progeny of workers, although for many substances there is a shortage of data in relation to this endpoint (see Chapter 7).

Additional recommendations may be necessary if significant exposure by routes other than inhalation is likely (see Chapter 10).

Adverse effects arising in the short term, long term, or beyond the end of the working life are to be taken into account when setting limits.

4.3 Individual susceptibility, special risk groups and sensitisation

The SCOEL will take into account available information on groups of people at special risk and this will be reflected in the advice it gives to the Commission. However, the variability of response between individuals at the same level of exposure, and the existence of special risk groups, may mean that the recommended OEL may not provide adequate protection for every individual. Depending on the specific chemical database, SCOEL might not recommend a health-based OEL for certain chemicals (Chapter 2, page 3).
Groups at higher risk in relation to a specific compound will be identified in the corresponding recommendation and available information provided, but the OELs are established for healthy workers.

4.4 Derivation of 8 hour TWA OELs

The process of deriving a recommendation for an 8 hour TWA OEL will follow the principles outlined in Chapter 3 (Section 3.2). This will include a review of the total available data-set on each substance in order, particularly, to determine:

(1) the critical effect (or effects) that will determine the level at which the OEL will be set. This means the effect(s) most likely to occur if exposure exceeds an OEL

(2) from the key study (or studies) describing the critical effect(s), the No Observed (Adverse) Effect Level (NO(A)EL). In those cases where it is not possible to establish

a NO(A)EL, a Lowest Observed (Adverse) Effect Level (LO(A)EL) may be determined.

Having established a NO(A)EL or LO(A)EL, the SCOEL will develop a recommended numerical value for an OEL. The OEL will almost always be set at a level lower than the NO(A)EL or the LO(A)EL, and its relationship to these figures will determined by the SCOEL (on the basis of their expert judgement) on a case-by case basis. In developing their recommendations, the SCOEL may take into account the following factors:

- the quality of the key studies
- whether these studies involve observations in animals or in humans (human data are to be preferred if the quality of the studies is appropriate and they complement each other)
- the nature and severity of the critical effects (including the potential for reversibility on cessation of exposure)
- whether the critical effects are well characterised and understood (in terms of extrapolation from animals to man or impact in humans) or whether they are unusual or can not be extrapolated
- the extent to which there is qualitative and quantitative agreement between different animal studies
- whether it has been possible to establish a NO(A)EL or whether the OEL is to be developed from a LO(A)EL
- the slope of the dose-response curve (the extent to which the incidence or severity of the effects increases with increasing exposure)
- any known differences in the susceptibility of different species to particular effects
- whether the effects are local or systemic
- whether the effects are caused by parent molecules or by metabolites
- available data on the mechanisms and kinetics of absorption, distribution, metabolism and excretion (e.g. half-lives and the potential for accumulation of the substance or its metabolites)
- whether particular groups of people are likely to be at special risk
- precedents established by the SCOEL in making recommendations on similar data bases.

The SCOEL intends, on the above basis, to make recommendations for OELs which conform with its established criteria (see 4.2). The ratio between a recommended value for an OEL and the NO(A)EL or LO(A)EL from which it is derived is known as the Uncertainty Factor (UF). The approach to UFs is described in Chapter 6.

The rationale behind the recommendation for each individual OEL will be set out in a summary document (SCOEL/SUM) in sufficient detail for the logic to be understood by other professionals in the field. This documentation will take particular note of the choice of Uncertainty Factor.

As a general rule, SCOEL recommendations for 8 hour TWA OELs will use, as preferred values, decimals of the integers 1, 2 or 5 ppm or mg/m^3, if scientific reasons do not suggest a more specific value.

However, it is the opinion of SCOEL that further discrimination, resulting in proposals falling in-between any two of these integers, suggests a precision that, in reality, is unjustifiable, given the limitations of the databases for the vast majority of the substances considered and the uncertainties involved in toxicological extrapolations.

5. SHORT TERM EXPOSURE LIMITS (STELs)

5.1 Need for STELs

An 8 hour TWA OEL is the usual limit recommended by the SCOEL for the purposes of preventing adverse health effects arising from exposure to a specific substance. There will, however, be substances for which an 8 hour TWA OEL alone provides insufficient protection. In such cases the SCOEL may decide also to recommend the establishment of a STEL, usually involving a 15 minute reference period.

STELs are needed where adverse health effects (immediate or delayed) are not adequately controlled by compliance with an 8 hour TWA. This is likely to arise for substances for which a critical effect is observed following a brief exposure (e.g. nuisance, irritation, CNS depression, cardiac sensitisation) and where the 8 hour TWA OEL is established at a level not very much lower than exposures at which there might be a risk of short-term effects occurring. Such a situation will be apparent from an initial review of the data base (see Chapter 3, para 3.2).

Even when there is compliance with an 8 hour TWA, there will be variability in exposure around the mean value when measurements are made over shorter periods. The SCOEL will derive STELs in situations where these variations are likely to produce exposures at levels sufficiently high to trigger adverse effects.

5.2 The aims and definition of a STEL

The aim of a STEL is to prevent adverse health effects and other unwanted effects (e.g. irritation, impaired alertness, impaired ability for self rescue, nuisance) due to peaks in exposure that will not be controlled by the application of an 8 hour TWA limit.

The STEL is a limit value above which exposure should not occur and usually relates to a 15 minute reference period. It should be noted that the STEL is not a 'ceiling' value ('ceiling' values are short term limits without a specific time reference period, implying that the limit should not be exceeded at any time during the work period or shift; see para 5.4, point 3).

STELs are intended for use in normal work situations and must not be used as a basis for determining measures to protect against emergency situations.

STELs will need to be supplemented by other precautions for substances that may be lethal at very high concentrations and for substances whose toxic or irritant effects are pronounced on exposure to high concentrations for very short periods.

5.3 Alternative approaches to the derivation of STELs

The scientifically most rigorous approach to deriving STELs requires a review of the complete data-set on each substance, in order to produce a regime for control of short term exposures (level, frequency, duration) which is tailored to the characteristics of the specific adverse effects produced by the substance in question. However, data-sets will in general be far from complete, leading to difficulties in making rigorous and well-founded evaluations. In addition, introducing undue complexity into control regimes may present practical problems in actual use that cannot realistically be overcome.

At the other extreme, a simple multiplier applied to the 8 hour TWA value has been used by some standard setting authorities. This arrangement is administratively simple but does

not take account of scientific data concerning variability in patterns of health effects between different substances. It cannot be justified scientifically and is primarily a practical way of ensuring good process control. In addition it is not relevant where the intention is to set a STEL before considering the need for an 8 hour TWA.

The SCOEL proposes to adopt a compromise between these two extremes, which permits STELs to be set in the light of the available relevant scientific data, and in a way that produces a control regime (level, duration and frequency) that is useful, in a practical sense, in the workplace. This approach is based on a case-by-case review of available data.

5.4 The SCOEL approach to STEL setting

The SCOEL will adopt the following approach:

(1) During the review of the overall data-set (see Chapter 3, para 3.2), the SCOEL will consider whether there are health effects that may arise from short term exposures that would not be adequately controlled by an 8 hour TWA limit, taking into account inherent variations in exposure even when there is compliance with the 8 hour limit.

Particular account will be taken of health effects which are not of the same type as those which would determine the level of an 8 hour TWA limit.

(2) The above consideration will include:
- systemic effects, including specific organ effects, CNS effects (e.g. narcosis, alertness) and cardiac arrhythmia
- corrosivity, irritancy, odour
- special risk groups
- effects of frequency/duration of exposure, including cumulative effects of repeated exposure peaks.

(3) When this review shows that there is a need for a specific STEL, and sufficient data exist on which to make a scientifically based recommendation, a numerical limit will be proposed, taking into account the availability of techniques for measurement and the practicability of implementation. When additionally the evidence shows that it is necessary to place restrictions on the duration and/or frequency of peaks (even assuming overall compliance with an 8 hour TWA limit), this will be recommended. For substances which would necessitate a STEL over a very short exposure duration (i.e. less than 15 minutes) the concept of a "ceiling value" might be used, provided appropriate instantaneous measurement techniques are available, such as direct reading instruments. These concentrations shall not be exceeded during any part of the working exposure.

(4) SCOEL may qualify the proposed limit with a statement, or notation, to indicate that it is based on limited data, if this is the case.

6. UNCERTAINTY FACTORS AND THEIR APPLICATION

6.1 Introduction

An 'Uncertainty Factor' (UF) is a factor used in the process of extrapolating from a necessarily restricted human and animal data base to wider human populations, in order to allow for uncertainties in the extrapolation process. The terms 'safety factor', 'assessment factor', 'extrapolation factor' and 'protection factor' have also been used in similar (and sometimes more specific) contexts. The rationale behind the use of the different terms is not always apparent. The SCOEL has decided to use the term 'Uncertainty Factor' because, in their opinion, it best describes the situation.

6.2 Historical approaches

'Safety factors' were initially developed in the early 1950s for the derivation of Acceptable Daily Intakes (ADIs) for food additives or contaminants. These ADIs were derived from NOAELs established in experimental animal studies and were intended to provide lifetime protection for an exposed general public. Since then several modifications and applications of these factors have been published and recent publications giving overviews of existing models are available- (WHO, 1994; ECETOC, 1995; Stevenson et al, 1995).

When developing limit values (e.g. ADIs for food additives and contaminants, water/air quality standards) for lifetime exposure of the general public it is internationally accepted that safety factors of 10, 100 or 1000 should be used, depending on the available experimental and epidemiological evidence. 100 is usually used as a default value. However, the application of a safety factor in a particular case is not automatic or easy to codify. It is subject to complex evaluation, sometimes involving expert consensus, on issues such as whether the toxicological data base is adequate, or whether a given effect should be considered as adverse.

6.3 The occupational situation

There is no generally agreed approach to the application of UFs in the process of establishing scientifically based OELs. However, the following factors are relevant:

- the working population may be more homogeneous than the general population. In particular very young, sick and old people do not form part of an occupationally exposed population.

- the working population is commonly exposed to airborne chemical substances for approximately 8 hours per day, 5 days per week, 240 days per year for a working lifetime (up to 45 years). This contrasts with daily uptake for a full lifetime, for which ADIs and similar limits are developed.

- in most EU countries the health of workers is expected to be controlled by periodic health surveillance and monitoring programmes.

For the above reasons it is often appropriate to apply lower UFs for the development of scientifically based OELs than those which are used to develop limit values for the general population exposed to environmental and consumer chemicals.

6.4 Definition of 'Uncertainty Factor'

The UF reflects the overall uncertainty of the data base from which a health based OEL is derived. It comprises all adjustment aspects which are related to health (e.g. route to route, inter- and intra-species extrapolation). The UF is a number by which a defined NO(A)EL)or LO(A)EL is divided to derive an approximate OEL.

6.5 The SCOEL approach to 'Uncertainty Factors'

The SCOEL has agreed the following general framework to be used when deciding on the value of a UF. Furthermore, it considers (for the reasons cited in 6.3 above) that adequate protection will be provided in the occupational situation by the use of UFs lower than those which would be required for the general population. This procedure will only be used where the adverse effects of concern can be shown to follow a conventional (threshold) toxicological model (e.g. it will not be used for genotoxic carcinogens of categories A and B; see chapter 8).

UFs must be established on a case-by-case basis and cannot be forecast or established in advance. Although specific factors could be grouped into similar circumstances, (e.g. poor human data, differences in the human-animal metabolism, etc), the interrelationship of many other characteristics inherent to every dataset makes a rigidly standardized approach less appropriate than, when data allow, a more in depth specific evaluation. Therefore, SCOEL will consider each substance individually, within the context of the agreed general framework.

The SCOEL will evaluate the available data base and identify the key study from which an OEL is to be derived (see paras 3.2 and 4.4). Ideally, this would be a well conducted human study by the inhalation route resulting in a well defined NOAEL for the critical effect, supported by other data. In practice, however, the data base will be less than ideal and the SCOEL has decided to take this into account by the application of an UF to reflect the deficiency. The overall data base must, however, provide enough information to derive a health based OEL.

In practice, four general categories of databases can be identified:

- the critical effect(s) has(have) been observed in several different studies involving several different species (including man). The studies follow well described and accepted methodologies and a NOAEL can be defined with considerable confidence. All toxicological endpoints are well characterised.

- there is less confidence in the data base. A NOAEL can be identified but is not supported by further data. The studies may not follow strict methodology.

- the data base falls short of accepted standards in some relevant aspects. Several toxicological endpoints not have been investigated or have given equivocal results. Nevertheless, a tentative NOAEL can be identified.

- the data base falls short of accepted standards in some relevant aspects. Several toxicological endpoints have not been investigated or have given equivocal results. A NOAEL cannot be identified and the data base allows the derivation of an OEL only on the basis of a LOAEL.

In general, the category into which the data base falls will determine the magnitude of the UF; the less confidence there is in a data base, the higher will be the UF.

Within this broad framework, the decision on the value of the UF in a specific case will be influenced by consideration of the scientific aspects of the key studies which provide the basis for the OEL, as detailed in Chapter 4, para 4.4).

The SCOEL will justify their decision on the choice of UF in their recommendation for an OEL, and will do this more explicitly when the decision on the UF is not covered by this framework.

7. REPRODUCTIVE TOXICITY

7.1 Introduction

As has been stated in Chapter 2, the objective of OEL setting is to prevent adverse health effects in occupationally exposed persons and/or their progeny. Thus the potential of each substance to produce adverse effects on various aspects of the reproductive process needs to be considered, even though the availability of relevant data in this field of toxicity is limited for quite a number of substances.

7.2 Technical background

Reproductive toxicity includes the impairment of male and female reproductive function or capacity and the induction of non-heritable adverse effects in the progeny (Karnovsky, 1965). The potential of each chemical substance to cause the following adverse effects should be considered:

(1) Effects on male and female fertility

Such effects are of concern to all men and women of a fertile age exposed to chemical substances in the workplace. They include adverse effects on libido, sexual behaviour, spermatogenesis or oogenesis, any interference with hormonal activity or physiological parameters impacting the ability to fertilise, as well as adverse effects on fertilisation itself or the development of the fertilised ovum up to and including implantation.

(2) Developmental toxicity

In its widest sense this covers any effect interfering with normal development both before and after birth. It includes embryotoxic/foetotoxic effects (such as reduced body weight, growth and developmental retardation, organ toxicity, death, abortion), structural defects (teratogenic effects), functional defects, peri-postnatal defects and impaired postnatal mental or physical development up to and including normal pubertal development.

In contrast to mutagens and many genotoxic carcinogens, the current state of scientific knowledge considers substances interfering with fertility or with pre-/postnatal development as likely to act by threshold mechanisms, thus permitting the determination of NOAELs.

However, it should be noted that some substances show adverse effects on reproduction at exposure levels considerably lower than those causing other forms of toxicity. Because of the relative sensitivity of the rapidly developing individual (from conception to puberty) to specific toxic effects, OELs established to protect adults cannot *a priori* guarantee the absence of pre- or post-natal adverse effects. Thus pregnant or lactating women may represent a special risk group in the workplace.

Unfortunately, only a few chemicals have been sufficiently well investigated to allow proper evaluation of their reproductive toxicity potential and the dose-response relationships of any adverse effects. It is against this background that the SCOEL has developed the approach described in this document.

7.3 Data base relating to adverse effects on fertility and development

Data on reproductive toxicity may derive from human experience or from animal tests. Definition and critical evaluation of the different types of adverse effect occurring during the various stages of the reproductive cycle are reviewed by Sullivan et al (1993).

7.3.1 Human experience

Although reproductive effects arising from chemical exposure have, for a few substances, been identified in humans, the relatively high spontaneous background of such effects makes it difficult to attribute a specific adverse effect to exposure at the workplace or in the environment (Sullivan et al, 1993; Kline et al, 1989).

7.3.2 Animal data

Study protocols are available for animal investigations into adverse effects on both fertility and development. Data may be available from such studies to indicate whether or not a given substance causes adverse reproductive effects.

7.4 The SCOEL approach

It is of concern to the SCOEL that for many substances only limited data are available on this particular aspect of toxicology. However, in the light of the above described technical and legal background, ("Framework" Council Directive 89/391/EEC and Council Directive 92/85/EC on pregnant workers) the SCOEL, when recommending OELs, will consider reproductive effects along with all other aspects of toxicity. The absence of relevant data will not normally be a factor in determining the size of an 'Uncertainty Factor', although it will be noted in the 'Summary and Recommendation' document.

For substances where available data do raise concern about reproductive toxicity, the SCOEL will take the following approach:

(1) Substances which have been shown to affect fertility

The SCOEL will take the observed adverse effects on fertility into account, recommending an OEL that is considered sufficiently low to protect workers against such adverse effects.

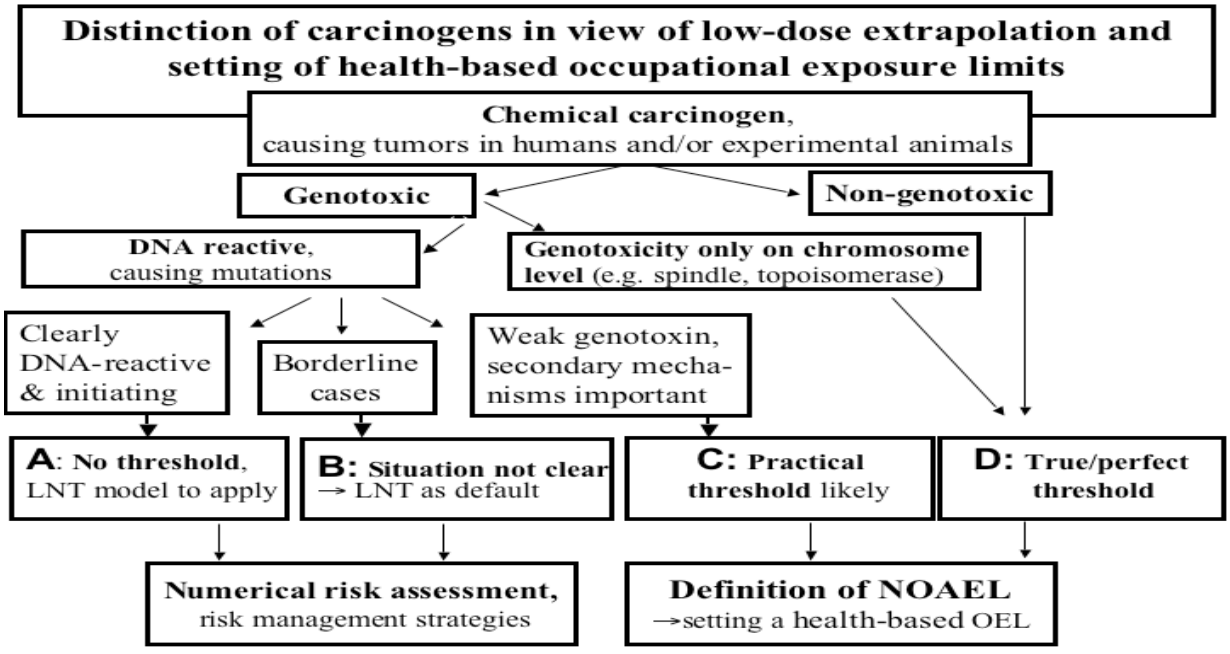
(2) Substances which have been shown to cause developmental toxicity

Where the available data allow the definition of a NOAEL for developmental toxicity (either on the basis of human or animal experience), the SCOEL will take this into account, recommending an OEL that is considered sufficiently low to protect workers against such adverse effects.

Where data indicate a developmental toxicity hazard but do not allow the definition of a NOAEL with some confidence, the SCOEL may decide to adopt a larger Uncertainty Factor in recommending an OEL.

8. THE EVALUATION OF CHEMICAL CARCINOGENS AND MUTAGENS

There is growing recognition that carcinogenic risk extrapolation to low doses (and standard setting) must consider the mode of action of a given chemical. So far, there is agreement to distinguish between genotoxic and non-genotoxic chemicals, yet further differentiations seem appropriate. For genotoxic carcinogens, case studies of chemicals point to a whole array of possibilities. For a number of apparently genotoxic carcinogens, practical thresholds are a matter of discussion. For instance, positive data of chromosomal effects only, in the absence of mutagenicity, may support the characterization of a compound that produces carcinogenic effects only at high, toxic doses. There is consensus that for non-DNA reactive genotoxicants, such as aneugens, thresholds should be defined. Specific mechanisms of clastogenicity have been repeatedly addressed as also having thresholds, such as topoisomerase II poisons or reactive oxygen species.
As summarised in the figure below, these and other mechanistic arguments, taken together, led SCOEL to the distinction of the following four main groups of carcinogens and mutagens in relation to setting OELs:



Group A: Non-threshold genotoxic carcinogens; for risk low-dose assessment the linear non-threshold (LNT) model appears appropriate.

Group B: Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases the LNT model may be used as a default assumption, based on the scientific uncertainty.

Group C: Genotoxic carcinogens for which a practical threshold is supported.

Group D: Non-genotoxic carcinogens and non DNA-reactive carcinogens; for these compounds a true ("perfect") threshold is associated with a clearly founded NOAEL.

Health-based OELs are derived by SCOEL for carcinogens of groups **C** and **D**.

If dataset allows, SCOEL might perform a risk assessment for carcinogens and/or mutagens placed in category **A** and **B**. In such cases, the corresponding SCOEL document (recommendation) will clearly state that a carcinogenic risk assessment has been carried out. It will contain a table summing up the concentrations explored and the associated risks calculated and won't show the frame with recommended OELs like it is the case for health-based values.

The category assigned by SCOEL to any carcinogenic or mutagenic substance evaluated, will appear in the frame of the front page following "SCOEL carcinogen group: X".

9. THE EVALUATION OF RESPIRATORY SENSITISERS

9.1 Introduction and background

'Sensitisation' may be defined as a condition of acquired specific alteration in the responsiveness of a biological system, initiated by exposure to a sensitising substance and, after an incubation period, characterised by evocation of enhanced reactivity upon re-exposure to the same or a closely related substance.

In the workplace, sensitisers may affect the respiratory system (and the conjunctiva) and also the skin. Although some sensitisers may affect both the respiratory system and the skin, different mechanisms are thought to be involved and a skin sensitiser will not necessarily affect the respiratory system. With regard to the establishment of OELs, the SCOEL is only concerned with evidence relating to respiratory sensitisation, as it is this effect, and not skin sensitisation, that is associated with exposure to and inhalation of airborne substances.

The criteria for classification of a substance with the Risk Phrase R42 ('May cause sensitisation by inhalation') have recently been widened to allow for the induction of sensitisation by non-immunological (as well as immunological) mechanisms. For some substances (for example those causing respiratory sensitisation via non-immunological mechanism) it might be possible to identify a threshold of exposure below which a state of sensitisation is unlikely to be induced. It is considered unlikely that such a threshold could be identified for substances acting via immunological mechanisms.

9.2 The SCOEL approach

The SCOEL will consider each substance on a 'case by case' basis.

Evidence relating to respiratory sensitisation is likely to stem almost entirely from experience in humans. The most useful data are likely to derive from epidemiological studies. Case reports rarely provide useful exposure/response data and animal models are not yet fully validated and applicable for OEL settings.

For those substances for which the data are sufficient to indicate that there is an apparent threshold for the induction of sensitisation, a health based OEL may be recommended by the SCOEL, following the principles outlined elsewhere in this Key Documentation. Where such a threshold cannot be defined with some confidence, it is the opinion of the SCOEL that health based OELs cannot be established, and the role of the SCOEL in these situations will be limited to offering advice to the Commission on the risk of respiratory sensitisation at particular exposure levels [along similar lines to that outlined for genotoxic carcinogens (see Chapter 8)].

The SCOEL also takes the view that it is not possible to set health based OELs which will provide protection against the elicitation of responses among persons who have already become sensitised to particular substances. With this in mind, it is the intention to recommend a 'sensitisation notation' for any substance for which the SCOEL recommends a health based OEL and which has also been classified as a respiratory sensitiser with the Risk Phrase R42.

A sensitiser notation will be indicated in the front page frame following "**Notation**".

10. STRATEGY FOR ASSIGNING A SKIN NOTATION

10.1 Need for a skin notation

In order effectively to control total systemic exposure to chemicals at the workplace, it is necessary to take account not only of exposure by the inhalation route, but also of dermal exposure, which may lead to skin penetration and a consequent increase in the total body burden. Dermal absorption will have a greater relative impact on total body burden (and thus present a greater health risk) when exposure by the inhalation route is controlled to relatively low levels, i.e. for substances which have low OELs. In some situations (e.g. field application of pesticides) the contribution from dermal absorption may greatly exceed the contribution from respiratory intake. It is thus necessary to assign a 'skin notation' to some OELs in order to warn of the possible significant contribution of dermal absorption to the total body burden.

It should be noted that a skin notation relates specifically to dermal absorption of the material (whether as solid, liquid or gas), i.e. it is determined by the toxicokinetic properties of the material in relation to the level at which the OEL is established. It does not relate to and is not intended to give warning of direct effects on the skin such as corrosivity, irritation and sensitisation, criteria for which are described in Annex VI of Directive 67/548/EEC.

10.2 Definition of a skin notation

A skin notation assigned to an OEL identifies the possibility of significant uptake through the skin.

10.3 The need for a criterion

In various national lists of OELs, the 8 hour TWA may be followed by a designation (e.g. Sk(in), S(kin), H(aut), Huid etc according to the national language). There are however no agreed criteria for assigning these skin notations and this has resulted in great discrepancies in the proportion of chemicals to which the notation is assigned in different national lists. A criterion is thus required to determine whether or not a skin notation is applied.

10.4 Factors relevant to the assignment of a skin notation

The following will determine the extent to which a chemical substance is absorbed through the skin:

- the amount of the substance (per unit surface area) in direct contact with the skin (i.e. the dose)
- the physicochemical properties of the substance (lipophilicity, molecular weight, volatility)
- concomitant exposure to a vehicle or other chemicals which may enhance the rate of penetration
- the duration of exposure
- the physical form of the substance.

In the majority of cases, dermal absorption of gases and vapours is of minor importance in relation to pulmonary absorption at the OEL. Direct skin contact with highly volatile liquids (i.e. those of low boiling point) is also not likely to result in appreciable skin absorption, since the liquid is likely to evaporate rapidly. Solids and liquids with boiling points above ambient temperature and low vapour pressure may give rise to skin exposure not only by direct contact, but also by impingement of aerosols on the skin. The skin of hands, forearms, face and neck come into contact with a volume of air several orders of magnitude greater than the volume inhaled during a working day. Thus in some circumstances even a low fractional impingement could result in a significant increase in body burden.

For substances that are absorbed through the skin, biological monitoring may be recommended.

10.5 The SCOEL approach

The SCOEL has agreed that there is a need to assign a skin notation if dermal absorption could contribute substantially to the total body burden and consequently to concern regarding possible health effects. 'Substantial contribution' to total body burden will be established on a case-by-case basis but may in general be of the order of 10% or more of the uptake from respiratory exposure at the 8 hour TWA.

Possible methods for obtaining quantitative data on skin penetration have been recommended (ECETOC, 1993; Kennedy *et al,* 1993). These include;

- direct measurement of percutaneous absorption in humans or animals using *in vivo* or *in vitro* models

- comparison of dermal and i.v. or i.p. LD_{50} values.

It is recognised that, in many cases, quantitative data on skin penetration may not be available.

Evidence of significant percutaneous absorption may be obtained from human studies such as:

- case reports of systemic effects following skin exposure

- substantial variation in biological monitoring data in groups with similar inhalation exposure

- phenomena such as subjective taste after 'skin only' exposure.

In the absence of other data, an indication of likely skin penetration may be inferred from physicochemical data, including volatility, or structure/activity relationships.

The SCOEL will use all available information as a basis for making an assessment of whether or not the criterion for application of a skin notation is met.

For substances readily absorbed dermally, evaluation of exposure by the inhalation route may underestimate the body burden. In these circumstances there may be a role for biological exposure limits or indicators in preference or in addition to atmospheric limit values.

A skin notation will be indicated in the front page frame following "Notation"

11. HEALTH-BASED BIOLOGICAL LIMIT VALUES (BLVS)

11.1. Introduction

Health protection of workers exposed to chemical substances is based on two complementary methodologies to assess the exposure: air monitoring and biological monitoring.

Biological monitoring entails the measurement of substances and/or metabolites in biological media, and the measurement of biological effects induced by the substance. Biological Limit Values (BLVs) are reference values for the evaluation of potential health risks in the practice of occupational health. They are established on the basis of currently available scientific data. Exposure concentrations equivalent to the BLV generally do not affect the health of the employee adversely, when they are attained regularly under workplace conditions (8 hrs/day, 5 days/week), except in cases of hypersensitivity.

In general, OELs and BLVs are based on similar quantities of internal exposure; in this case, the BLV is related to a group mean. In cases of a high health impact of individual peak exposures, a BLV may be conceived as a maximum level for individual workers.

The interpretation of biological monitoring data requires expertise in the field of occupational medicine. Ethical considerations must well be taken into account. SCOEL will evaluate the need to recommend a BLV for a particular substance on a case by case basis.

11.2. Approaches to biological monitoring

Biological methods used to assess exposure and/or risks to health fall into two main categories:

(1) Determination of the substance or its metabolite in a biological medium (biological exposure monitoring)

Most methods fall into this category, with the medium of choice usually being blood, urine, or occasionally, exhaled breath. The method may either be specific for a particular substance or general for a group of related substances. The level determined may reflect exposure over widely different time periods, depending on the kinetics of the substance, the medium involved and the time of sampling.

A specific method of growing applicability to measure effective exposure is the determination of macromolecular adducts of toxicants or their metabolites (e.g. adducts to haemoglobin, to serum albumin or to DNA). The determination of haemoglobin adducts provides an integrated measure of the effective internal exposure over a longer period of time, due to the life span of erythrocytes (~4 months).

(2) Measurement of biological effects (biological effects monitoring)

This category involves the measurement of parameters of biological response (e.g. serum cholinesterase activity for organophosphates).

11.3 Advantages of biological monitoring

Biological monitoring offers advantages over atmospheric monitoring in assessing risk to health under certain circumstances. Most importantly, chemicals may enter the body through the skin (compounds with a skin notation) or the gastrointestinal tract (e.g. lead compounds), in addition to the inhalation route. Inadequate personal hygiene or inappropriate protective clothing may in such circumstances lead to a body burden significantly higher than that which would have occurred via the inhalation route alone. In addition, inter-individual variation in toxicokinetics, as well as in other physicochemical and biological factors, may lead to differences in the amount absorbed for a given atmospheric concentration. Also, there may be intra-individual variations in exposure, due to changes in the working conditions within a shift. Biological monitoring may be able to take all these factors into account, as well as covering any non-occupational exposure.

Especially for compounds with a skin notation (see chapter 10) biological monitoring may be preferable, if methods are available. Unfortunately, for many substances the data are too limited to support a biological monitoring method. In general, SCOEL will set BLVs for compounds with a skin notation as a priority.

11.4 OELs and BLVs

In the first instance BLVs represent the levels of determinants which are most likely to be observed in specimens collected from a worker exposed to the chemical in question exclusively by inhalation, at the level of the OEL.

Exceptions are the BLVs for substances for which the OELs serve as protection against non-systemic effects (e.g. irritation or respiratory disorders) or for substances, which require biological monitoring due to other routes of absorption, in particular the skin. BLVs for such chemicals can be based on the avoidance of systemic effects and it is therefore possible that the internal exposure exceeds the pulmonary uptake resulting from exposure at the level of the OEL.

BLVs do not indicate a sharp distinction between hazardous and non-hazardous exposures. Due to biological variability, it is possible for an individual's measurement to exceed the BLV without incurring an increased health risk. If, however, measurements in specimens obtained from a worker on different occasions persistently exceed the BLV, or if the majority of measurements of specimens obtained from a group of workers at the same workplace exceed the BLV, the cause of the excessive values must be investigated and proper action taken to reduce the exposure.

BLVs for working schedules other than eight hours exposures, five days a week, may be extrapolated on toxicokinetic and toxicodynamic bases. Attention should be paid to determination of the correct sampling time point. In any case, BLVs should not be applied, either directly or through a conversion factor, in the determination of safe levels for non-occupational exposures.

11.5 Biological media

The choice of biological medium depends on kinetic factors, the convenience of sample collection and the possibility of sample contamination.

(1) Blood. Since this is the main vehicle for transport and distribution, most systematically active substances and their metabolites can be found in blood. The medium is useful for inorganic chemicals and for organic

chemicals, which are poorly metabolised and have a sufficiently long half-life (e.g. metals).

(2) Urine. Urine collection is easier, less invasive and more readily accepted by workers. It is usually suitable for water-soluble metabolites of organic substances and for some inorganic chemicals.
The concentration of a substance in urine usually reflects the mean plasma level during the period of urine accumulation in the bladder. End of shift sampling is appropriate for rapidly excreted substances, such as solvents; 24-hour specimens (although rarely collected) may be more representative in some cases. The concentration of a substance in urine will depend on the rate of urine production, and correction of results on the basis of creatinine concentration or density may be necessary. Contamination during collection can be a source of error.

(3) Breath. Exhaled air analysis may be used to estimate exposure to volatile organic substances (solvents), although it is much less frequently used than blood or urine sampling. The method is non-invasive, but involves a risk of external contamination.
Concentrations will vary depending on whether they are measured in "end exhaled" air (alveolar) or in "mixed exhaled" air (normal breathing). Timing of sampling is very critical in determining whether the measurement reflects very recent exposure or exposure during the previous day. Concentrations can also be influenced by a variety of physiological factors.

Whichever medium is chosen, it is important to establish a sampling strategy, based on knowledge of the kinetics of the biological marker in question.

11.6 Analysis

Careful attention must be paid to both pre-analytical (sample collection, transport and storage) and analytical methodology to ensure accuracy.

Each aspect of biological monitoring should be conducted within an effective quality assurance (QA) programme. The appropriate specimen must be collected, at the proper time, without contamination or loss, and with use of a suitable container. Donor identification, time of exposure, source of exposure, and the sampling time must be recorded. The analytical method used by the laboratory must have the accuracy, sensitivity, and specificity needed to produce results consistent with the BLV. Appropriate quality control specimens should be included in the analysis, and the laboratory must follow routine quality control rules. The laboratory should participate in an external quality control programme.

11.7 Interpretation of results

Like any results of laboratory investigations, biomonitoring results have to be evaluated given knowledge of the whole situation. Thus biomonitoring data may be influenced by for example:

- the dynamics of pathophysiological processes,
- the short-term effects of exposure-free periods,
- the long term effects of ageing,
- the specific workplace conditions,
- intensive physical activity and unusual conditions of atmospheric pressure and
- any individual background exposures

Due to the variable nature of concentrations in biological specimens, dependence should not be placed on the results of one single specimen measurement, but on measurements of multiple sampling, or on analysis of a repeat specimen within a suitable period, depending on the representativeness of the sample. Individual observations below the BLV do not necessarily indicate a lack of neither health risk nor compliance with the OEL. Given confidentiality, it may be possible to use the results on a group basis to determine whether working conditions are satisfactory or not.

Use of BLVs should be applied by a knowledgeable occupational health professional. Toxicokinetic and toxicodynamic information is taken into account when establishing specific BLVs. Therefore, knowledge of the metabolism, distribution, accumulation, excretion and effects is helpful in an effective use of biomonitoring. If applicable, knowledge of background levels in reference populations is required.

The BLV is a guideline for the control of potential health hazards to workers and should not be used for other purposes.

11.8 The SCOEL approach to BLVs

Where appropriate, the SCOEL will recommend BLVs on the basis of currently available scientific data, which indicate that concentrations or levels of activity equivalent to the BLV are unlikely to result in adverse effects on health.
BLVs may be derived in one of three ways:

(1) When studies in humans (occupational field studies or experimental laboratory studies on volunteers) are available, linking adverse effects with concentrations of the chemical or its metabolites in biological media, the no-observed-adverse-effect-level (NOAEL) may directly be used to derive the BLV that is related to this level.

(2) If such studies are not available but an OEL has been set and studies in humans provide a link between airborne concentrations of the compound and concentrations of the compound or its metabolites in biological media, a BLV may be set in a way that it corresponds to the OEL. Supporting evidence may be drawn from toxicokinetic modelling. This implies that any re-evaluation of an existing OEL must be paralleled by a re-evaluation of the corresponding BLV. The two exposure limits (OEL, BLV) are generally based on equivalent effects of substances on the exposed worker.
However, for substances for which the OEL is not established on the basis of systemic effects but because of local irritation, a BLV may still be based on systemic adverse effects. In such (exceptional) cases where OEL and BLV are based on different end points, the two values may not necessarily correlate.

(3) In case of biological effect monitoring, the BLV is directly derived from suitable studies in humans. The documentation should then explicitly deal with the question of the adverse nature of this effect in view of standard setting.

BLVs derived by the first and third method above can be regarded as directly health-based and these methods are, in principle, to be preferred. Supporting studies are, however, likely to be less well documented than those supporting the second type.

BLVs derived by the second method are measures of exposure, which, for substances with health-based OELs, can be regarded as adequate to prevent adverse health effects.

The documentation of a BLV will include a discussion of the toxicokinetic and toxicodynamic parameters that determine or limit the sampling time. The sampling time is very important and must be observed very carefully, especially for substances with short biological half-lives (of several hours or less). Substances which accumulate over longer periods (half-lives in the order of days or longer, e.g. lead) may not require a specific sampling time, but steady-state conditions must have been reached after a certain exposure period.

Sampling times may be standardised for practical reasons (prior to shift, during shift, end of shift, end of work-week, or at any time).

Spot urine specimens may be concentrated or diluted within wide margin. The World Health Organisation has recommended limits of specific gravity between 1.010 and 1.030 and or urinary creatinine between 0.3 and 3.0 g/litre to be accepted. Specimens falling outside either of these ranges should be discarded, and another specimen should be collected. Workers consistently providing urine outside these ranges should be referred for medical examination.

Some BLVs, referring to urinary excretions, are expressed relative to creatinine concentrations. In first instance, this refers to compounds for which the relevant studies are only documented based on urinary creatinine values.

11.9 Biological guidance values

Where toxicological data cannot support a health-based BLV, a biological guidance value (BGV) might be established. This value represents the upper concentration of the substance or a metabolite of the substance in any appropriate biological medium corresponding to a certain percentile (generally 90 or 95 percentile) in a defined reference population.

A value exceeding the BGV might help to identify the need for an expert consideration of the working conditions. Unlike BLVs, BGVs are not health-based and therefore do not set a limit between absence or presence of adverse health effects.

12. ANALYTICAL MEASUREMENTS METHODS

(Discussion on-going)

13. REFERENCES

Chapter 3 - General principles

Sherwin, R.P. (1983), What is an adverse effect? Environ. Health Perspect. 52, 177-182

European Commission (1996) Criteria for the qualitative evaluation of human neurobehavioural studies of neurotoxicity, Report EUR 17390 EN [Key document produced by the Institute of Occupational Health of the University of Birmingham (Dr. Anne Spurgeon) and Prof. Francesco Gamberale (Sweden) after intensive discussions with SCOEL]

IGHRC (2009) Chemical Mixtures: A Framework for Assessing Risk to Human Health (CR14). Institute of Environment and Health, Cranfield University, UK.

Kromhout, H.J. (2002) Design of measurement strategies for workplace exposures. Occup Environ Med 59, 349-354

Comité Européen de Normalisation (CEN): Workplace Atmospheres – General requirements for the Performance of procedures for the Measurement of Chemical Agents (prEN 482).
[Standard] Brussels: CEN, 2005

Chapter 6 - Uncertainty factors

ECETOC (1995), Assessment factors in human health risk assessment, ECETOC Technical Report No 68, Brussels, August, 1995

WHO (1994), IPCS Environmental Health Criteria 170: Assessing human health risks of chemicals: Derivation of guidance values for health based exposure limits, World Health Organisation, Geneva

Stevenson H, Bos PMJ, de Raat WK (1995), Review of applied factors to derive health based recommended exposure levels, TNO Report No V95.092, TNO Nutrition and Food Research, The Netherlands.

IGHRC (2003) Uncertainty factors: Their use in human health risk assessment by the MRC Institute for Environment and Health, University of Leicester, UK

Chapter 7 - Reproductive toxicity

Karnovsky, 1965, Mechanisms of action of certain growth-inhibitory drugs, in: Wilson JG, Warkany H (eds), Teratology: Principles and Techniques, University of Chicago Press, Chicago.

Kline J, Stein Z, Susser M, 1989, Conception to birth - epidemiology of prenatal development, Oxford University Press, Oxford.

Sullivan FM, Watkins WJ, van der Venne M Th, 1993, The toxicology of chemicals - Series 2, Reproductive Toxicity, Volume 1, Summary reviews of the scientific evidence, Commission of the European Communities, EUR 14991 EN.

Chapter 8 - Carcinogens and Mutagens

Bolt, H.M. & Huici-Montagud, A. (2008) Strategy of the scientific committee on occupational exposure limits (SCOEL) in the derivation of occupational carcinogens and mutagens. Arch. Toxicol. 82: 61-64.

Chapter 9 - Respiratory sensitisers

Most recent revision of Annex VI to the Dangerous Substances Directive (67/548/EEC) (equivalent to guidance from ECHA to the new EC Classification, Labelling and Packaging Regulation)

Chapter 10 - Skin notation

ECETOC (1993), ECETOC Technical Document No 31 (Revised), Strategy for assigning a 'skin notation'.

Kennedy Jr., G.L., Brock, W.J. and Banerjee, A.K. (1993), Assignment of skin notation for threshold limit values based on acute dermal toxicity, Appl. Occup. Environ Hyg. 8, 26-30.

Environmental Health criteria 235 on Dermal absorption (http://www.who.int/ipcs/methods/dermal_exposure/en/index.html)

Chapter 11 - Biological Limit Values

DFG (yearly updated) - Maximum Concentrations at the Workplace and Biological Tolerance Values for Working Materials, Report No 31, Deutsche Forschungsgemeinschaft, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, VCH, Weinheim

Lauwerys R. and Hoet P. (1993), Industrial Chemical Exposure Guidelines for Biological Monitoring (2nd edition), Lewis Publishers (CRC Press), Boca Raton, Florida

WHO Geneva (1996), Guidelines on Biological Monitoring of Chemical Exposure at the Workplace

ACGIH (yearly updated), Threshold Limit Values (TLVs) for Chemical Substances and Physical Agents and Biological Exposure Indices (BEIs), Cincinnati