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Occupational exposure limits – approaches and criteria

Proceedings from a NIVA course held in Uppsala, Sweden, 24–28 September 2001

Gunnar Johanson (Ed.)

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Foreword

This volume of Arbete och Hälsa contains the proceedings of the Nordic Institute for Advanced Training in Occupational Health (NIVA) course *Occupational exposure limits – approaches and criteria, third international course*, held in Uppsala, Sweden, 24-28 September, 2001. The course was planned by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The main objectives were to: describe and differentiate between the various approaches and criteria used to set an occupational exposure limit (OEL), identify the problems of comparing OELs from different countries, and analyse an OEL based on background information.

A variety of occupations were represented, including administrators, chemists, occupational physicians and hygienists, researchers, and toxicologists. Seven lecturers, all with profound experience of criteria work, attended the entire course and participated actively during lecture sessions as well as group work sessions. The multitude of nationalities and disciplines represented among participants and lecturers created a good basis for exchange of experiences and thoughts.

The participants were asked to bring with them to the course a poster that briefly described the OEL setting process in the participant's country. These posters were at display along the entire course, were frequently visited during intervals and breaks, and gave rise to several spontaneous discussions. During the last session of the course, the posters were used as a starting point to compare the OEL procedures in European countries, the EU and the US.

A main task during the week was to prepare a short summary document for a selected substance. The document should contain the scientific basis for an OEL and include a recommended health-based OEL and any other recommendations, such as skin notation. The efforts of these group works were presented and discussed during the last day of the course.

The following pages contain summaries of most lectures given. Although they do not cover the entire course, I believe the text may serve as valuable reference material for a variety of users.

On behalf of NEG, I want to express my gratitude to all the lecturers and participants for contributing to a successful course. Special thanks to Gunilla Rasi at NIVA, Helsinki, for excellent course administration, and to Anna-Karin Alexandrie at the National Institute for Working Life, Stockholm, for skilful technical editing of this volume.

Stockholm December 23, 2003

Gunnar Johanson, Professor
Course leader, Chairman of NEG

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Basic concepts in toxicological risk assessment

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Introduction

This presentation aims to briefly describe some of the most important, basic concepts in toxicological risk assessment. Toxicology has a multidisciplinary character and it is neither possible to cover all concepts, nor to describe them in detail. For this purpose the interested reader is referred to textbooks such as Casarett and Doull's Toxicology (2) and Stacey's Occupational Toxicology (3), to mention some. Many of the concepts included in this presentation can also be found in the ILO Encyclopaedia (1). Another good starting point is the Toxicology Tutor developed by the US National Library of Medicine available at http://sis.nlm.nih.gov/Tox/ToxMain.html.

Toxicity, hazard and risk

Toxicology is the science of poisons and their effects, and with the problem areas involved (as denoted by the terms: clinical, industrial, and regulatory toxicology). It could also be described as the scientific study of poisons, their actions, their detection, and the treatment of conditions produced by them. Occupational toxicology deals with chemical substances present in the work environment. These chemicals need not necessarily be considered as poisons, i.e. very toxic. The words toxic, toxicology etc. are derived from *toxon* (Greek for bow, later *toxicum*, Latin for poison (on bow)) and *logos* (Greek for reason or word).

Most chemicals studied in toxicology are foreign to the body, these are called *xenobiotics*.

Toxicity is the intrinsic capacity of a substance to adversely affect an organism. It can also be described as the quality or degree of a substance being poisonous.

Hazard is the potential for the toxicity to be realized in a specific situation. Expressed in another way, hazard is a potentially dangerous condition as a result of exposure to a substance during a specific situation or at a specific site.

Risk is the probability of a specific adverse effect to occur as a result of this exposure.

Risk assessment and risk management

Toxicological *risk assessment* is the process of describing the toxicity, hazard and risk of a chemical substance or product. The outcome of the risk assessment is often a so-called criteria document. Important input data categories can be animal data on toxicity and mechanisms, *in vitro* data on toxicity and mechanisms, case reports, epidemiological studies, and experimental human volunteer data on toxicokinetics and toxicodynamics.

Risk management deals with the actions taken to reduce the risks. Risk assessment and management may also deal with other risks that are not discussed here, such as those of economic investments, traffic accidents, work procedures etc. Risk analysis is a broader term that includes risk assessment, risk characterization, risk communication, risk management, and policy relating to risk.

Successful risk assessment and management, as in occupational exposure limit (OEL) criteria documentation and OEL setting, depends on a number of conditions, which can be summarized as: legitimacy, transparency, scientific methods, and reasonable values.

Legitimacy in the process is achieved by conforming to recognized principles and accepted rules and standards including, in some cases, legislative procedures. This includes governing via an unbiased organization and independent experts, with no special interests.

The process will gain from *transparency*, i.e. documented and publically available procedures and results. This includes publication of

- names and affiliations of experts,
- criteria and work-procedures used,
- criteria documents,
- conclusions.

By a *scientific approach* is meant that the best available scientific data are retrieved and critically evaluated. The conclusions should follow from the scientific data in a way that is easy to understand, and references should be given to all referred data. The scientific data are preferentially taken from the international, scientific, peer-reviewed literature. Peer-reviewed and easy-to-access reports enhance the possibility for critical examination by external reviewers and, thus, also enhances transparency and legitimacy.

The above prerequisites contribute to credibility, which is essential to successful risk management. Another element that is important and should follow from the prerequisites is that *reasonable standards* are set.

Acute and chronic toxicity

Acute exposure has short duration. In toxicity testing, typically an oral dose is administered to rodents at a single dose or repeatedly for a few days. Inhalation

exposure is typically carried out for a few hours or repeatedly 6-8 hours daily for a few days.

Chronic exposure has a much longer duration. Typically, as in many cancer tests, chronic exposure of rodents is daily or 5 days/week for 2-years, corresponding to nearly life-long exposure. Intermediate exposures are sometimes termed subacute or subchronic.

Acute effects occur or develop during or shortly after short exposures (hours-days). Acute effects may range from clearly reversible (such as mucosal irritation) to clearly irreversible (such as death).

Chronic effects occur or develop after prolonged exposure (months-years) or persist or develop further after exposure has ceased (as with cancer).

Toxicokinetics and toxicodynamics

Toxicokinetics is the quantitative description of the behaviour of a xenobiotic in the organism. A common way to describe the kinetics is by concentration-time curves and half-times for the substance itself or its metabolites in blood, plasma, urine etc. The toxicokinetics may be divided into different types of processes: absorption (uptake), distribution, biotransformation (metabolism), and excretion. The acronym ADME (Absorption, Distribution, Metabolism, Excretion) is often used for these processes. The term elimination may include excretion as well as biotransformation.

Toxicodynamics refers to the relation between amount or level of the xenobiotic at the target site and any effect from, for example, receptor binding to disease.

The toxicokinetics and -dynamic processes may be described as a chain of relations from external exposure over target dose to adverse effect and disease (Figure 1).

Dose concepts

Dose is the amount of xenobiotic that enters the organism. For substances that are deliberately administered, such as pharmaceutical drugs that are injected or taken as tablets or in animal toxicity testing where the test substance is given by gavage, the dose is easily defined. For exposure at the workplace the dose may be more difficult to define. Common alternative ways to describe the dose are: external dose, absorbed dose, target dose and body burden (see also Figure 1).

External dose is often used as a dose surrogate for air pollutants. It is the product of the duration of exposure and the average concentration in air during that time. Expressed in a more mathematical way, external dose is the time integral of the concentration in air. The true dose is thought to correlate with the external dose under standardized conditions. However, the relation between external and true dose depends on a number of factors, for instance the physical activity during exposure (affects pulmonary ventilation and thus amount inhaled

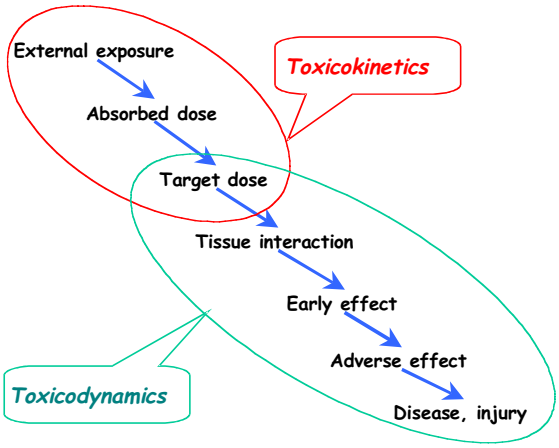

Figure 1. The chain of relations between external exposure, target dose and adverse effect.

per time unit) and the affinity of the substance to tissues (affects the fraction of the inhaled amount that is absorbed).

Absorbed dose usually refers to the amount of substance that reaches the systemic blood circulation. In many cases absorbed dose is equal to administered dose, that is, the *bioavailability* is *100%*. However, for substances taken orally the bioavailability may be substantially lower than 1 if the substance is e.g. acid labile, metabolised by the microbial flora in the gastro-intestinal tract, or only slowly penetrating the gastro-intestinal wall. The systemic bioavailability may also be reduced due to so-called *first-pass metabolism*. In this case the substance is absorbed through the gastro-intestinal wall and then follows the portal system to the liver where it is metabolised to a large extent before it reaches the systemic circulation (see also Figure 1).

Target dose is the amount of substance that reaches the specific tissue or cell target. Target dose may also designate the maximum concentration near the target or the product of time and concentration, i.e. the time integral of concentration (often called AUC, area under the concentration-time curve). It is difficult to measure the target dose. However, there is often a close relationship between target concentration and blood or plasma concentration. Therefore the two latter, or their AUCs, are commonly used as surrogates for target dose (see also Figure 1).

Body burden is the amount of substance present in the body at a given time. Immediately after a bolus dose, such as an intravenous injection, the body burden is equal to the dose. During continuous or repeated exposure, the dose increases with time, whereas the body burden will eventually approach a plateau (steady-state) level where the dose rate is equal to the elimination rate.

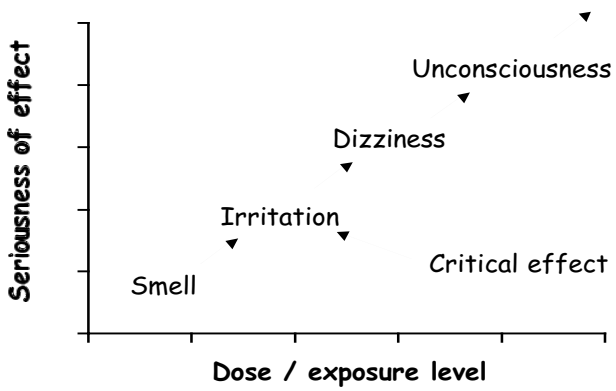

Figure 2. Dose-effect relationship.

Haber's rule

Haber's rule states that the toxic response is related to the inhaled concentration of a chemical multiplied by time of exposure. For other routes of exposure, such as repeated oral administration, it states that the response is related to total dose. This rule forms the basis of most OELs, which are usually expressed as 8-hour time-weighted averages (TWA), corresponding to a normal working day.

Haber's rule should be seen as a default approach and not a law, as there are numerous well-known exceptions and limitations. The rule is obviously not applicable to very rapid effects, such as irritation. Further, there is an upper limit in time, which is different for different substances and effects (minutes for irritation, years for PCB).

Dose-effect and dose-response

The *dose-effect* relationship describes the relation between the dose and the seriousness of a yes/no effect (Figure 2). It may also describe the relation between the dose and the magnitude of a specific effect, such as elevation of blood pressure or rating of eye irritation. The *critical effect* is the adverse health effect that first appears at increasing doses. This is usually the least serious effect. The term critical reflects that this effect, and the level at which it is first seen, determines a critical limit. Below this limit no adverse effect are expected to occur.

The *dose-response* relationship describes the relationship between dose and number of individuals affected by a specific effect. The number of individuals is expressed as a fraction of the population, for example 0.32%, 3.2 per thousand

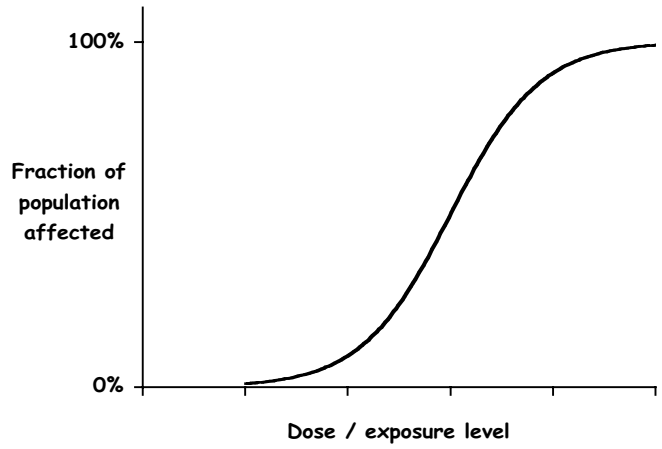

Figure 3. Dose-response relationship. As the response (fraction affected) approaches 0%, it is increasingly difficult to estimate accurately.

workers, or 320 x 10^{-5} (Figure 3). The fraction may also be seen as a risk for an individual. This is, however, misleading since the value only reflects the average risk for all individuals. In reality, depending on genetic and environmental factors, some individuals are at higher risk than others.

The no observed adverse effect level (NOAEL) and/or the lowest observed adverse effect level (LOAEL) are frequently used in the absence of more complete dose-response data, or to extract key information from dose-response data. The values of LOAEL and NOAEL depend on which effects are being measured, the sensitivity of the measurement, the number of subjects or animals in the study, and the dose and dose spacing used.

The NOAEL is the highest dose not shown to cause a specified adverse effect. When applied on the critical effect it gives an idea of an upper limit of an exposure that will not result in adverse effects. The NOAEL may therefore serve as the starting point to derive health-based exposure limits. The LOAEL is the lowest dose shown to cause an adverse effect. It may well be that an ever lower dose (hitherto not tested) will also cause effects. Thus, on theoretical grounds, one cannot rely only on a LOAEL to derive a safe limit.

One problem with both the NOAEL and the LOAEL is that their values depend on the doses and the dose spacing used in the study. This is illustrated by horizontal bars in Figure 4. A more serious problem is that the values of the NOAEL and the LOAEL depend on the statistical power of the study. Thus, using a realistic number of subjects or animals, it is only possible to detect effects that hit several per cent of the study group. This is illustrated by vertical bars in Figure 4.

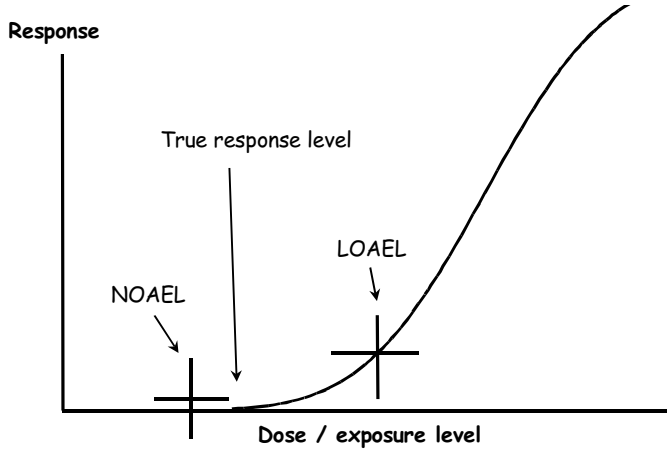

Figure 4. The values of NOAEL and LOAEL in relation to the ”true” response level depend on the dose spacing (illustrated by horizontal bars) and the confidence limits of the measured effect (illustrated by vertical bars).

Extrapolations

Due to high costs and ethical considerations toxicity studies are usually carried out in a small number of animals. Therefore, only relatively high responses (high up at the dose-response curve) can be demonstrated. However, for humans the response of interest is that at low doses. This response is not readily obtained from direct observations. Different approaches for *high to low dose extrapolation* are used for different effects. For direct acting carcinogens it is common to apply linear extrapolation with no threshold. This usually means that the response (i.e. the increase in cancer frequency over the background) at the lowest dose with reliable data is extrapolated by a straight line to origin (zero response at zero dose). For irritants (i.e. substances with mucosal irritation as critical effect) it is though that there is a distinct threshold and a steep dose-response curve (small variability in sensitivity in the population). Hence, the threshold can be estimated fairly accurately from, or even be substituted by, the NOAEL.

Most knowledge on toxic effects is obtained from animal studies and the translation to humans requires some kind *species extrapolation*. A common default approach is to translate the dose on an anthropometric basis, i.e. by correcting for body weight (bw), body surface area ($bw^{0.67}$), or overall metabolic capacity, which has been shown to correlate to $bw^{0.75}$. If special circumstances are known, for example that the effect is mediated via a metabolite and that the metabolism differs between the two species, or that the two species differ in the expression of a particular effect, these circumstances are also incorporated in the species extrapolation. Usually, no correction for species is needed when the dose is expressed

as an exposure level in air, since pulmonary ventilation correlates with overall metabolism.

A third type of extrapolation is that between different routes of exposure. Since many rodent studies are carried out by gavage, the most common *route extrapolation* is from oral administration (in rodents) to inhalation exposure (of humans). Two major complicating issues in route extrapolation are that the effects may be related to local exposure, such as irritation of the respiratory tract, and, in the case of systemic effects, that the degree and pattern of first-pass metabolism may differ widely between the routes of entry.

Assessment factors

An *assessment factor* is a formal, arbitrary number with which one divides a NOAEL or LOAEL to finally obtain an OEL or other limit value. The term may allude to the final overall factor as well as subfactors that cover different aspects. Other names commonly used are *safety factor* and *uncertainty factor*. The term assessment factor is preferred since it emphasises that the choice of a particular numerical value is performed within the risk assessment procedure, and that safety as well as uncertainty issues are involved. The sizes of different subfactors depend on the severity of effect (a safety aspect), the quality of the toxicological data including the need for extrapolations (an uncertainty aspect), and how one chooses to account for the (unknown) variability in sensitivity in the population (uncertainty and safety aspects). The subfactors are commonly multiplied so that, for example, factors of 10 for severity, 5 for extrapolation from oral to inhalation, 2 for extrapolation from rodent data to man, and 2 to account for population variability, yields an overall assessment factor of 10 x 5 x 2 x 2 = 200. By this procedure, even relatively small subfactors may result in an overall factor that seems unrealistically high, judging by general toxicological experience. The rules for use of assessment factors are often vague or arbitrary. As a consequence different risk assessors will apply these factors differently. It is therefore important that the numerical values of the factors and their rationales are clearly documented for each substance.

Combined effects

By *additive effects* one means that the effects of a combined exposure is the sum of the individual effects of the chemicals. An additive interaction is likely when two or several substances have the same mode of action, such as for example the narcotic effect of many organic solvents. If additivity prevails, and assuming that two substances A and B are equipotent, the effect caused by combined exposure to 2 ppm of A and 3 ppm of B will be the same as that caused by exposure to 5 ppm A only or 5 ppm B only. The interpretation and application of additivity may be complicated by two factors, namely that the substances may have different

potency and that the dose-effect curve is non-linear so that doubling the dose gives more (or less) than doubling of the effect. If the combined effect is higher and lower than expected from additivity the effect is said to be synergistic, and antagonistic, respectively.

A *hygienic effect* can be calculated for mixed exposure to air pollutants, provided that additivity can be assumed. The hygienic effect is the sum of exposure levels of individual substances, weighted in relation to their individual OELs. The calculation is performed as:

$$\text{Hygienic effect} = \frac{Conc_1}{OEL_1} + \frac{Conc_2}{OEL_2} + \frac{Conc_3}{OEL_3} + \ldots$$

Thus, under exposure to a single substance, a hygienic effect of 1 corresponds to exposure at the OEL. More information about hygienic effect may be found in the Swedish provisions on OELs and measures against air contaminants, available at http://www.av.se/english/legislation/afs/eng0003.pdf.

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Criteria documents as a basis for OELs

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Introduction

What is a criteria document? According to an English dictionary, a document is "an original or official paper relied on as the basis, proof, or support of something". A criterion is defined as "a standard on which a judgement or decision may be based". From these definitions it is quite clear that a criteria document is good basis for the decision of an occupational exposure limit (OEL). A criteria document may also be looked upon as a review paper, especially prepared for the purpose of setting an OEL.

Then, what should an ideal criteria document contain? It should contain a complete, but concise, review of all relevant data. The best available published information is the prime requirement. The most important data are the toxicological data, but also data on kinetics, exposure and uptake must be included. A table of contents for a document may contain the following headings:

- Identity
- Chemical and physical data
- Analytical methods
- Occurrence
- Toxicokinetics
- Toxicological data (including several subheadings)
- Mutagenicity, carcinogenicity, reproductive toxicity, immunotoxicity
- Dose-response/dose-effect relationship
- Summary and conclusions
- References

The desirable content of these chapters will shortly be described below.

Contents of criteria document

Identity

The identity of the substance is preferentially presented through the unique CAS number. Also the chemically correct name should be given as well as the most common synonyms, and internationally used trade names. The purity of the substance in commercial products and common impurities may also be given in this chapter.

Chemical and physical data

In the chemical and physical data chapter the chemical formula (summary and structure(s)), the aggregation state, form and colour are appropriate. Furthermore, the melting point, boiling point, density (at 20°C), vapour pressure and solubility (in water and/or other solvents) should be given. Odour threshold, octanol/water partition coefficient and flash point are other data that could be appropriate. Finally, the conversion factors ppm to mg/m^3 (at 20°C and 101.3 kPa) should be given.

Analytical methods

The title analytical methods is more or less self-evident and includes techniques for sampling and analysing levels of a substance in air and in biological tissues. The reliability of older methods should be discussed.

Occurrence

In the occurrence chapter a short overview of where in the working environment the substance may occur. Available quantitative or semi-quantitative data should be given with a clear distinction between personal exposure and background workplace exposure. Available data on biological monitoring could also be included in this chapter but would probably be better in the kinetics chapter. Normally there is no need to give data on production and use (as they are not relevant for setting OELs).

Toxicokinetics

The toxicokinetics chapter should contain data on the ways a substance is absorbed, distributed, biotransformed and excreted in the body. The absorption rate should be given quantitatively, if possible. All absorption routes (pulmonary, dermal, intestinal) should be described. The distribution part of the chapter should discuss the transport of the substance or its metabolite(s) to organ and tissues. The mechanism of biotransformation and metabolites formed should be presented. Variations in biotransformation due to species differences or genetic factors may be at hand. The excretion (or elimination) of the substance and/or its metabolites should be covered. Biological half-time could have been measured or calculated from kinetic models, and should then be included.

Toxicological data

The toxicological data chapter is the most important part of the criteria document as it provides the key information on which an OEL should be based. The studies should be exhaustively written and the data should be critically discussed, especially when they may have relevance for the OEL. Primary sources should

preferentially be used but high quality criteria documents or reviews from others may also be used.

As mentioned above several subheadings may be used in the toxicological chapter. First, it is reasonable to separate human data and animal data. Second, one may divide the human or the animal data by organs that are affected. Third, among animal data especially, it may be rational to differentiate between single dose, short-term and long-term exposure.

The human data consist mainly of four different types; controlled experimental data, epidemiological data, clinical data and case reports. In controlled experimental data (often voluntary young male persons) the exposure usually is well defined, and an effect exposure relationship may be at hand. In epidemiological studies the exposure levels are not so well defined (mixed exposure is common). These data, however, must be validated very critically as the may be affected by confounding factors etc. ”Negative” epidemiological data should be given special attention. Clinical studies and case reports may give support to other studies but case studies should generally be taken as a memento of possible effects.

Animal data are more clear-cut than human data. It should, however, be pointed out if they are established according to good laboratory practise (GLP) or not. Numerical data should be given as mean values and range and/or standard deviation should be presented.

Mutagenicity, carcinogenicity, reproductive toxicity and immunotoxicity

In the part dealing with mutagenicity both *in vitro* and *in vivo* data should be given covering different endpoints. Carcinogenicity data should be divided, as for other toxicological data, between animal data and human data. Full details should be given, and the ”degree” of carcinogenicity could follow the IARC concept.

In the reproductive toxicology paragraph effects on male and female fertility, embryo- and feototoxicity, and teratogenicity should be presented. The immunotoxicity part of the chapter should also include allergic sensitization.

Up to this point in the criteria document all available appropriate data should have been presented and no new information should be given in the two last paragraphs (dose-response and dose-effect or summary and conclusions). These two paragraphs should further evaluate the data presented, and, if possible, a critical effect should be given.

Dose-response/dose-effect relationship

In the dose-response/dose-effect relationship, data from the different studies presented should be given in a table starting with the lowest exposure level. If the data base is huge different tables for different types of studies (human–animal; short-term–long-term etc.) could be used.

Summary and conclusions

In the final chapter, summary and conclusions, a short and precise summary should be given of the critical studies and effects. Comments on combination effects and on susceptible individuals would be appropriate here. From the dose-response/dose-effect relationship the lowest exposure level giving effect (lowest observed adverse effect level, LOAEL) or highest exposure level without any effects (no observed adverse effect level, NOAEL) should be pointed out. The critical effect; the effect seen at the lowest exposure level should be given. Special comments on dermal absorption, carcinogenicity and reproductive effects should also be included in this chapter.

References

The references should be given in a proper way. References to unpublished paper and to personal comments should be avoided.

Concluding remarks

Only for few substances there exist data to every heading. For some more substances the data base is not complete but sufficient as a background for the decision of an OEL. In other cases it would be appropriate to mention the lack of studies/data. Gaps in knowledge that are expected to have an impact on the critical effect should be presented.

A draft criteria document could be written by a single scientist experienced in toxicology or by a group of scientists. There exist good ”instructions to a document author” and/or guidance on how to write criteria document. The draft should then be discussed within a group of experts. It is of great importance that the experts chosen do not have a direct relationship to industry. Representatives from the employers and employees central organisations may attend the expert group meeting as observers.

The expert group may be of ad hoc type or a standing committee. In an ad hoc committee the members are chosen to each meeting depending on their expertise about the substance(s) to be discussed. In a standing committee the evaluations are more similarly for different substances thereby keeping continuity in the decisions.

In some cases the committee itself proposes a numerical OEL value. They are then using different kinds of extrapolation models, not always explained. In my opinion this is not a scientific issue and the numerical value should be decided on a governmental level, especially when the OELs have a legal status. A criteria document which is well drafted and discussed scientifically in a committee to reach a consensus about the conclusions is the best possible background for the decision makers in setting an OEL.

Information retrieval

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Introduction

In this paper, the subject of information retrieval from databases in occupational toxicology is treated. General principles about searching for scientific literature are described and a couple of databases with information on occupational toxicology, biomedicine and chemistry will be presented. The paper is based on experiences from literature searching for the occupational exposure limits criteria work at the Swedish National Institute for Working Life.

General principles in literature searching

Databases

Availability. Modern computerized databases, with a good interface between the user and the system, are necessary prerequisites for a successful search result. The technical communication facilities thus must work and the vendor-customer agreements be fulfilled, e.g. a valid *customer identification code (user ID)*.

Databases with online access. International vendors are supplying different kinds of databases, which are of great value for systematic searching in the scientific literature in order to find ”good” references and to ”cover” a subject of interest. Well developed and powerful search procedures, frequent upgrading and updating, high quality with peer reviewed papers, fast access etc are advantageous and such platforms usually give excellent results on toxicologic or chemical questions. Direct access to the international databases (either online or via Internet, see below) are thus of utmost importance for a successful outcome of information for the criteria work.

Databases on CD-ROM. Many scientific databases are also available on CD-ROMs and may be inexpensive alternatives for searching or they can serve as complements to other electronic information systems.

Internet and the World Wide Web. Internet is growing extensively and is frequently and increasingly used by different groups of information searchers. Most of the scientific databases now are available over the web and the searching is performed in a similar way as online or on CD-ROM. Often, you need a user ID (see above) to get access to the data, even if general information about the system is available to all visitors of the specific web site.

Internet also has platforms for searching by use of ”global” search engines (e.g. Alta Vista), which often can be of value. However, in the case of literature searching for scientific purposes, they should be used with caution, since there is no quality control of the outcome.

Selection by discipline. Selection of a set of *relevant databases* should be done, primarily by discipline (e.g. work environment, toxicology, medicine, chemistry etc.). Up to 5-7 different databases is suggested as an appropriate number.

Selection by structure. Selection of databases can also be done by structure, i.e. *bibliographic databases,* where each record is a literature reference, or *factual databases*, where each record may give information on a specific chemical substance. It is of value to combine different kinds of sources, e.g. you get a summary of compiled physical, chemical and toxicologic information from a factual database and find the original papers and the latest literature from bibliographic databases.

Producers and vendors. The difference between the *producer* of a specific database and the *host* or *vendor,* who makes the database available to customers, should also be noticed. Different vendors have their own user interface; a specific database can thus be accessed in several systems by different methods.

Terminology and searching aids

Search language etc. Once you have access to a set of databases of your choice you need to know the terminology of each system. In *command based systems* a couple of command words are used, for instance S (search), D (display), P (print) etc. On the other hand, in *menu based systems,* questions are given by the system and should be answered by the user. In Internet searching with *search engines* such as Alta Vista you just write some relevant word(s) and the search is performed over the web, resulting in outputs depending on how often the word(s) occur together etc.

Boolean operators. In most of the relevant systems the *Boolean logic operators* AND, OR, NOT can be used. The operator AND combines different concepts and gives hits where two or more separate terms occur in the same record. The operator OR renders search results, where all the records contain at least one of the chosen terms. The operator OR thus widens a search task with alternative words for ”the same” concept (e.g. neoplasms OR cancer). The operator NOT excludes a certain term or set of hits and is often useful when you analyse the search results. The Boolean operators must be written according to the rules of each system, with small letters or capitals or either.

Truncation. The use of *truncation symbols* or *wild cards*, e.g. *, ?, $ etc, means that different suffices or grammatical forms of a word are ”substituted” by the sign and searched together, (e.g. toxic* instead of toxic OR toxicologic OR toxicity etc.). It is important to keep a specific part of the chosen word(s).

Keyword searching. Many databases use descriptive *keywords*; each record thus has a couple of terms attached, which are searchable. In *thesaurus-based* systems

the keywords follow a hierarchical structure of terms grouped together in main categories. The important medical database Medline (see below) is indexed with highly structured keywords, i.e. MeSH-terms (Medical subject headings).

CAS-numbers. The *CAS registry numbers* or chemical identification numbers of chemical compounds, set by the Chemical Abstracts Service of the American Chemical Society, are searchable in many of the databases of relevance here.

Search techniques

The use of a good strategy for searching with specific terms gives the most powerful possibilities for a satisfactory result with an appropriate number of references. The strategy can always be refined and a new searching performed, hopefully with an improved result. If there are few hits, you could try to broaden the search by the use of alternative terms, e.g. specific keywords, truncation etc or choose another database. If you get many hits, you can limit the numbers by further combination of search terms, limitation as to the time period covered, only reviews, only human data etc.

Some databases of value in occupational toxicology

A presentation of a set of *databases* that the author has used on a regular basis in literature searching for the occupational exposure limits criteria work at the Swedish National Institute for Working Life will now follow.

Bibliographic databases

Arbline[1] is produced by the library of the National Institute for Working Life; Arbline constitutes its public catalogue. At present, Arbline comprises about 65 000 records on work environment and other branches of working life. Many scientific papers from Sweden and other countries are included as well as books, conference publications, criteria documents etc. The references are indexed according to the thesaurus of the library.

Arbline is available via Internet; unfortunately you cannot, at present, use the CAS-numbers for search in this form of the database. You cannot borrow the documents from abroad, but Arbline could still be useful as a reference tool, and you may find the internationally published papers via local libraries.

Nioshtic is produced by the US National Institute for Occupational Safety and Health (NIOSH). The version of Nioshtic used by us at present is the OSH-ROM from SilverPlatter Information Ltd; Nioshtic is one of six different databases with

[1] The database Arbline has recently been remodelled and is now available at http://www.arbetslivsinstitutet.se/biblioteket/english/default.asp. CAS registry number are now searchable in Arbline. At present, Arbline comprises nearly 73 000 records; many of the new records are linked to full text electronic sources.

over one million records. Nioshtic and the updated database Nioshtic-2 are available from several other vendors, too.

Toxline is produced by the US National Library of Medicine (NLM) and contains literature on toxicologic and biologic effects of drugs and other chemicals. Toxline is available from several vendors online and on Internet as well as on CD-ROM (e.g. SilverPlatter Information Ltd). The database now includes over one million records.

Medline and its Internet version PubMed, where searching is done for free, are produced by NLM. Medline is the most distinguished database in biomedicine with over 11 million records. The excellent index system (MeSH-terms) used in Medline and related databases has already been mentioned. Medline is available from several vendors online, via the Internet and on CD-ROM.

Chemical Abstracts is produced by the American Chemical Society. It is the largest database on chemical information and includes over 18 million records. Chemical Abstracts is made available by STN International (the Scientific and Technical Information Network) as well as by several other vendors.

Factual databases

Cheminfo and *Registry of Toxic Effects of Chemical Substances* (RTECS) are two important factual databases on chemical substances, available as CD-ROMs from the Canadian Centre for Occupational Health and Safety (CCOHS).

Cheminfo is produced by CCOHS; the database summarizes occupational health and safety information on over 1 300 chemicals of importance for work environment. Cheminfo is also available on the Internet.

RTECS is compiled by NIOSH and comprises toxicologic information, including exposure limits etc, for over 140 000 chemical substances. RTECS is also available online and on the Internet.

Registry file is related to Chemical Abstracts; it is a factual database where chemical structures, CAS-numbers etc can be found. Registry file covers about 32 million substance records.

Suggestions on search strategy in the exposure limits criteria work

When you begin a new task to summarize the biomedical information on a specific chemical compound, you should first check the basic information from a factual database, e.g. Cheminfo, RTECS etc. Try to find the relevant CAS-number(s), which are of great value in further searching; you may find the correct numbers in databases, handbooks or catalogues.

In the next step, you should search for reviews on the state-of-knowledge of the subject, for instance by search in a specific database (Toxline or Nioshtic) for criteria documents, reviews or summaries. Please, note that in some of the versions of Nioshtic, the CAS-numbers should be written without hyphens. At this step, you may find some distinct keywords, MeSH-terms, alternative search terms,

specific toxic effects etc, and another search in the same database as well as in other available databases should be performed. In databases on work environment, you could make combinations with search terms from *toxicology*. In a medical or toxicologic database, you could instead include *occupational* or *work* related terms etc. You should also try to *widen* the search, using the operator OR between terms of similar meanings, and take advantage of the *truncation* possibilities. The different search steps may be structured together, e.g.:

- 107-13-1 or acrylonitrile
- toxic* or adverse or poison*
- cancer* or carcinog* or tumour* or neoplas*
- epidemiolog* or cohort.

Further, in the next step, you should make combinations of different sets of hit, using the operator AND (e.g. #1 and #2 and #3 and #4). Browse the references and look for relevant terms that could be used, while still on session. If you find new interesting references, you can easily exclude those, which already have been printed (or downloaded) with the operator NOT. The references are preferably printed with the abstracts, and the search strategy should also be printed.

After the search session, the references should be analysed; this is quickly done because the input terms often are ”highlighted”. You could enter the system again for an iterative search directly or later.

At last, the relevant original documents should be obtained via your library or from electronic document suppliers etc. The *reference lists*, especially from the latest published papers, are other important sources for references.

General summary and concluding remarks

In this paper, an introduction into information retrieval and a presentation of some databases of value for the occupational exposure limits criteria work have been treated. Factual databases give basic information on a specific chemical substance that can be used for further searching in the large scientific databases recommended. With this strategy you can easily learn about the accepted knowledge on the chemical(s) of interest as well as find the latest scientific information.

Finally, good routines for document delivery are another important matter. Today, many electronic document systems offer automatic delivery of their papers, if you have a subscription, but that topic will not be further dealt with here.

Setting occupational exposure limits in the European Union

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Abstract

The objective of setting occupational exposure limits (OELs) in the European Union (EU) was introduced into EU legislation some 20 years ago. In 1991, the first set of 27 indicative limit values (ILVs) was proposed by the European Commission (EC). At about the same time, the EC assembled a group of independent scientists concerned with the derivation of OELs. In 1995, the status of this group was formalised into the Scientific Committee on Occupational Exposure Limits (SCOEL).

The SCOEL plays a key role in setting OELs in the EU. This committee recommends to the EC "health-based" or "pragmatic" OELs. "Health-based" OELs are recommended for chemicals for which a threshold dose for adverse effects can be identified, and "pragmatic" OELs for chemicals for which such a threshold dose is assumed not to exist. Special attention is paid to the way in which the SCOEL evaluates carcinogens.

A separate committee, the Advisory Committee for Safety, Hygiene, and Health at Work (ACSHH), consisting of representatives from governments, employers' organisations and trade unions, evaluates the feasibility of the introduction of OELs recommended by the SCOEL. This committee recommends operational OELs to the EC that ultimately sets and promulgates ILVs or binding limit values. ILVs are set for chemicals with "health-based" OELs that are considered not to entail feasibility problems. Binding limit values are set for chemicals with "pragmatic" OELs as well as for chemicals with "health-based" OELs that, for the time being, are considered unfeasible at the workplace.

A personal view is presented on the use of deficient databases by the SCOEL, and on some aspects of the working-methods and membership of the SCOEL.

Introduction

Occupational exposure limits (OELs) have been a rather common feature of the industrialised world for the past 50 years or so (3, 12). They were 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 atmosphere (3).

The objective of setting OELs in the European Union (EU) was introduced into EU legislation by Council Directive 80/1107/EEC, later on amended by Council Directive 88/642/EEC, dealing with the protection of workers from risks related to exposure to chemical, physical and biological agents at work (3). Under this Directive, two types of OELs were defined, binding limit values and indicative limit values (ILVs). In 1991, the first set of 27 ILVs was proposed by the European Commission (EC) and agreed by Member States on the basis of pre-existing national positions. At about the same time, the Commission assembled an advisory group of independent experts in the various disciplines concerned with the scientific issues related to the derivation of OELs. This group of scientists from the various Member States began its work in 1990. In 1995, the status of this group has been formalised by its maturation into the Scientific Committee on Occupational Exposure Limits (SCOEL) via Commission Decision 95/320/EC. In 1998, the importance of setting OELs in the EU was underlined by the adoption by the Council of Directive 98/24/EC, dealing with the protection of the health and safety of workers from risks related to chemical agents and defining the role and legal status of exposure limits (3).

The major task of the SCOEL is to study all available relevant scientific documentation on the toxicological and other relevant properties of chemicals, and to recommend to the EC substance-specific OELs. A crucial aspect of the OELs recommended by SCOEL is that they are based on toxicological and other health sciences-related data and considerations only. Next, technical and socio-economic feasibility aspects of the OELs recommended by SCOEL are discussed in a separate committee, the Advisory Committee for Safety, Hygiene, and Health at Work (ACSHH).

The present paper describes the general procedure for setting OELs in the EU, with emphasis on the role and the activities of the SCOEL. Special attention is paid to the way in which the SCOEL evaluates carcinogens. A personal view is given on aspects such as incomplete databases, intra- and inter-committee inconsistencies, consensus about committee decisions for instance on limit values, advantages of a permanent (versus an occasional) committee, and selection of committee members.

Objectives and uses of OELs

The objective of establishing OELs is to set limits for exposure to chemicals via the airborne route such that exposure, even when repeated on a regular basis throughout a working life, will not lead to adverse health effects in exposed workers and/or their progeny at any time, as far as can be predicted from the contemporary state of knowledge. Generally, the OELs recommended by SCOEL represent the highest exposures which are regarded by SCOEL to be consistent

with the above health criteria (3). However, in some cases it is not possible to recommend an OEL that meets these health criteria. Therefore, SCOEL distinguishes two categories of OELs: "health-based" and "pragmatic" OELs. *"Health-based" OELs* are established in those cases where a review of the available scientific data leads to the conclusion that a clear threshold dose can be identified below which exposure to the chemical in question is not expected to result in adverse health effects. "Health-based" OELs will ultimately lead to the promulgation of ILVs by the Commission, provided no feasibility problems are expected at the workplace. When for the time being the introduction of a "health-based" OEL entails feasibility problems, the EC will set and promulgate a binding limit value. *"Pragmatic" OELs* are established in cases where it must be assumed that any level of exposure to the chemical in question, though small, might carry some finite risk. Examples of properties for which it may not be possible on the basis of current knowledge to define a threshold of activity are mutagenicity, genotoxic carcinogenicity and respiratory sensitization. For chemicals possessing such properties, ultimately binding limit values will be set that are considered to carry an accepted (low) level of risk (3, 8).

When setting OELs, Member States should take ILVs into account but they are not legally bound to set the same limit values. With respect to binding limit values, Member States are legally bound to include them in their own legislative regulations concerning exposure to chemicals at work.

The principal intended use of OELs is to provide standards or criteria against which measured exposure levels in workplaces may be compared in order to ensure that actual exposures are low enough and control is adequate to protect health. OELs 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 one (3). Correct and appropriate use of OELs in practice requires expertise and experience, particularly in situations where there is exposure to more than one substance, where routes of exposure other than inhalation may be significant or where working patterns are non-standard (3).

General procedure for setting OELs in the European Union

Scientific Committee on Occupational Exposure Limits (SCOEL)

General approach

The SCOEL has adopted a "case by case" approach to the setting of OELs, considering each substance individually. The SCOEL recommends to the EC either "health-based" or "pragmatic" OELs. Such recommendations are based on reviewing all available toxicological data and data on other relevant properties of the chemical in question. Key elements of such a review are:

- adequacy of the data base,
- establishment of the (nature and severity of) adverse effect(s) critical for deriving the OEL. Are the critical effects local or systemic? Are they caused by parent molecules or by metabolites? Are data available on the mechanism and kinetics of absorption, distribution, metabolism and excretion? Are they well characterised and well understood in terms of extrapolation from animals to man or are they rather unusual? ,
- identification of the relevant study characterising the key effect(s) and judgement of the quality of the key studies. To which extent is there qualitative and quantitative agreement between different animal studies or between findings in animals and humans? Are particular groups of people likely to be at special risk?,
- establishment of whether the chemical acts via a non-threshold or a threshold mechanism,
- assessment of the dose-response relationship for the key effect(s) including the "no-observed-adverse-effect-level" (NOAEL) or "lowest-observed-adverse-effect-level" (LOAEL) for chemicals for which a threshold mechanism of action is assumed,
- setting an 8-hour time weighted average (8 hour TWA) OEL for "health-based" OELs (see also the section on preferred values),
- calculating the cancer risk at specific exposure levels for non-threshold genotoxic carcinogens (see also the section on carcinogens and mutagens),
- establishment of a "short-term exposure limit" (STEL) if needed,
- assignment of a skin notation if deemed necessary, and
- finally documentation of the entire process. For each individual OEL the rationale will be set out in sufficient detail for the logic to be understood by other professionals in the field, taking especially note of the choice of the size the uncertainty factor (3).

Since a draft of the final (summary) document is made publicly available, the final summary document incorporates public comments if considered relevant. Finally, the definite summary document is published by the Office for Publications of the European Communities (OPOCE) in Luxembourg.

For details on the criteria the SCOEL applies in carrying out its task, in particular with regard to establishing the relationship between exposure level and health effects, the reader is referred to EC (3).

Preferred value system

As a general rule, for recommendations of "health-based" 8 hour TWA OELs, SCOEL will use preferred values, implying that OELs will be rounded up or down to decimals of the integers 1, 2 or 5 ppm or mg/m^3 for instance 0.05, 0.1, 0.2, 0.5, 1, 2, 5, 10 or 50 ppm or mg/m^3 etc. SCOEL believes that further discrimination, resulting in proposals falling in-between any two of these integers or their decimals, would suggest a precision that is unjustifiable in view of the limitations of the data base for the vast majority of the substances discussed and the uncertainties involved in toxicological extrapolations (3). However, the use of

the preferred value approach is not undisputed. Occasionally, representatives from industry have criticized its use, arguing that preferred values have no scientific basis and may lead to toxicologically unnecessarily low values. Indeed, the Dutch Expert Committee on Occupational Standards does not use this system (10), whereas some other committees on setting OELs such as the German "MAK Kommission" (Senatskommission zur Prüfung gesundheitschädlicher Arbeitsstoffe) and the international committee on Updating of Occupational Exposure Limits do use the system (2, 5).

Carcinogens

For (most genotoxic) carcinogens for which, on the basis of current scientific knowledge, it is not possible to identify levels of exposure below which there is no cancer risk, SCOEL will estimate degrees of cancer risk at various exposure levels, if the data base allows to do so. This will lead to the recommendation of a "pragmatic" OEL and finally to a binding limit value.

In addition to recommending to the EC "pragmatic" OELs for such "non-threshold" carcinogens, the SCOEL may also be requested by the EC to assist the Commission in setting numerical limit values for such carcinogens by examining existing scientific dossiers, examining and commenting on any proposals from the Commission, and generally in advising the Commission in the light of the most recent state of occupational medical and toxicological knowledge (3).

For (non-genotoxic and indirectly acting genotoxic) carcinogens for which it might be possible to identify a threshold of activity, the SCOEL will recommend "health-based" OELs, provided adequate data are available. For these "threshold" carcinogens, OELs are derived, using the procedure for non-genotoxic/non-carcinogenic chemicals, and, thus, are primarily based on NOAELs or LOAELs for the relevant adverse effect (3). For this category of carcinogens eventually ILVs may be established (8).

Advisory Committee for Safety, Hygiene, and Health at Work (ACSHH)

The ACSHH, the so-called Tripartite Committee, discusses and evaluates the technical, social and economical feasibility of the introduction of OELs recommended by SCOEL. This committee consists altogether of six representatives, two each from governments of Member States, employers' organisations, and trade unions. The ACSHH recommends OELs to the European Commission that ultimately sets and promulgates the ILVs or binding limit values (8).

Incomplete databases

It is not exceptional that the available toxicological database for a widely produced chemical or even for a high-production-volume chemical is incomplete. Nevertheless, experts may decide to recommend an OEL, using their expertise and experience and applying a relatively large uncertainty factor to compensate

for the lack of information. In other cases, the experts may regard the database as being too poor to justify the recommendation of an OEL. Although the kind of deficiency may vary widely, in my view conspicuous and serious deficiencies are the absence of repeated-exposure inhalation and reproduction toxicity studies.

With respect to the lack of *inhalation toxicity studies*, route-to route extrapolation e.g. using the data from oral toxicity studies, cannot always be applied, for instance when the critical effect of a chemical in all likelihood is local irritation. Moreover, route-to-route extrapolation should be regarded as a necessary evil anyway.

The definition of OEL includes protection of workers' progeny (3). However, although *reproduction toxicity studies* are lacking, often OELs are recommended and finally ILVs or binding limit values are set. This is in my view a serious shortcoming of the entire procedure unless the available toxicological data make it most unlikely that effects on reproduction will occur at the recommended OEL. The seriousness of the lack of data from reproduction studies is known for a long time. Koëter (6) examined the data bases of 37 chemicals and found that for 35% of the compounds parameters related to fertility and reproduction were more sensitive than those measured in adequate subchronic toxicity studies. Obviously, fertility and reproduction appear to be sensitive parameters that should be included in toxicity testing at a relatively early stage (7).

Inconsistencies

Inconsistencies in the way OELs are derived within a committee such as SCOEL may creep in and differences between committees in OEL values for the same compound and based on a very similar database do occur. Clearly, the setting of "health-based" or "pragmatic" OELs should be as consistent as possible but consistency in my view should not be a "goal in itself". There is little consensus about the way to achieve consistency (4). There is some support for a uniform system for the evaluation of substances: a classification by type of effects and types of studies, and using more or less fixed correction, extrapolation and uncertainty factors (1, 9). The weakness of such a system is that it may not be used as a supplement to, but at the expense of the input of expertise and experience. Hundreds of evaluations conducted over the years have shown that expertise and experience in various disciplines (and sub-disciplines to be called up if necessary) thrown together within groups of dedicated experts are indispensable for proper evaluations (4). Databases differ both qualitatively and quantitatively, are often far from complete, and contain studies that vary widely in their relevancy and adequacy. The consultative process nearly always involves intense discussion on matters such as the toxicological relevance of certain effects, the overall "no-observed-adverse-effect-level" and the size of the uncertainty factor to be used. It is my conviction that fixed factors for all kinds of (theoretical) situations are not very helpful and cannot guarantee objectivity. In my view, OELs

should be based on reliable and relevant data evaluated by groups of competent, experienced and dedicated individuals with expertise in different disciplines (4, 11). When this leads to inconsistencies within or between committees, so be it.

Consensus on committee decisions

As mentioned above, the key elements of a committee like the SCOEL are experienced individuals with expertise in different relevant areas, discussing the available data on a personal basis *with the intention to reach consensus*. The discussions may be trenchant and feelings may run high but consensus is nearly always reached on the basis of convincing argumentation. To reach consensus may take a couple of meetings, the "time-out periods" being used to collect additional data or to consult other experts. The "time-out period" is a practical way to avoid minority views, and to offer the opportunity to re-study reports and papers. In my experience, an OEL is hardly ever recommended after a single SCOEL meeting. All of a sudden a member may raise a question or touch upon an aspect that so far has not or insufficiently been considered but which turns out to be of major relevance. So, in my opinion, a "time-out period", which is the rule rather than the exception, is indeed extremely helpful among other things to avoid minority views (4).

Advantages of a permanent committee and selection of its members

In my perception, there is quite a difference between permanent (standing) and occasional (*ad hoc*) committees. Members of standing committees such as the SCOEL gradually get to know each other, learn each others' expertise and are willing to accept each others' peculiarities, all of which promotes mutual confidence and a relaxed atmosphere. Such settings warrant openness and a vulnerable attitude during the debate, leading to optimum results.

What type of individuals is needed in a committee such as the SCOEL? The best one in each discipline but with (a) at least a feeling for and some experience in risk assessment and standard setting, (b) the willingness to listen to their fellow members' scientific arguments and to look for consensus, and (c) the willingness, time and opportunity to study documents and to attend the SCOEL meetings. Thus, expertise, experience, dedication and opportunity (rather than social background and position) should be the major criteria for selecting the members of such committees. When a member is not genuinely interested in doing a good job, this is extremely disturbing and insulting to the other members, and also irresponsible towards workers and the society in general. Thus, the selection of committee members is a rather important issue (4).

Concluding remarks

Standard-setting is time-consuming, and thus, a costly operation. Therefore, the use by SCOEL of criteria documents and other relevant reports available in Member States should be encouraged, and co-operation with the Existing Chemicals Programme should be streamlined and intensified. Indeed, for the risk assessment of occupational exposure the SCOEL should be involved in this Programme early on in the process. To achieve this the necessary skilled man-power and pecuniary means should be made available to the responsible unit of Directorate-General V in Luxembourg.

Since occupational standard setting in the EU has moved into an era in which standards are expected to be supported by detailed toxicological evidence, more complete databases and more workplace-oriented fundamental and applied toxicological studies are warranted.

As a standing committee of independent scientists, the SCOEL plays a key role in setting OELs. Therefore, the EC and the Member States should do their utmost in looking for and finding qualified, dedicated members for the SCOEL.

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Setting occupational exposure limits in the Netherlands

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Abstract

In the Netherlands, occupational exposure limits (OELs) are established according to a three-step procedure. *In the first step*, the Dutch Expert Committee on Occupational Standards (DECOS) establishes a health-based recommended (HBR)-OEL, using toxicological and other health sciences-related data and considerations only. The HBR-OEL is finalised and published not until the draft report (containing the recommended value for the HBR-OEL) has been made public and sent to experts who are invited to comment. *In the second step*, the Subcommittee on MAC (maximum accepted concentration) values (that consists of representatives of employers' organisations, trade unions and governmental departments and which is a subcommittee of the Social Economical Council of the Netherlands) evaluates the technical and social-economical feasibility of the introduction of the limit values recommended by DECOS. The Subcommittee on MAC values recommends operational MAC values to the Minister of Social Affairs and Employment who, *in the third (administrative) step*, sets and promulgates the definitive MAC values that have force of law.

In addition to classification and labelling of carcinogenic substances, health-based calculated occupational cancer risk values (HBC-OCRVs) are established by DECOS for non-threshold (genotoxic) carcinogens.

Areas of attention highlighted in the present paper are discrimination between sensory irritation and olfactory stimulation, desirability of dermal exposure limits, and lack of reliable exposure data.

An international project (initiated by the Netherlands) that deals with the re-evaluation of over 150 MAC values suspected of having no sound toxicological basis and/or offering insufficient protection to workers, is briefly discussed.

Introduction

The first occupational exposure limits (OELs) were published in Germany in 1887. Since then lists of OELs have been issued in the USA and in several European countries. The first list of threshold limit values (TLVs) of the American Conference of Governmental Industrial Hygienists (ACGIH) appeared in 1947. In the Netherlands, the ACGIH TLV list was used until 1978 when the

Directorate-General of Labour of the Ministry of Social Affairs and Employment (MSAE) published the first official list of maximum accepted concentrations (MACs) which was largely similar to the ACGIH TLV list of 1977 (24). Since 1978, new MAC values have been established in the Netherlands according to a three-step procedure, comprising a first health-based step, a second feasibility step, and a final administrative step (24).

OELs may contribute a great deal to attaining and maintaining a good quality working environment and, thus, to the health and well-being of people at work, provided OELs are introduced and applied in a proper and realistic way by taking into account possible implementation problems which may necessitate a stepwise introduction (20).

Key elements of a procedure for setting OELs are toxicological data, a permanent committee of experienced experts in various disciplines of health sciences, a separate standing committee for the evaluation of technical and socio-economic feasibility of limit values recommended by the health experts, indeed strict separation of health and feasibility considerations, transparency of the whole process, and, finally, OELs that have force of law (7).

The present paper briefly describes the Dutch three-step procedure for setting MAC values, highlights the classification and hazard assessment of carcinogens, and addresses some areas of concern such as the question whether the entire procedure is too time consuming, the potential problem of confusing olfactory stimulation and sensory irritation, and lack of proper exposure data. In addition, an international project initiated by the Netherlands in 1997 that deals with the re-evaluation of the health aspects of about 150 "old" MAC values suspected of having no sound toxicological basis or offering insufficient protection to workers, is briefly discussed.

The Dutch three-step procedure

Before describing the three-step procedure, it may be stressed that this procedure is used for both carcinogenic and non-carcinogenic substances, and that in the first step health-based limit values are recommended for all chemicals except for subcategory Ia (genotoxic) carcinogens. For Ia carcinogens exposure-(tumour) response relationships are established and cancer risk values are calculated (see next section on carcinogens).

In the *first step*, the Dutch Expert Committee on Occupational Standards (DECOS) establishes a health-based recommended (HBR)-OEL. DECOS is a permanent committee of the Health Council of the Netherlands (HCN), one of the major scientific advisory boards for the government. Under the responsibility of DECOS, a criteria document is produced and published that contains data on the toxicological and other relevant properties of chemicals, a critical evaluation of these data and also the HBR-OEL. A draft of the criteria document, called the Public draft document, is submitted for comments to experts from industry and

trade unions, and in fact is available to experts world-wide. DECOS studies all comments submitted and, if these are considered relevant, alters the draft document accordingly. If the changes are significant, including a different value for the HBR-OEL, the draft document goes public again. Finally, the criteria document is published by the HCN. The two crucial aspects of this first step are: the HBR-OEL is based on toxicological and other health sciences-related data and considerations only, and the HBR-OEL is finalised and published not until the draft criteria document has been made public to experts who are invited to comment (6).

In the *second step*, the Subcommittee on MAC values, a permanent committee of the Social Economical Council, discusses and evaluates the technical, social and economical feasibility of the introduction of the HBR-OEL. This Subcommittee consists of representatives of employers' organisations, trade unions and governmental departments. The Subcommittee recommends an operational MAC to the MSAE. This recommendation, complete with argumentation, is publicly available. A major aspect of this second step is that it shows whether the recommended MAC value is identical to the HBR-OEL, and if not, the reason for the difference (6, 8).

In the *third step*, the MSAE sets and promulgates the MAC values. Clearly, the aim is to have all MAC values identical to the HBR-OELs, preferably right from their introduction but if this is not feasible, then in the foreseeable future (6, 7, 8).

Carcinogens

Classification

Since 1978, in the Netherlands, carcinogens have been classified into two broad categories viz. genotoxic (category I) and non-genotoxic (category II) carcinogens (10, 15, 18). In 1996 (11), category I carcinogens have been divided into two subcategories, subcategory Ia and subcategory Ib. Subcategory Ia carcinogens act *via* stochastic processes i.e. the carcinogens themselves or one of their metabolites can bind directly to DNA, leading to an irreversible DNA modification, with the implication that no threshold dose can be derived below which the carcinogen would be expected not to induce cancer. Examples of such carcinogens are vinyl chloride, benzo(a)pyrene and chromium VI compounds. Subcategory Ib carcinogens can induce DNA damage via indirect processes such as for instance inhibition of DNA repair enzymes or elevation of endogenous free-radicals, with the implication that a threshold for genotoxicity, and thus, also for carcinogenicity can be assumed. Examples of such carcinogens are arsenic, cadmium compounds and crystalline silica (11, 17). Non-genotoxic (category II) or epigenetic carcinogens do not induce irreversible DNA modifications and act by a non-stochastic mechanism such as for instance stimulation of cell growth or gene expression, implying that for these carcinogens a threshold dose can be derived (11). In those (exceptional) cases where the available data on carcinogenicity and mutagenicity

do not allow classification, but a quantitative cancer risk assessment is nevertheless deemed desirable, precautionary such a substance is treated as if it were a Ia carcinogen. An example is wood dust (12, 22). This classification system is generally accepted in the Netherlands as the scientific basis for the regulation of carcinogenic substances.

In addition to this system for the classification of carcinogens, the Netherlands use a labelling system as required by the European Union (EU). This labelling system uses standard phrases based on the above distinction between category I (genotoxic) and category II (non-genotoxic) carcinogens. The standard phrases, which are meant to be informative refinements of the EU classes, are presented in Table 1.

Health-based calculated occupational cancer risk values (HBC-OCRVs) for subcategory Ia genotoxic carcinogens

For genotoxic carcinogens without a threshold (subcategory Ia carcinogens) in the Netherlands, the linear multistage, non-threshold model is used to extrapolate linearly from the lowest dose showing excess tumours in animals or humans (11, 23). The rationale for extrapolating from the lowest dose is that at higher doses

Table 1. Standard phrases used for classification of carcinogens in the Netherlands.

Standard phrases	Comparable with EU class
This compound is known to be carcinogenic to humans • it is a genotoxic carcinogen • it is a non-genotoxic carcinogen • its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is a genotoxic carcinogen.	1
This compound should be regarded as carcinogenic to humans • it is a genotoxic carcinogen • it is a non-genotoxic carcinogen • its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is a genotoxic carcinogen.	2
This compound has been extensively investigated, but there is insufficient evidence of a carcinogenic effect to warrant a classification as "known to be carcinogenic to humans" or as "should be regarded as carcinogenic to humans". It is a suspected human carcinogen.	3(A)
This compound has been insufficiently investigated. While the available data do not warrant a classification as "known to be carcinogenic to humans" or as "should be regarded as carcinogenic to humans", they indicate that there is a cause for concern. It is a suspected human carcinogen.	3(B)
This compound cannot be classified.	not classifiable

the shape of the dose-response curve could be affected by toxicity. Other extrapolation models can be used for Ia carcinogens, if there are convincing data that such a different approach is more appropriate (23). DECOS uses a standard procedure for the derivation of the so-called health-based calculated occupational cancer risk values (HBC-OCRVs) for subcategory Ia carcinogens (9). The major elements of this procedure are selection of the key study, calculation of the carcinogenic activity expressed as incidence per unit daily dose or per unit air concentration (in principle using the linear, multistage, non-threshold extrapolation model), and then calculation of the HBC-OCRV i.e. calculation of the additional lifetime cancer risk in workers (= humans exposed at the workplace). For this latter calculation DECOS assumes that humans weigh 75 kg, live 75 years, and inhale per day 18 m^3 of air, and that workers are exposed 8 hours per day, 5 days per week, 48 weeks per year for 40 years and inhale 10 m^3 of air during an 8-hour working day. Using the HBC-OCRV, DECOS finally calculates air concentrations associated with two reference lifetime cancer risk levels for workers viz. 4×10^{-3} (upper or ban level) and 4×10^{-5} (target level). These reference cancer risk values for the workplace have been defined by the MSAE. For details of the various calculations the reader is referred to HCN (9). It may be emphasised that for establishing HBC-OCRVs the three-step procedure described above is fully applied, including a public draft document and a criteria document published by the Health Council, followed by the second *feasibility* step and finally the third *administrative step* in which the Minister establishes a legally binding occupational exposure limit.

Ordinary MAC values for subcategory Ib and category II carcinogens

For subcategory Ib and category II carcinogens (carcinogens for which a threshold value can be established; see above) HBR-OELs and MAC values are established, using the "No-observed-adverse-effect-level/Uncertainty factor" approach which is also applied to non-carcinogens (9, 11).

Procedure too time consuming?

The complete procedure for setting a MAC value may take several years. Such a long period of time is incompatible with concepts of speed, forcefulness, promptness and responsiveness (19). However, in my view carefulness and quality should prevail in order to maintain the credibility of both the process and the experts involved, and, most importantly, the credibility of the established MAC values. Since there are always constraints of finance and the availability of experienced and skilled manpower, fewer carefully established MAC values are to be preferred over more MAC values of doubtful repute. Moreover, the relatively long period between the publication of the (draft) HBR-OEL and the setting of the legally binding MAC value gives industry the opportunity to think about or to take already measures, if necessary, to meet the new (lower) value. When reliable

exposure data clearly show that a (much) lower exposure limit than the one being discussed by DECOS would not involve any technical or economic difficulty, it has been suggested (5) that it would save time to stop the discussion and to immediately recommend a low (exposure-based) OEL. In my view such a pragmatic approach should not be pursued and DECOS should complete its deliberations and recommend a health-based OEL. Of course in step two or three of the procedure an exposure-based MAC value can be suggested or set without compromising the process.

Olfactory stimulation not to be confused with sensory irritation

Both odour (olfactory stimulation) and sensory irritation (trigeminal nerve stimulation) are chemosensory effects. They serve as warning signals and do not lead to cell or tissue damage. An unknown odour is a warning signal to which we do not have an appropriate response; it may cause uneasy arousal but odour *per se* does not make us sick. A known odour very often does not lead to uneasy arousal because we know the (absence of) consequences; this is so-called positive bias. Sensory irritation is characterized by a burning sensation in the nose and inhibition of respiration from that site; clearly it is an adverse effect. Since in the literature a clear-cut distinction between odour and irritation is not always made, this may be a source of confusion, in particular when we are confronted with an irritant with a strong odour. At present a number of objective methods is available to distinguish between sensory irritation and olfactory stimulation (1, 3). To be able to make such a distinction is important for a correct interpretation of the chemosensory effects of chemicals. For a correct interpretation of these effects it is also crucial to understand the difference between *adaptation* and *habituation*. *Adaptation* is the decrease in sensitivity to a prolonged stimulus; once adapted to a certain stimulus there is no longer an effect of this stimulus; however, an adapted status is to be considered an unwanted status. *Habituation* is the decrease in responsiveness to a prolonged or repeated stimulus; this is an unconscious coping behaviour which is subject to cognitive influences; the stimulus is still there but since we are used to it and we know that it does not harm us, we do not notice it anymore. In my experience, in studies on chemosensory effects both phenomena are often mixed up which may lead to wrong conclusions. The major flaw is that when adaptation is reported, it may in fact be habituation, which means that there is no adaptive response (1, 4).

Dermal exposure limits

For workers, a major route of exposure is through the skin. However, no dermal occupational exposure limits (DOELs) exist. What does exist is the so-called “skin notation” which is a warning system against substantial absorption of a chemical through the skin, implying that the MAC value of the chemical in question may

not sufficiently protect the worker against its toxic effects. At the request of the Dutch Ministry of Social Affairs and Employment, a concept has been developed for setting health-based DOELs (2). A DOEL limits the amount of a chemical on the skin, (external dermal exposure) and consequently limits the potential dermal uptake of a chemical. The establishment of a DOEL is based on either the percentage skin absorption (estimated for a specific dermal exposure area) or on skin absorption rate (= the flux defined as the skin permeability constant multiplied by the concentration gradient across the stratum corneum; in fact Fick's first law of diffusion). Recently, a Committee of the Health Council of the Netherlands published a draft report dealing with the possibilities of regulating dermal occupational exposure (16). In addition to the "skin notation" and the DOEL, the Committee discusses the use of biological limit values (BLVs). A BLV limits the total amount of a chemical taken up by the body, and thus is a limit value for the total internal "toxic load" of that chemical. The Committee recommends to use BLVs whenever possible, recognising that the data and methods of analysis allowing the derivation of BLVs are often lacking. The Committee realizes that this is often also true for the derivation of a DOEL, implying that the derivation of a MAC value with "skin notation" is the only realistic alternative. Finally, the Committee developed a four-step procedure to find out whether the assessment of the health risk from dermal exposure to a specific chemical has high, medium or low priority (16).

Lack of reliable exposure data

Without reliable data on exposure OELs cannot be used to characterize the potential health risk of workers. Moreover, in the past deliberate and systematic underreporting of occupational exposures has occurred with rather serious consequences for the interpretation of epidemiological studies, using these flawed exposure data, particularly in case of "positive" results. *"The only problem in human exposure assessment is the lack of knowledge and information"* as stated by Marquart *et al*. (21)! Very often data are lacking on the form and way in which a substance is being used, rendering exposure assessment very difficult. Data on (measured) exposure levels are often very limited or completely absent, indicating the necessity to use models for exposure assessment. However, most models lack validation, occasionally leading to outcomes which differ remarkably depending on the model applied. Obviously, substantial efforts are needed to improve worker exposure assessment. "Learning by doing" and "learning by example" are processes that eventually will improve exposure assessment (21).

Health-based reassessment of MAC values

At the request of the MSAE, in 1995 TNO Nutrition and Food Research (Zeist, the Netherlands) assessed the degree of health protection of the MAC values of

almost 300 substances as published in the (Dutch) MAC list of 1994. Most of these MAC values were borrowed from the ACGIH TLV list, and they were suspected of having no sound toxicological basis or offering insufficient protection to workers (14). TNO concluded that for 109 substances the MAC value was too high from a health protection point of view, with deviations ranging from a factor of 2 to 250. For another 106 substances the toxicological data base was judged to be too poor to justify the recommendation of a health-based OEL (13). In 1997, the MSAE requested the HCN to re-evaluate these substances in a condensed procedure and to recommend health-based OELs. The MSAE further requested the HCN to invite scientists from outside the Netherlands to participate in this re-evaluation project (13).

After consultation of several regulatory authorities of European countries, in 1997 the HCN formed an international committee (Committee on Updating of Occupational Exposure Limits) of acknowledged experts in toxicology, epidemiology or occupational medicine, with experience in setting OELs. The committee consisted of 12 members from eight different countries, one corresponding member, one advisor from the MSAE, one observer from the HCN, and one scientific secretary of the HCN. All members were invited *à titre personnel*, except for the corresponding member representing ACGIH. Except for some minor details, the committee followed a procedure for establishing HBR-OELs very similar to the first step of the Dutch three-step procedure for setting OELs (see above), including the production of a public draft document and a final criteria document published by the HCN. This criteria document will then be used by the Subcommittee on MAC values to recommend an operational MAC value, and finally the Minister will set a legally binding MAC value.

In the end, the MAC values of about 150 substances were re-assessed (13). In August 2001, the final reports (criteria documents) for 17 substances have been published; it is expected that the reports of the remaining substances will be completed in the course of 2003.

Concluding remarks

Occupational standard-setting should be a continuing activity because OELs may contribute a great deal to attaining and maintaining a good quality working environment. Indeed employers and employees are guided by standards. Crucial aspects of a procedure for setting OELs are transparency of the entire process and strict separation of health and feasibility considerations. Moreover, OELs should be legally binding. For those genotoxic carcinogens for which an exposure level without any cancer risk is assumed not to exist, so-called non-threshold carcinogens (subcategory Ia carcinogens), in the Netherlands lifetime cancer risk values for workers are calculated, using a linear, multistage, non-threshold extrapolation model. An international project initiated by the Netherlands in 1997 deals with the re-evaluation of the health basis of the MAC value of a substantial

number of chemicals. These MAC values were suspected of having no sound toxicological basis or offering insufficient protection to workers. Ultimately, the MAC values of about 150 chemicals were re-assessed. For a considerable number of these chemicals the data base was found to be too poor to justify the recommendation of a health-based OEL or even to comment on the existing MAC value in terms of (much) too high or about right.

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Occupational exposure limits in Sweden - socioeconomic and technological aspects

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Introduction

Sometimes there is a thinking that the Nordic countries have the same system preparing limit values. There is a Nordic way of looking upon the problem in the field of Occupational Safety and Health, maybe also some similarities in the systems preparing the occupational exposure limits (OELs), but there are also differences in decision-making. What is described is the Swedish model as it has worked in the past, and is working today. Which model that will be used in the future, nobody knows.

Discussing OELs, and the way they are issued, demands that the legal ground for the limit values is defined. It is not useful to compare different values if their legal background differs from binding regulations to recommendations. For a number of substances different countries have issued different values. One of the reasons could be that the limit value in one country is mandatory but in another is just a recommendation/guidance. This will, from natural reasons, have implications on the value decided.

There is also a need to describe, or be aware of, the ”environment” in which the limit value is valid. The Swedish regulation on limit values is one part in a system. That system, creating the Work Environment Policy, is based on a number of cornerstones, like

- Strong political support of improving working conditions
- Strong frame-work oriented law
- Far-reaching delegation of power to the SWEA
- Strong and well-educated safety representatives
- High degree of unionisation, blue-and whitecollar
- Access to qualified research
- Good statistics on injuries and ill-health
- Qualified and effective supervision and control by the competent authorities
- Well-educated and, in an international comparison, progressive employers

This means that the regulations as such can interact with other intervention tolls, in quite another way, compared to societies where those other parts are notas active or, in some cases, maybe not even existing. So, the existing OELs in Sweden must be looked on, having this background in mind.

The legal base for the Swedish OEL setting.

The base in Sweden is the Work Environment Law and Ordinance. This act draws up the frame for different actions taken by the Swedish Work Environment Authority (SWEA).

One section in the act reads " the work environment shall improve due to the social and technical development". In reality this means that even without any change in the scientific data, the OEL could be lowered as a consequence of what is said above.

In the act the SWEA is given the mandate to issue legally binding regulations without taking the matter to the government whatever the costs for the society. This reflects a political unanimous decision in the seventies when the act was issued by the parliament and has been unchanged since that. The SWEA though has to carry out a description of the consequences. I will not call it a cost-benefit analysis. Even if it is possible to calculate the costs, the benefit is more difficult to calculate. There is no tag available making it possible to calculate human damage or suffering in economic terms at an individual level.

Within the frame of the Work Environment Act the ordinance on limit values interacts with other regulations. So, you have to look upon them as a package which should be enforced. Every single part in it is connected into a chain. The way the Swedish regulations work together is illustrated in Figure 1.

This means that it is easier for the Labour Inspectorate, (L.I.),13/02/02 to use coercive measures against an employer if monitoring shows that the actual level of contaminants is above the limit values, but the L.I. has still the possibility to use other regulations, for example the ordinance about measures against air contaminants. As the OELs define the highest acceptable level, the L.I. has the power to demand the employer to further reduce the level of exposure.

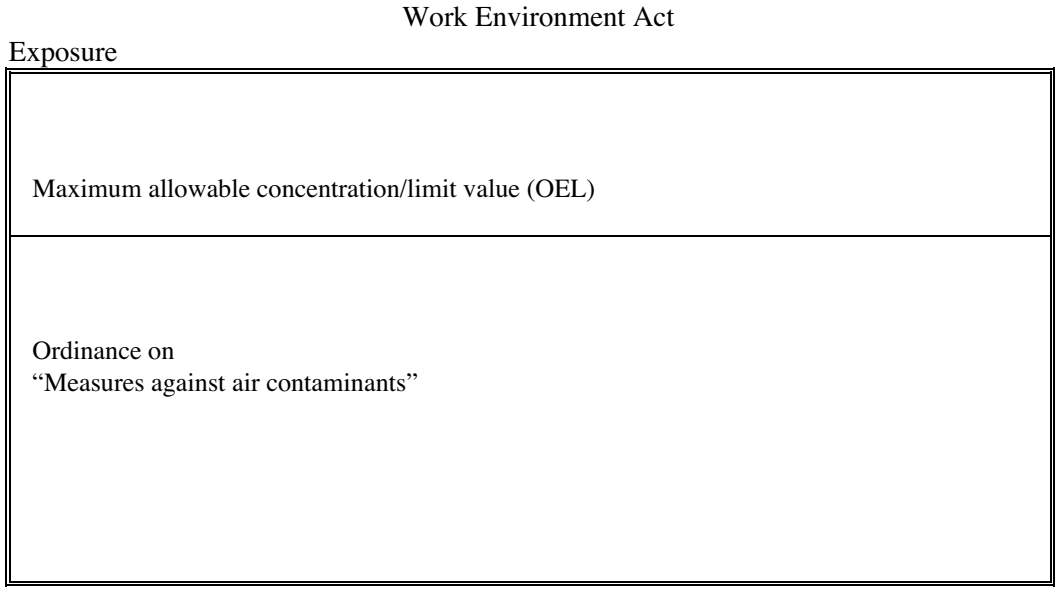

Figure 1.

The competent authority, in Sweden the SWEA, has a number of actions to choose when deciding how to tackle a work environment problem related to airborne exposure. OELs is one method among others;

- Limit values
- Regulations/restrictions of the handling
- Substitution
- Banning

You can use either one or a combination of these tools. The Swedish asbestos policy is probably the first example of what today is called the substitution principle. The policy started with a limit value in the sixties, followed by different regulations and restrictions of use in different branches and terminated by a total banning in the beginning of the eighties. This can illustrate the principle of decreasing the "collective dose". By issuing a limit value, and nothing else, you decrease the exposure but not the number of exposed. By issuing also restrictions of use in different branches, you also restrict the number of exposed which leads to a lower "collective dose".

This method could always be challenged. How can the authorities accept exposure in one branch, but not in another? This leads to further problems, the risk with alternatives. Which impact will a low limit value have on the employers´ choice between different products? If a low limit value leads to a transition to other substances without, or with a higher limit value, and those substances are not investigated and there are no scientific data, what are the consequences? This is a reality that all regulating authorities have to take into consideration. The SWEA will not accept the thought of having different limit values in different branches or at different companies. The base for the regulations must be scientific data combined with social, technical and economic aspects. This leads to the conclusion that if some companies can't comply with the regulations, they have to take action. In the short term this could mean use of respirators, but normally not in the long term. If they still can't comply with the OELs the final consequence could be closing the activity down.

The asbestos case is also an example of the problem of monitoring effects of different governmental interventions like limit values. The activities mentioned above resulted in a dramatic decrease in the import of raw asbestos. The results are visible from Figure 2. The effects on human health are harder to document. There are at least three diseases recognized as related to asbestos exposure; lung-cancer, mesothelioma and asbestosis. The number of reported cases of asbestosis increased as a result of the exposure. With a latency period of maybe 20 years from start of the exposure, the number of reported asbestosis cases had a maximum in the beginning of the eighties, while the reported number today is one or two annually. Even in this case the effect of different activities in the seventies pays off a decade or two later. In the case of mesotheliomas the situation is even more difficult. Mesothelioma has a very strong relation with asbestos exposure,

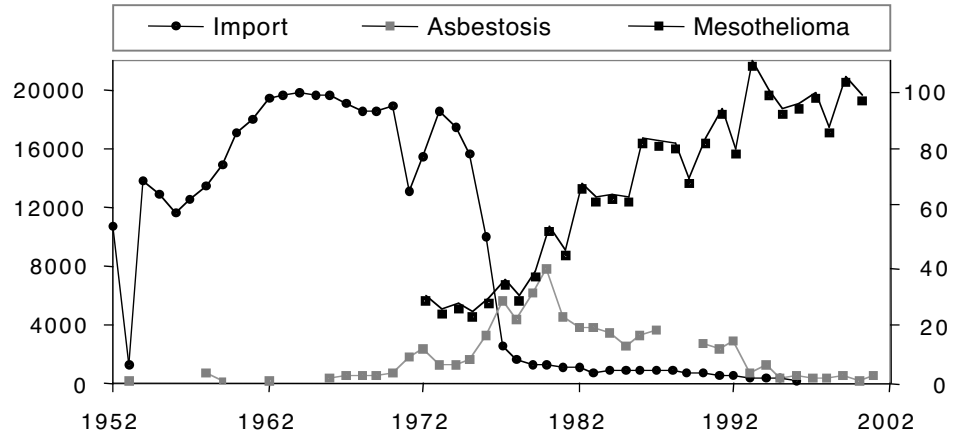

Figure 2. Number of imported raw asbestos in relation to number of cases with mesothelioma and asbestosis.

but also a long latency-period, maybe 30 years and more. That means that the result of interventions; regulatory, information, activities from the safety representatives and decisions from the employers mainly in the construction sector not to use asbestos, are not possible to monitor in Sweden until maybe 2005 and later. As shown in Figure 2 the number of mesotheliomas reported have still not decreased. In maybe 10 years from now it will be possible to monitor, by comparison with countries which choose a more asbestos friendly policy in the eighties, the real effect of the interventions decided in the seventies. This case shows the need of having supplementary intervention tools to support and strengthen the regulations on OEL. It also shows the problem of lack of methodology to monitor effects of changes in the OELs or other governmental activities, at least when it concerns substances with long latency periods.

The Swedish system of setting OEL

The system of setting OELs in Sweden is described in Figure 3, keeping in mind what has been said above, about the OELs as one out of several tools available to improve working conditions.

Up till 1992 the system was tripartite, even in decision-making. Since then the employers have left the directorate of SWEA, leading to a decision in the government to change the appointments in the directorate even for those representing the employees. Today the board members represent the working life, without direct representation of the social partners.

To support the staff of the SWEA in preparing proposals for new OELs the social partners are invited to appoint representatives in the process preparing the proposed OELs. When the staff of SWEA has enough data, the social partners are invited to comment on the material. The work with the OELs goes on until the

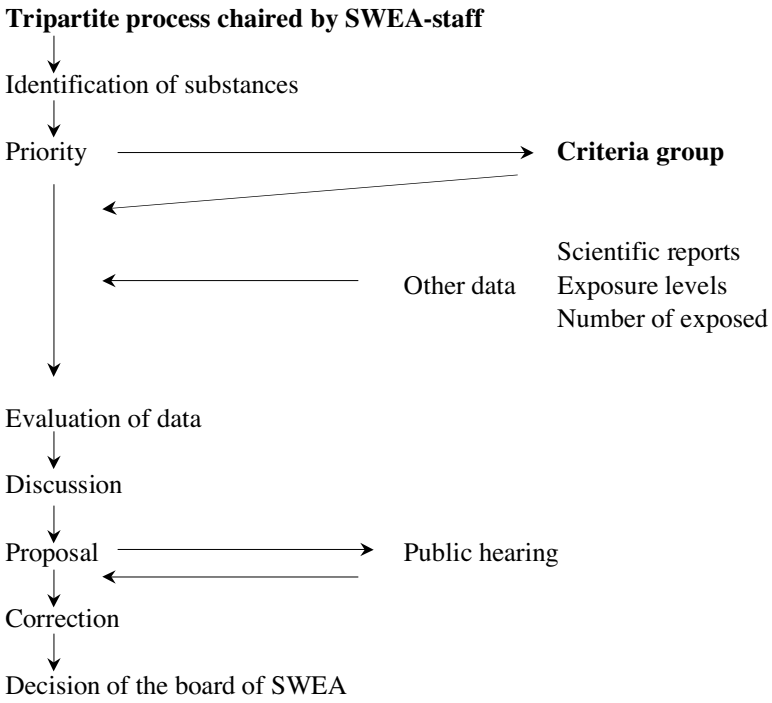

Figure 3. The system of setting OELs in Sweden.

available material has been commented on and analysed. One of the most important tasks of the tripartite process is to support the SWEA-staff in choosing those most prioritised substances to be sent to the Criteria-group, in order to ask for a scientific report. Normally the capacity of that group limits the number of substances to maybe 10 annually. The Criteria-group is a scientific-group, chaired and administered by the National Institute of Working Life (NIWL).

The group and its work is the responsibility of NIWL. The scientists appointed to this group are chosen by NIWL, like any other scientist appointed to carry out work related to the writing of a criteria document. The SWEA has no role, other than observer, in this activity. The expected, and wanted, outcome from the Criteria-group is a consensus document, containing the scientific data about the substance, and hopefully also targeting a critical effect and a dose-response/dos-effect relationship. The Criteria group does not propose any OEL.

Together with other data the group takes into consideration the scientific report. Based on the document, the group has to consider different values, considering technical possibilities, social and economic consequences.

The final preparation of the proposals to the Board of SWEA, and eventual corrections due to comments received in the public hearing, is a matter for the staff of SWEA. At the same time the proposal is sent to the Board, an invitation to participate in a new revision is sent out, and the work according to Figure 3 above starts again.

There are often questions whether the regulating authority deciding about a limit value takes into account other data than the scientific about health effects. The answer to that is, yes of course. If not, every limit value should be zero, as

that is the only definite level where you could guarantee that employees are not injured. Which impact other facts have when it comes to the setting of the actual value, is depending of the risk, or which is the critical effect. The higher the risk, the lesser impact from economic or other factors.

Another way of handling such a problem is of course to use the date when the limit value is entering into force as a modifier. If the date is adjusted in a way meaning that the entering into force of the limit value is later than normal, it gives the employers a better possibility to take measures. A similar way is to use the proposed limit value as a "planning value" saying that this is something which will come in a couple of years, or that the planning value is valid for new plants to be built from a certain date.

If the OELs in different countries are compared you will very often find different values, even if the scientific base is the same. This could reflect a number of decisions. One explanation, the simplest one, is that countries often revise their OELs in cyclic periods. If you compare a just recently revised OEL with one in a country which issued the OEL maybe ten years ago, of course this does not necessarily show a difference in risk assessment, but simply a practical difference of where the regulating authorities are in the work with revision of the values. On the other hand it could reflect either the legal base for the OEL, where it is easier to lower an OEL if it is just a recommendation, compared to a situation where it is legally binding. It could also reflect a difference in the evaluation of the critical effect. In some countries irritation for example is not accepted as a critical effect, while others accept it, leading of course to different conclusions. One of the most well-known example of such differences is the evaluation of the risks connected to exposure to solvents, where specifically the Nordic countries have had one approach to the problem, and many other countries have not accepted low level exposure as a critical effect.

Conclusion

The Swedish system of OEL-setting has a long history of tripartism, which has shown being successful. The OELs are based on scientific reports produced in the “scientific world”, without influence from the staff of the competent authority. The scientific report does not contain any proposals of values, but defines normally a critical effect and a dose-response/dose-effect relationship.

The proposed limit value is based on the criteria document and other relevant available information, taken into account technical development and economic factors. The higher the risk, the lesser consideration is given to economic factors.

The competent authority, SWEA, does not have to consult the government before issuing the legally binding occupational limit values. The ordinance on limit values is revised roughly every third year.

Management of TLV and BEI by ACGIH

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Abstract

The American Conference of Governmental Industrial Hygienists (ACGIH) has established and maintained a list of occupational exposure limits for use by industrial health professionals in preventing work-related disease associated with chemical exposures. Proper application of these exposure limits, the threshold limit values (TLV) and biological exposure indices (BEI), requires a firm understanding of the basis and procedure for their establishment, and of the quantitative aspects of their implementation.

The TLV and BEI are set up by two expert committees who consider available scientific data relating health risks to exposure. The process of developing exposure limits is based heavily on evaluation of the peer-reviewed scientific literature and is coupled with professional judgement. The TLV and BEI are reviewed frequently, and adjustments are made rapidly where new data dictate.

Quantitative aspects of the TLV include the selection of proper averaging time, the need to account for the presence of multiple compounds in a worker's environment, and for the presence of several sources of variation in exposure and measurement. Less quantitative features of TLV implementation include the presence of substances which may cause cancer or sensitization, and the overall process of making decisions regarding the presence of health risk, based on exposure measurements and comparison to the relevant TLV. Each of these issues is reviewed in the presentation to follow.

Complementary to the TLV, the BEI represent the levels of the chemical agents or their metabolites to be expected in the body fluids of workers with exposure at the TLV. Their establishment imposes some additional requirements on the available scientific data: these relate to the need for detailed information on the biological fate of inhaled chemicals, and on the relationship between internal dose and health risk. As examples, the BEI for lead, toluene, and methoxyethanol are presented to illustrate their application and to explore the recommended interpretation of the results of occupational biological monitoring.

Introduction

General characteristics of occupational exposure limits

Standards and guidelines limiting exposure to chemical and physical agents in industry have been established to prevent the development of the specific occupational diseases that could otherwise result from higher levels of exposure. A further goal is to prevent their possible contribution to the onset, progression or severity of chronic illnesses initiated by non-occupational agents. The degree of protection to be provided must extend over the full span of a working career.

At present there are occupational exposure limits for over 700 compounds, out of the 60 000 or more chemicals used in manufacturing and commerce. The occupational exposure limits are of great value in protecting worker health and safety, but their use and interpretation requires a thorough understanding of the data upon which they are based, and of the process and rationale followed in their development.

Basis for occupational exposure limits

The great majority of occupational exposure limits are set, appropriately, on the basis of a biological effect using the rationale outlined above, without regard for economic or other factors. There are a few occupational exposure limits for which this cannot be said, however, and their interpretation again requires some understanding of the procedure by which they were set.

Biological effects

The documents supporting each standard will generally indicate the biological response or responses which the standard aims to prevent or minimize. As time passes and data accumulate, the specific biological effect addressed by the standard may change. In some cases a second standard has been added for a given compound to control a newly discovered chronic response where the original standard dealt only with an acute reaction.

Analytical factors

A final factor which must be considered in standard-setting is the current state of analytical sensitivity for the agent in question. The practicing industrial hygienist must have access to sampling and analytical techniques able to detect the agent at and below the proposed standard. In a small number of cases this factor has taken a predominant role. The most important example is the standard for asbestos fibres in air, which was recently revised downward and set at the lowest level detectable by readily available techniques. It was again acknowledged that this standard probably will not provide adequate protection against cancer in exposed workers, but the alternative was to set the standard at a lower level for which only very expensive analytical procedures can be used.

ACGIH

The American Conference of Governmental Industrial Hygienists (ACGIH) is a private group organized in the late 1930's, consisting of industrial hygienists and other occupational health professionals employed by a wide variety of government agencies. Despite its name the ACGIH has no statutory authority – its occupational exposure limits are only recommended guidelines for good practice and are not directly enforceable by law.

Characteristics of TLV committee

The threshold limit values (TLV) are set by a committee of the ACGIH. The committee consists of members of the conference, aided by unpaid consultants who generally are employees of industry. The committee meets several times each year to review each of its TLV, and publishes a revised list annually. As a result of this continuing review, new data on a compound can be incorporated rapidly into the rationale for the TLV, and its value can be adjusted if necessary to reflect the new information. Thus the TLV are widely regarded as current, reflecting the most recent data available. Since the TLV committee may act rapidly, without the bureaucratic encumbrances of a government agency, it has been able to establish TLV for over 700 substances, and to revise a large proportion of them at least once, in its more than 50 years of existence.

TLV preface

The intent of the TLV committee in developing the guidelines is described in the preface to the TLV booklet (3). The reader is strongly advised to read the preface carefully, and to refer to it often in practice, when TLV or other guidelines are applied.

> Threshold Limit Values (TLV) refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects. Because of wide variation in individual susceptibility, however, a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit; a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational illness. Smoking of tobacco is harmful for several reasons. Smoking may act to enhance the biological effects of chemicals encountered in the workplace and may reduce the body's defense mechanisms against toxic substances.
>
> Individuals may also be hypersusceptible or otherwise unusually responsive to some industrial chemicals because of genetic factors, age, personal habits (e.g., smoking, alcohol, or other drugs), medication, or previous exposures. Such workers may not be adequately protected from adverse health effects from certain chemicals at

concentrations at or below the threshold limits. An occupational physician should evaluate the extent to which such workers require additional protection.

These limits are intended for use in the practice of industrial hygiene as guidelines or recommendations in the control of potential workplace health hazards and for no other use, e.g., in the evaluation or control of community air pollution nuisances; in estimating the toxic potential of continuous, uninterrupted exposures or other extended work periods; as proof or disproof of existing disease or physical condition; or adoption or use by countries whose working conditions or cultures differ from those in the United States of America and where substances and processes differ. These limits are not fine lines between safe and dangerous concentrations nor are they a relative index of toxicity. They should not be used by anyone untrained in the discipline of industrial hygiene.

The TLV, as issued by ACGIH, are recommendations and should be used as guidelines for good practices. In spite of the fact that serious adverse health effects are not believed likely as a result of exposure to the threshold limit concentrations, the best practice is to maintain concentrations of all atmospheric contaminants as low as is practical.

----------ACGIH TLV/BEI Booklet, 1998 (3)----------

Documentation

The booklet containing the TLV tables gives only brief information regarding the basis for the TLV, in terms of biological effect addressed and supporting data. These are contained in a much larger ACGIH publication, the “Documentation of the threshold limit values and biological exposure indices”. This contains a summary of the data and rationale for each TLV, with citations from the scientific literature used in developing the adopted value. It is a very important reference to which users of TLV should look for much useful information in interpreting the values. The documentation is revised annually.

Present controversies

A criticism of the TLV committee has been raised repeatedly over the years. The problem stems primarily from the misuse of the TLV by other organizations. Despite the committee's disclaimer in the preface that the TLV are not absolute boundaries between safe and unsafe conditions, and should not be given legal status, they have been adopted in part by many states as legally enforceable occupational exposure limits. As with many other occupational exposure limits, these have been interpreted by many employers as the sharp boundaries between legal and illegal, implying safe and unsafe. Hence, while the TLV committee has made some effort to establish the philosophy that its guidelines are meant to represent good industrial hygiene practice, (meaning that the employer should take every effort to keep contaminant levels as low as possible*, but always below the TLV*), their adoption by government agencies has caused their misinterpreta-

tion, and a misunderstanding of good practice. The chief complaint lodged against the committee, and perhaps the entire Conference, is the perceived lack of energy in making its views known, both to industrial hygienists and to regulatory agencies.

Application of threshold limit values

TWA

Unless otherwise noted the TLV is to be applied as a time weighted average (TWA). This means that the average concentration over the 8 hour work shift should be below the value given in the table; fluctuations above the TLV are permitted, within limits, as long as there are sufficient fluctuations below the TLV to keep the average below the limit. The mathematical expression for the TWA calculation is:

$$\text{TWA Concentration} = \sum C_i \times \Delta t_i / \sum \Delta t_i$$

where C_i is the average concentration over time period Δt_i

Δt_i is a period of time during which one sample is taken.

A series of such samples is taken to cover the entire period, so that the denominator in the expression equals 8 hours.

Excursions

Although fluctuations about the average are allowed for most materials in the TLV list, it is recognized that there should be limits to these brief peaks as well. Two approaches have been taken in attempting accomplish this. Where data exist describing the human responses to brief exposure to the agent in question, a short term exposure limit (STEL) accompanies the TWA value in the table. Thus for carbon dioxide, for example, there is a TWA value and a higher STEL. STEL are meant to apply to a fifteen minute period of exposure, meaning a time-weighted average over that time. These TLV are meant to be applied in addition to the 8 hour TWA. Where no data are available with which to set a STEL, an excursion factor limit of 3 has been used: the thirty minute peak is thus to be limited to three times the 8 hour TWA as a general rule of thumb.

Ceiling

Substances known to produce adverse effects very rapidly, say within minutes of the onset of exposure have been given special treatment by the ACGIH. Their TLV are specified as ceiling values, indicated in the table with a capital C before the value. This TLV is an airborne concentration never to be exceeded, using the best available methods for sampling and analysis. Again, fluctuations in concent-

rations are permitted, but the largest fluctuation must not exceed the ceiling value. Thus no averaging is done for these substances, but very careful measurements, using high quality instruments, are required.

Mixtures

Exposures to mixtures of two or more compounds in air pose serious difficulties for interpretation of guidelines and occupational exposure limits. No general approach has been agreed upon to account for possible interactions among components of a mixture, but the ACGIH has offered a recommended approach. When no information is available regarding interaction, two compounds present together should be assumed to produce additive effects if their biological reactions are similar. Thus, two compounds producing irritation at similar sites within the respiratory system may be assumed to act additively: the response to the mixture is the sum of the responses calculated if the compounds were present singly at the same concentration. If the two compounds produce different biological responses – one is an anesthetic and the other is a carcinogen – then in the absence of information regarding interactions, the compounds should be assumed to act independently: each compound is evaluated as if the other were not present. Numerical examples of the calculations which apply to these two situations are given in Table 1.

Carcinogens

The ACGIH committee treats cancer-causing agents in two ways, depending on the extent of available data. When exposure data are sufficient, a TLV has been assigned; In addition, a notation system has been developed which is intended to show the nature and strength of the evidence that a substance is carcinogenic. The categories presently in use are: A1, Confirmed human carcinogen; A2, Suspected human carcinogen based on data in animals and insufficient data in humans; A3, confirmed animal carcinogen with unknown relevance to humans for substances where available epidemiologic evidence does not confirm an increased risk of cancer in exposed humans; A4, Not classifiable as a human carcinogen based on inadequate data; and A5, Not suspected as a human carcinogen since available data are adequate and negative.

Non-standard work schedules

The TWA guidelines apply explicitly to a work schedule of 8 hour shifts, with 16 hours between each shift at an assumed concentration of the agent of near zero, for five days with a two day weekend before the cycle begins again. Deviations from this standard work schedule are becoming more common, but correcting the TWA values to account for this is difficult, and ACGIH has made no recommendation. It is probably not sufficient to adjust only for the increase in exposure which occurs if the shift is, say, 10 hours long instead of 8; one should also adjust

Table 1. Application of the threshold limit values when two or more contaminants are present (Source: ACGIH TLV/BEI Booklet 1998:81-83 (3)).

A. Additive effects: Instead of comparing the concentration of each component to its TLV separately, the following additive criterion is used:
Calculate $\sum C_i/T_i$ where C_i is the concentration observed for compound i
T_i is the TLV for compound i
If the result is greater than 1.0, then the equivalent TLV of the mixture has been exceeded.
Example: Air contains 250 ppm of acetone (TLV = 500 ppm), 150 ppm of sec-butyl acetate (TLV = 200 ppm) and 100 ppm of methyl ethyl ketone (TLV = 200 ppm). All have mild pulmonary irritant and anesthetic effects. The criterion is:
$\sum C_i/T_i = 250/500 + 150/200 + 100/200 = 0.50 + 0.75 + 0.50 = 1.75$
The equivalent TLV of the mixture has been exceeded.

B. Independent effects: Compare each component to its respective TLV separately. If any component is present in excess of its TLV, then the guideline is exceeded.
Example: Air contains 0.045 mg/m^3 of lead (TLV = 0.05) and 0.7 mg/m^3 of sulphuric acid (TLV = 1). One is neurotoxic and hematotoxic, the other is a potent respiratory irritant. The criteria are:
$C_1/T_1 = 0.045/0.05 = 0.9$ $C_2/T_2 = 0.7/1.0 = 0.7$
Neither TLV has been exceeded.

for the shortened recovery period between the longer shifts, but no simple method for doing this has been proposed.

TLV for particulate matter

For chemical substances present in inhaled air as suspensions of solid particles or droplets, the potential hazard depends on particle size as well as mass concentration because of: 1) effects of particle size on the deposition efficiency and site within the respiratory tract, and 2) the tendency for many occupational diseases to be associated with material deposited in particular regions of the respiratory tract.

The Chemical Substances TLV Committee has recommended particle size-selective TLV for crystalline silica for many years in recognition of the well-established association between silicosis and respirable mass concentrations. The committee is now re-examining other chemical substances encountered in particulate form in occupational environments with the objective of defining: 1) the size fraction most closely associated for each substance with the health effect of concern, and 2) the mass concentration within that size fraction which should represent the TLV.

The particle size-selective TLV (PSS-TLV) are expressed in three forms:

1. Inhalable particulate mass TLV (IPM-TLV) for those materials that are hazardous when deposited anywhere in the respiratory tract. The inhalable fraction is that portion of airborne particles entering the nose and/or mouth during

breathing. This fraction is often less than unity owing to settling of airborne particles due to gravity, and to effects of local air movement which may prevent particles from being inhaled. The quantitative definition of IPM is shown in Figure 1, as a graph of particle aerodynamic diameter versus the fraction of particles, by mass, that are inhalable at each diameter. This criterion is based on a series of investigations of particle collection by human head models in wind tunnels under conditions designed to provide realistic representations of human exposure. It should be noted that for particle aerodynamic diameters above 100 μm, too few data are available; the inhalable mass fraction is unknown, but does not vanish at these diameters.

2. Thoracic particulate mass TLV (TPM-TLV) for those materials that are hazardous when deposited anywhere within the lung airways and the gas-exchange region. This fraction represents those particles which escape capture by the surfaces in the head airways region – the nose, mouth and throat – and enter the trachea during inhalation. Figure 1 indicates the dependence of this fraction on aerodynamic diameter, and indicates that at 10 μm the thoracic fraction is 50%. This criterion is based on experimental measurement of deposition in the head airways conducted in human volunteers given controlled exposure to aerosols, and it is in close agreement with the PM(10) criterion now used by the United States Environmental Protection Agency in regulating outdoor concentrations of particulate matter.

3. Respirable particulate mass TLV (RPM-TLV) for those materials that are hazardous when deposited in the gas-exchange region. The latter is defined as the portions of the lungs containing alveoli where oxygen and carbon dioxide are exchanged between air and circulating blood. Anatomically, this includes all surfaces distal to (downstream during inhalation) the terminal bronchioles, the smallest airways which do not incorporate alveoli. Figure 1 indicates the respirable fraction as a function of aerodynamic diameter. This criterion is also based on experimental measurements of particle deposition within the conducting airways during inhalation in human volunteers, and it indicates the fraction of airborne particles which escape collection in the head or conducting airways, and therefore are able to penetrate to the deepest portions of the lungs. It should be noted here that the RPM measurement does not necessarily reflect deposition of these particles in the gas-exchange region: some of the respirable particles which penetrate to this level during inspiration do not deposit and are carried out with the next exhalation. The measurement of the respirable particulate mass concentration therefore represents the maximum potential exposure of the gas exchange region, if complete deposition were to occur.

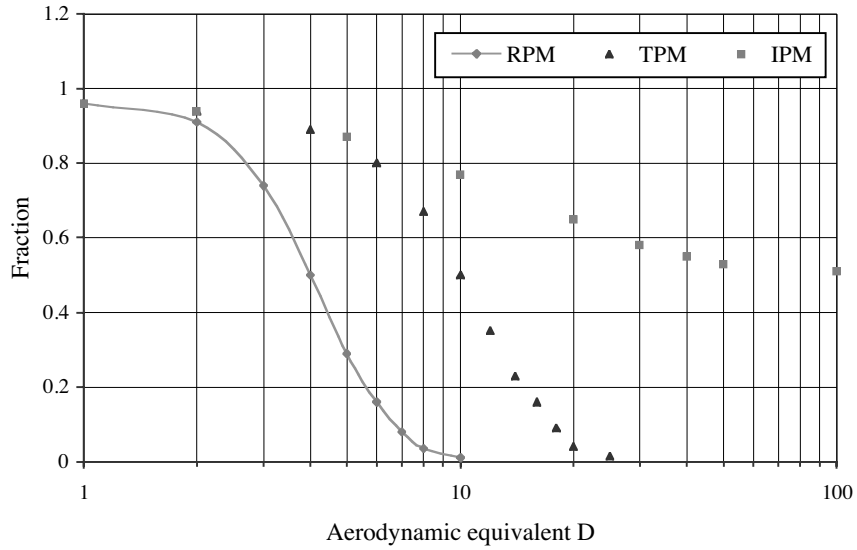

Figure 1. ACGIH particle size selective criteria

The most significant difference from previous definitions is the increase in the median cut point for a respirable particulate matter sampler from 3.5 μm to 4.0 μm; this is in accord with the International Organisation for Standardization/ European Committee for Standardization (ISO/CEN) protocol.

Application of the new criteria

Airborne particle standards such as the TLV are now being revised to incorporate these criteria, when data are available associating health risk with the appropriate measure of exposure. There are two general approaches to the measurement of the concentration of particles within one or more of these size fractions. The first method is to determine the particle size distribution in the sample from the workplace by a suitable technique such as a cascade impactor or some equivalent aerodynamic particle sizing instrument. Then, the appropriate particle size selection criterion is applied to the data. This is illustrated in Figure 2. The figure shows a hypothetical particle size distribution determined for example by a cascade impactor, plotted as the mass concentration per unit size interval versus the aerodynamic diameter. These data represent the distribution of mass concentration in the ambient air, before inhalation. To determine the inhalable particle mass concentration, the criterion must be applied as shown in Figure 2: the mass concentration in each size interval must be multiplied by the inhalable mass fraction corresponding to that size interval, and the resulting products are summed to yield the inhalable mass concentration. Note that for size intervals less that 1 μm in aerodynamic diameter, nearly 100% is inhalable, while for size intervals of 30 μm or greater in aerodynamic diameter, the inhalable portion is approximately 50%. A similar method would be followed to determine the thoracic or respirable mass concentrations, each requiring determination of the airborne size distribution followed by application of the appropriate criterion.

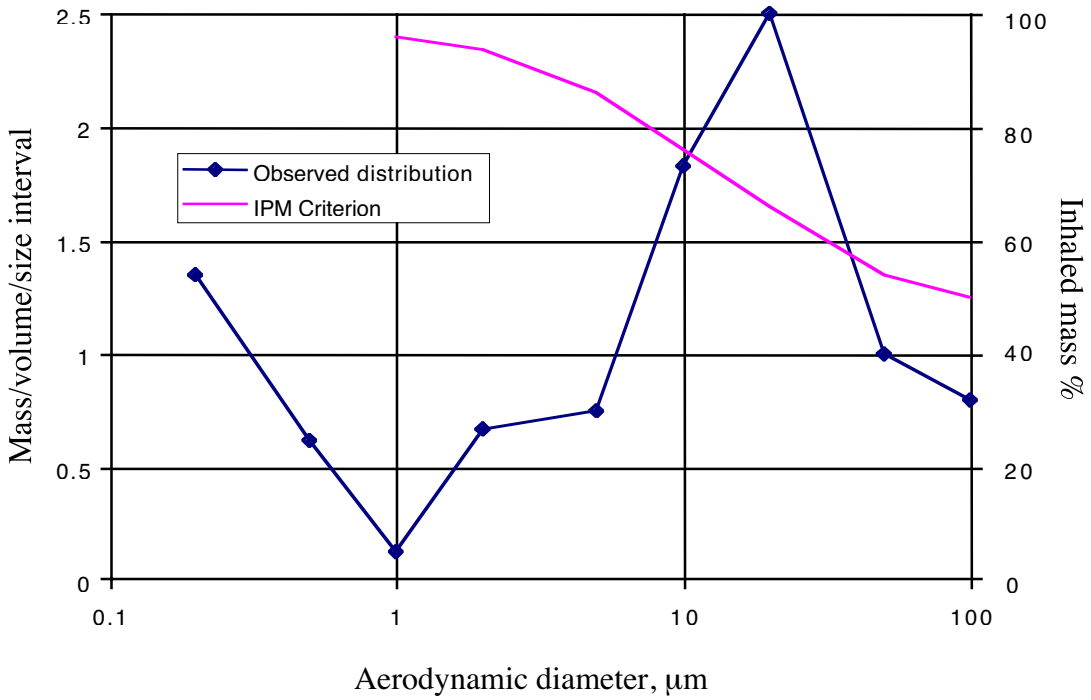

Figure 2. Application of size criterion

The second method is to use a particle sampling device whose collection efficiency matches that of the size selection desired. That is, if one wishes to determine the respirable particle mass concentration then a sampler designed to collect particles with the same efficiency as the criterion should be employed. A number of devices are available to accomplish this. One example is the combination of a cyclone placed upstream of a particle filter, and devices such as the 10-mm nylon cyclone have been available commercially for many years. Analyses of available data indicate that the recommended flow rate of 1.7 litres per minute allows the 10-mm nylon cyclone coupled with a filter collector to approximate the particulate matter concentration which would be measured by an ideal respirable particulate mass sampler as defined above. A number of TLV have now been developed which specify an airborne particle concentration as the respirable mass fraction. These include TLV for crystalline silica and for elemental cadmium and its compounds.

In contrast, devices for direct measurement of the inhalable and thoracic fractions of airborne particulate matter have only recently been introduced, and their performance has not yet been completely validated. For inhalable particulate mass concentration measurements, a device developed by the Institute of Occupational Medicine in Edinburgh, Scotland, has been recommended. Generally referred to as the IOM sampler, this device is designed to collect particles with an efficiency that matches that of the human respiratory system. With the emergence of this method for determining inhalable particle mass concentrations, new TLV may be se and existing TLV may be revised based on this fraction.

Comparison of new and older particle sampling methods

One problem with this development is the need to determine the relationship between particle mass concentrations determined by the older filter method and the newer inhalable method. The older method has been thought for many years to collect all particles with nearly 100% efficiency regardless of aerodynamic diameter. This traditional "total" particle sampler would be expected to result in particle mass concentrations higher than or equal to those produced by the inhalable particle sampler when both were employed in the same environment. A series of experiments has now been conducted in a wide variety of work places where airborne particles of different composition and size distribution were found. In each setting, simultaneous samples were taken using the traditional "total" filter method, and the newer IOM sampler designed to collect the inhalable particle fraction. The two results were compared by calculating the ratio, S, of the inhalable to the "total" particle mass concentrations.

$$S = \frac{\text{Mass concentration by IOM sampler}}{\text{Mass concentration by "total" sampler}}$$

If both sampling devices operated as anticipated, the value of S should be equal to or less than unity. In nearly all cases, however, the observed value of S was greater than unity, and ranged as high as 3.2 in some work places. Table 2 presents a summary of recent studies comparing the two sampling methods. This seemingly contradictory finding has now been determined to arise from the incomplete collection efficiency of the "total" particle sampling method. Filter cassettes as used by most industrial hygienists do not in fact perform with 100% collection efficiency at all particle diameters. Their efficiency is in general less than that of the IOM sampler, especially when a substantial fraction of the particles being sampled are at diameters above 10 μm. On the other hand, when most of the particle mass is in particles with diameters of 2 μm or less there is close agreement between the two methods. The data for samples from a welding shop in Table 2 reflect this consideration.

A major consequence of this set of observations is that measurements taken with the IOM sampler, or other device shown to conform to the IPM criterion, should not be compared to a TLV which has been specified as "total" particle mass concentration. From the data shown in Table 2, such a comparison could lead to a judgement of overexposure which may be incorrect. The TLV committee is now reviewing this problem and expects to provide advice on the matter soon. It does not appear likely that the existing particulate matter TLV specified as "total" mass concentrations will be adjusted to match the newer inhalable criterion, since the adjustment is dependent on the particle size distribution present in the specific work place being evaluated. New particulate matter TLV, however, will be specified as one or more of the three size-selective fractions, whenever data are available to support doing so. This newer specification will also be applied to

Table 2. Summary of recent studies comparing "total" and inhalable particle concentration measurements. Adapted from Werner *et al*. (12).

Industry	"Total" Sampler	Inhalable sampler	Component sampled	Ratio S
Borates/ Boric acid	37 mm closed face	IOM	Total aerosol	2.20
Nickel mine	37 mm closed face	IOM	Nickel	3.20
Nickel mill		IOM	Nickel	2.72
Nickel smelter A		IOM	Nickel	1.65
Nickel smelter B		IOM	Nickel	2.84
Nickel refinery		IOM	Nickel	2.12
Nickel alloy	37 mm closed face	IOM	Nickel	2.29
Nickel plating A	37 mm closed face	IOM	Nickel	2.02
Nickel plating B		IOM	Nickel	3.01
Lead smelter	37 mm closed face	IOM	Lead	1.77
			Cadmium	1.76
Machine shop	37 mm closed face	IOM	Cutting oil	2.96
Woodworking	Closed face, 4 mm opening	IOM	Wood dust	1.79
Welding repair shop			Total aerosol	0.95
			Aluminium	1.36
Woodworking	Closed face, 5.5 mm opening	IOM	Wood dust	1.79

some existing particulate matter TLV, again where size-selective measurements are available.

Thoracic particulate fraction

As for the thoracic particulate mass criterion, one device has been introduced within the past two years which is claimed to conform. This device incorporates a cascade of virtual impactors coupled with filters for collection, and is designed to separate airborne particles into three fractions: the first stage contains the respirable fraction; the sum of particles found on stages one and two represents the thoracic fraction; the sum of particles found on all three stages represents the inhalable fraction. Validation data are now being collected with this new sampler, and should be available soon. At this point there are no particulate matter TLV containing the thoracic particulate mass specification since few measurements have been made which have been demonstrated to meet the criterion. As new devices are introduced, it is anticipated that data will accumulate and it will soon become possible to develop thoracic particulate matter TLV.

Biological exposure indices

Biological monitoring is generally described as the planned and repeated collection of specimens of tissue or body fluid, for the purpose of estimating the chemical composition of the body's internal environment. The repeated aspect differentiates *monitoring* from *sampling*, and emphasizes the point that temporal

changes in chemical composition are just as important as the estimates at a single time.

Occupational biological monitoring must be viewed as complementary to, and not a replacement for, the more traditional measurement of airborne concentrations of chemical agents. It provides additional information which can be of great value in evaluating and controlling risky exposures. This form of exposure monitoring invokes some additional requirements, however, one of which is the existence of reference values against which observed biological concentrations may be compared in order to form judgements about the acceptability of the work place conditions.

One substantial collection of reference values for biological monitoring in work places is the list of biological exposure indices published by the ACGIH. Organizations such as this, together with governmental regulating agencies, perform a key role at the interface between science and policy: ideally, their mission is to use the best available scientific and technical data to set recommended or regulatory limits that will minimize the health risks to workers while maximizing the benefit to society of the economic activity associated with the work.

The defining characteristics of the BEI

The BEI are reference values intended as guidelines for the evaluation of potential health hazards in the practice of industrial hygiene. Thus, when BEI are used by physicians, nurses, engineers or industrial hygienists, their principal application should be to support prevention of injurious exposures.

The BEI are developed by the BEI committee of the ACGIH, which consists of volunteer scientists and practicing professionals with expertise in occupational medicine, toxicology, industrial hygiene, analytical chemistry, biostatistics and epidemiology. The present committee members include specialists from the USA, Japan, Germany, Switzerland, Taiwan and the United Kingdom, employed in academia, government or private industry (the last category of members does not have voting privilege, but otherwise participates fully in the process.) The committee meets twice per year to develop new reference values and to conduct a regular review of existing BEI as new data emerge. Several values have undergone significant revision as a result of such review. Examples will be described below.

The BEI are intended for use in biological monitoring where the goal is the determination of the worker's internal dose, or biologically effective dose, of a chemical. The determinant may be the parent compound itself, metabolite(s), or a characteristic reversible biochemical change induced upon absorption. The index values represent the level of the determinant most likely to be observed in specimens collected from a worker with an internal dose equivalent to that arising solely from inhalation exposure at the TLV concentration. Thus most of the BEI are closely linked to the corresponding TLV, and are based on preventing the

same health effect addressed by the TLV. This does not imply, however, that airborne concentrations and biological levels must always be correlated in exposed workers, since routes of absorption in addition to inhalation are possible. Where this occurs, comparison of biological levels to the BEI takes on special importance, since the BEI represents the acceptable internal exposure regardless of the route(s) of entry.

Present status - procedure for establishing a BEI

Establishing a BEI has evolved since the early days of the BEI committee into a staged process consisting of a) feasibility analysis, b) development of a proposed BEI, c) formal publication of that proposal with an invitation for comment from all parties, d) review and possible revision of the proposal, and e) final adoption by the voting members of ACGIH. At each stage, the actions of the committee are subject to review by the ACGIH Board of Directors, elected in turn by the membership. One of the critical decisions in the process is the initial one, as to the feasibility of establishing a new BEI. In the course of making this decision the committee considers several criteria which are discussed in a written feasibility assessment prepared by one or two committee members. The criteria are:

Extent of systemic absorption and disposition
Substances must be absorbed into the circulation to the extent that target tissues remote from the site of entry are affected, and so that accessible biological fluids or tissues will contain the chemical or its metabolite in detectable concentration. An industrial chemical with potent toxic properties which exerts its effect only topically or only at the site of absorption is not a candidate for setting a BEI since biological monitoring is unlikely to generate information useful for preventing or minimizing exposure.

Size of the exposed worker population
Although there is no specific quantitative requirement for this aspect, data on the size of the population are needed. In general, exposures to workers should occur in more than a single industrial facility, and preferably in the work places of more than one company. Equally important is the recent trend in these data, as a substance whose use in industry is decreasing may be of much less interest than one whose production and use are growing. The influence of this factor may be diminished for a substance with very potent toxicity for which other feasibility criteria are particularly compelling, such as the glycol ethers which may penetrate the skin in significant amounts.

Existence of a TLV for the substance
The great majority of BEI are directly related to the corresponding TLV. They address the same health outcome and represent the expected internal dose corresponding to inhalation at the TLV. Exceptions to this criterion have been made in the past, and they establish a precedent for similar future exceptions

where the other feasibility criteria argue strongly for establishing a BEI. The present exceptions are BEI for classes of compounds inducing methemoglobinemia, and for those inhibiting acetyl cholinesterase.

Toxicokinetic data in humans are available
There should be sufficient data of high quality, which describe the absorption, systemic distribution, metabolism, storage, and excretion of the compound or its metabolites. These are necessary to support the selection of the appropriate analyte, the tissue or fluid to be sampled, and the timing of the sample. The committee requires that the toxicokinetic studies be published in the peer-reviewed scientific literature, so that their quality can be assessed by all interested parties. In some instances validated toxicokinetic models have been used where experimental human data were not sufficient. Further, toxicodynamic data may also be appropriate in instances where the anticipated BEI would be directly related to health effect rather than to an airborne concentration. This particular means of developing a BEI has been used only rarely to date.

Analytical chemical methods are available
Data in the peer-reviewed literature must demonstrate that a method exists for assay of the determinant with acceptable accuracy, precision, and sensitivity. These performance characteristics must permit analysis of the determinant in the recommended tissue or fluid sampled, at levels both below and above the anticipated level of the BEI. Inadequate analytical methodology will preclude the development of a reference value.

An affirmative feasibility decision launches the development of a proposed BEI by one or two members of the committee. The written proposal will include the identity of the industrial chemical or category of substances addressed, together with its CAS number and chemical formula. The recommended BEI includes the identity of all determinants – parent compound, metabolite(s), biochemical change – together with the medium to be sampled, the time of collection relative to the exposure period, and the numerical value of the index expressed as a concentration or percentage of normal. In many instances there will also be a notation which marks one or more special considerations for the BEI, such as the need to account for background levels in workers due to exposure outside the work place.

The proposed BEI is supported by a document which reviews the scientific data used in developing the reference value, and which contains a synoptic rationale for the recommendation. The documentation must conform to a standard format incorporating relevant physical and chemical properties of the chemical, toxicokinetic data, discussion of possible non-occupational exposure, the value and rationale for the corresponding TLV, a discussion of sampling and analytical methods for the determinant(s), anticipated biological levels without occupational exposure, the timing of appearance of the determinant, factors affecting inter-

pretation of the measurement, the justification for the recommended BEI together with a critical assessment of the current data available, and finally a description of reference values recommended or required by other organizations. All literature used in the preparation of the documentation is cited, and a copy of each item must be provided for archiving.

The BEI committee then conducts a thorough review of the proposed BEI and its documentation. A member not involved in the preparation of the proposal is assigned to lead this review, during which special attention is paid to the correspondence of the BEI to the TLV if that approach has been used, or to the relationship to health effects data if not. Conformance to the feasibility assessment is considered, and the practical aspects of sampling, analysis, and interpretation are examined. The review process is one of scientific judgement based upon the weight of available evidence, and does not include a quantitative risk assessment. The approach in most cases has been to select the level of each determinant which is most likely to result from inhalation exposure at the TLV. The decision takes account of typical workers' physical activity during exposure, and pays particular heed to experimental or epidemiologic data on the toxicokinetics of the compound. The final recommendation is invariably a consensus of the voting members of the committee. Revisions to the documentation are often agreed upon at this stage in response to comments from the committee members.

The proposed BEI must remain on the list of "Notice of intent to establish or change" for at least one year, after which the committee reviews all comments received as well as any new scientific date to emerge. Revisions may be made to the BEI and its documentation, after which another consensus is reached regarding adoption. If proposed BEI is revised at this point, the new proposal must spend another year on the Notice of Intent. After the required notice period, a recommendation for adoption is again reviewed by the Board of Directors and the ACGIH membership. Final adoption results in publication of the BEI in the booklet as an established reference value, and the incorporation of the new documentation into the three-volume set published by the ACGIH, containing all the documentation for the TLV and BEI.

A significant aspect of the TLV and BEI procedure is the periodic reexamination of the adopted reference values. Generally the original authors of the documentation are expected to monitor the scientific literature for new data which may bear on the BEI. A proposal for revision may be presented at any time, and can be acted on within one year of presentation. In this way the collection of BEI can be kept consistent with current science, and thus will be of maximum utility to occupational health practitioners. The annual publication of the TLV/BEI booklet reveals numerous revisions as a consequence of this continued surveillance. The frequent updating of the ACGIH reference values stands in marked contrast to the much slower (legislatively mandated) process of the US Occupational Safety and Health Administration in revising its regulations governing the same substances.

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Occupational exposure limits - an ethical dilemma[1]

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Introduction

Occupational exposure limits have been a feature of the industrialized world for more than fifty years. The concept of exposure limits has been important for the improvement of the working environment. The process of establishing occupational exposure limits has, however, varied between countries, and the concepts of such limits have been poorly described.

Control of risks from exposure to chemicals requires first of all a scientific assessment of the potential effects at given exposure levels (risk assessment). Based on the results of the risk assessment, and taking into consideration other factors, a decision making process aimed at eliminating or reducing the risk under consideration, can be started (risk management). This internationally accepted risk assessment paradigm includes the four steps: Hazard identification, dose-response assessment, exposure assessment and risk characterization. This framework provides a basis for a structured review of information relevant to estimating health outcomes of exposure to chemicals. The paradigm differentiates between the scientific approach of risk assessment, and the human value-loaded approach of risk management taking into consideration also technological, economical, socio-political and other cultural considerations.

It is important that both the biomedical and toxicological scientific criteria, and the feasibility criteria (socio-political, economical, technological and cultural) are made visible in the procedure of setting occupational exposure limits. Feasibility and socio-political considerations are, and have always been, important in this process, but these processes have not always been visible. These considerations are based on value judgements, but they are not always clearly separated from the scientific process.

Human value judgements are, however, also present in the apparent scientific risk assessment process, though most often hidden and thus visible neither to experts nor to the public. Thus, the public and even some biomedical experts are led to believe that it is possible to suggest pure scientifically based exposure limits, which subsequently are used as a basis for the risk management process.

[1] This presentation is a revised copy of a presentation with the same title published in Arbete och Hälsa 1993;15:123-135.

This involvement of science in risk management by the participation of the scientist by profession, in deciding numerical values for occupational exposure limits is a violation of some of the most important normative values of science. Both scientific objectivity and the closely related principles of disinterestedness and unbiasedness are violated. On the other hand, no research is perfect from the scientific normative point of view. Both models and results are always subject to subjective analysis, but the scientific method usually minimizes this objectivity problem. In addition, we are all biased – experts and lay people – by contextual human values in the form of personal, social, cultural, or philosophical emphases which typically influence the research processes. Contextual human values are generally accepted in the risk management process, but such values may unacceptably influence the results (the exposure limits) if they are believed to be part of an objective scientific judgement. This is the case if scientists as such participate in developing numerical values for acceptable risk. Even risk characterization may be a dubious task for science in this process. Whether or not to classify a substance as a carcinogen is not only a normative process. Clearly, value judgements are part of the process.

Science in our culture in a way represents the truth, but the scientific truth in a risk assessment/risk management paradigm is not necessarily the social truth. The social truth – the occupational limit value – must be judged fair and just. Contextual human values from stakeholders – and the scientist by profession is not a stakeholder in this process - are important and necessary in the risk management paradigm. This problem cannot, of course, be completely solved, but the problem clearly indicates that the scientist – as a scientist – should not unduly and invisibly influence the risk management process from the power position of science. There is nothing like a pure health based limit value based on scientific facts; all limit values are based on human value judgements. Thus, both the risk assessment and the risk management paradigms include human value judgements with moral content and ethical problems.

Toxicological background of the occupational exposure limits

I will in the following discuss some aspects of the four steps in the risk assessment paradigm to explain my arguments above.

Hazard identification

Communicating risk to workers and to the public is a prerequisite for worker and public participation in the procedure of setting exposure limits, and thus a necessity for the ideal procedure as described previously. There always is, however, a conflict between the principles of critical hypothesis testing and communicating risk. Probably the requirements of establishing a scientific truth ideally require too much time before risk communication and prevention should be initiated. On the other hand, we live in a risk oriented society where the risk paradigm by itself

may constitute a health hazard. This is an ethical problem with no scientific answer, a problem that is handled by all of scientists, laypeople, based on our own value judgements. The so-called precautionary principle – used and misused – is a part of this problem. A further discussion of use and misuse, and of the scientific and moral problems of this principle, is outside the scope of this presentation. I will give an example from the Norwegian classical literature to illustrate the risk communication problem.

In the play "An enemy of the people" by the Norwegian author Henrik Ibsen, Dr. Stockman ended up as "an enemy of the people" when he informed the authorities and the public about the bacterial contamination of the water used for the flourishing health baths in the community. And he himself as expressed in the play, expected official credit and public appreciation. His statement that the man standing alone is also the strongest may bear some implication for the process of improving the working environment by revealing information of conflicting interests to the parties involved (workers and management). The authorities and the public in this case also wanted Dr. Stockman to let the consequences influence his scientific conclusions, but he did not and became "an enemy of the people".

There are too many examples where consequences have influenced scientific conclusions. This is an important ethical problem with many aspects in to-days human genome research. Should we refrain from doing some experiments because of misuse possibilities of methods or results? And what constitutes a *misuse*?

Dose-effect and dose-response assessments

The interaction between a chemical and an organism can be described by two different concepts, the *dose-effect* and the *dose-response*. The *dose-effect* denotes the relationship between the dose and a graded effect, or different effects, in the individual. The *dose-response* describes the relationship between the dose and the frequency of a given effect in the population.

At the molecular level, the graded dose-effect may represent a dose-response if receptors or binding sites are taken to represent individuals in a population. Different effects thus represent other classes of binding sites or receptors. The general requirements of a dose-effect relationship are that there is a reproducible relationship between dose and effect, and that increasing doses generally lead to an increased number of effects or more serious effects. In other words, there is a reproducible relationship between the dose and the induced pathology (type-I-toxicology).

It is convenient in the context of exposure limits and risk management in general, to distinguish between the two different operational concepts of dose-effect and dose-response, even if these are not universally accepted risk assessment and risk management paradigms. These two concepts, however, also make it easier to understand the philosophy and ethical dilemmas of exposure limits.

Validity of the dose-effect, dose-response and threshold concepts – risk characterization.

It is important to note that the operational concept of dose-effect as described above is not equally valid for all kinds of effects. Mutagen and carcinogen effects are the exceptions most often discussed, but there are also other effects involving specific biological mechanisms that do not follow ordinary dose-effect principles. These are foetal cellular differentiation or immunological processes (allergy or immunotoxicological effects) where there are no reproducible correlations between dose and the induced pathology (type-II-toxicology). This has important implications for the setting of occupational exposure limits for some chemicals.

For mutagen and carcinogen effects, even the lowest dose, because of specific biological mechanisms (e.g. cell proliferation), may cause the most serious effect (death). Neither the requirement of increasing doses causing more serious effects, nor that small or limited doses may be without effects are present in such cases. The generally accepted risk assessment paradigm denotes these effects as effects with no threshold, a statement that I think is a serious misconception. All effects have thresholds at the individual level. The dose-response represents the distribution of the individual thresholds for a given effect for any effect in any population. Even cancer, in case of the single hit carcinogenesis theory, is a stochastic process. The distribution of cancer in a population exposed to one molecule, which theoretically may cause cancer given the single hit theory, represents the distribution of the thresholds between individuals for this effect, as for all other types of effects.

The distribution of the thresholds is the dose-response curve, which, on the other hand, has no threshold. The population threshold, or expressed differently, the dose-response threshold, is nothing but a statistical power problem and as such not a biological threshold. This is equally true for all kinds of effects. With increasing doses, the probability of one hit may increase linearly, but in each point of this linearly increase there is a probability distribution for cancer as a result of the hit. Consequently, the differences between cancer and mutations and other effects do not relate to thresholds, but to the simple fact that even the "lowest dose" (one molecule) may cause the most serious effect (death) – the requirements of dose-effect concept are not present.

Thus, even if genotoxicity, carcinogenicity and exposure in sensitised individuals should be treated differently from other effects, this cannot be substantiated or explained by thresholds or no thresholds.

Dose-effect and dose-response in setting occupational health limits

No generally applicable function can be given for the dose-effect relationship for different chemicals, but the dose-response function is, as mentioned, ideally described by the normal distribution. Toxicologically, the occupational exposure limit, when agreement has been reached on the effect that should be prevented, is

the numerical dose value that represents the acceptable frequency of the chosen effect in the exposed population.

The risk management process therefore involves two different value judgements. The first is the selection of critical or adverse effect; and to define the value loaded terms *critical* and/or *adverse*, the second is to choose the acceptable probability of this effect to be found among exposed individuals. And the scientist, as a scientist, should not participate in any of these value judgements.

The concepts of ethics and morality

In this part of my presentation I will go through some principles of ethics and ethical argumentation that I feel are important for understanding the concept of occupational exposure limits.

Health based occupational limits

The intention of the above short toxicological review has been to demonstrate that the occupational exposure limits has never been, and can never be, a problem of biomedical sciences alone. Feasibility including socio-political, cultural and economical considerations, and therefore also the concepts of ethics and morality are always involved in the process.

It is impossible to discuss the moral dilemmas of exposure limits without understanding both the concepts of toxicology and those of ethics and morality. The claim that it is possible to develop purely health-based limits demonstrates that such understanding is not generally acknowledged. A health based occupational limit is a nonsense-term, which should not be used. The term signals, and some people even seems to believe, that it is possible, if health related research only is applied, to suggest a scientifically based numerical value for risk acceptance. Both the risk concept and the health concept are, however, loaded with contextual human values, and not even scientists live in a social and cultural vacuum. The scientist may hopefully be able to estimate the probability of different effects at different doses, and these estimates may be denoted as health based. Suggesting an occupational limit, on the other hand, is always a political decision with a number of ethical problems. The scientist must, of course, be allowed to participate in the process as an ordinary citizen. I would still recommend, however, that the scientist be not invited to play both these roles in the practical limit setting process. The separation between roles has been experienced to be difficult, and the public may misinterpret the roles to believe the limits are scientifically based only. The necessity of toxicological knowledge in setting occupational exposure limits is generally accepted, but the theories of ethics and value judgements have been neglected.

Morality – a concept of right and wrong

Morality is usually regarded as the principles and values of a person or of a group. Such principles and values determine the behaviour in specific situations. Morality is thus a behaviour pattern based on certain assumption of right and wrong. Important moral problems that always have been discussed throughout the history of philosophy are how the concepts of right and wrong should be interpreted. Other problems are how to define moral virtue, or what is morally right or wrong, and how to explain the morality or behaviour of a person or of a group.

Ethics – a methodological approach to morality

Ethical dilemma in the heading of this presentation indicates that there are problems in applying the concepts of ethics in the discussion of the morality of establishing occupational exposure limits. The implication of ethics as a theoretical and systematic system for the description and treatment of moral problems does not have a general support. Etymologically it is perhaps no reason to separate the two concepts ethics and morality. Ethics is of Greek origin and morality comes from Latin. Both have to do with conduct and behaviour. Being accustomed to the reduction principles of models in the natural sciences it seems, however, reasonable to regard ethics as the methodological approach to morality - as research is the methodological approach to science. Given these methods and the understanding how to use them - and only then - it is possible to discuss the morality of the concept of occupational exposure limits, and to participate in the discussion of specific numerical values without the subjective involvement of interpersonal destructive moral rejection and denouncement.

Ethics as the methodological approach to morality is not to be regarded as a subject for specialists alone. It is necessary to understand one's own interpretation of the concepts of ethics and morality as well as the concepts of biology and toxicology to take part in any process of establishing occupational exposure limits - generally in any standard setting process. The rejection of these requirements with a general denial of the involvement of human value judgements in all kinds of standard setting is destructive in the process of establishing just exposure limits.

I feel that it is important openly to discuss the moral aspects both of the concept of exposure limits and that of setting the actual numerical value. The goal of such discussions is not to put the fellow human beings on a scale of "bad" or "good" dependent on individual attitudes, but to obtain an intellectually balanced and reflected attitude to the many normative and human value loaded problems in toxicology and in occupational health.

Normative or provisional- and descriptive ethical theory

The normative or provisional ethical theories suggest principles and appraisals for morally correct and acceptable behaviour. Possible questions are: *What should we*

do? Or: *How should we behave?* The biblical: *Thou shalt love thy neighbour,* as the most important moral virtue is an example of normative ethics. The parallel to occupational exposure limits should be: The working environment should never cause health impairments.

Descriptive ethical theory refrains from providing what to do or not to do, but limits the description to the principles and practice of morality. Questions like: *Are there generally acceptable important moral virtues among different cultures?* Or: *What is the content of the concept of high moral virtue?* Setting occupational exposure limits the corresponding problem should be: *How to evaluate acceptability in risk assessment?*

Ethics may thus serve descriptive and analytical purposes only and is thus different from morality. Also normative ethics must have a descriptive and analytical part to differentiate it from preaching, even if there is a close connection between theological and philosophical ethics, and thus between religion and morality.

Teleological and deontological ethics

There is almost an indefinite number of ways to describe and characterize ethical theories. It is outside the scope of this presentation and this course to give a complete overview. For the purpose of this course it is, however, important to discuss the differences between ethics based on the concept of moral value and that based on the concept of duty.

If moral value is the basic concept it becomes important to define and describe the concept of high moral value. Dependent on the chosen definition different ethical theories like *hedonism* with pleasure as the ultimate goal, *eudemonism* with a corresponding stress laid on happiness or satisfaction, or *utilitarism,* which advocates utility as the ultimate moral virtue, have been suggested.

Value oriented ethical theories are often *teleological* or aimed towards a given goal (gr. telos) for human behaviour. Important in these theories is therefore the ways and means to reach these goals. Behaviour in a manner consistent with duty is not a virtue by itself, but only a method to reach a given goal. The implications for the principles of occupational exposure limits should be obvious: *Some workers must suffer to the benefit of the majority (the society as a whole).*

Ethical theories based on moral duty *(deontological ethics)* have the opposite approach to the relationship between moral virtue and duty. Behaviour in a manner consistent with duty is a virtue, only if based on duty, and for that cause alone. It seems that this duty cannot be rationally explained, but depends on the consciousness within oneself, of the choice one ought to make between right and wrong. The duty itself is the highest moral virtue without taking into consideration results or consequences of the behaviour or duty determined action. From the occupational exposure limit or occupational health point of view, there are good reasons for hesitation if exploitation of ongoing developments in biotechnology and molecular biology would be regarded as the duty of the scientist. On the other

hand, we may need a consciousness within ourselves to limit the utilitaristic approach offered by a corresponding teleological model.

Moral virtue – scientific knowledge and the free will

A classical ethical problem, which obviously relates to occupational exposure limits, is the relationship between moral virtue and scientific knowledge. Some philosophers (Socrates and Plato) seem to have meant that knowledge in some form was both necessary and sufficient for high moral virtue. Those who regard volition and emotion as more important for behaviour oppose this rationalistic and intellectual approach to morality, which indicates that morally unacceptable behaviour is based on mistakes or lack of knowledge.

Closely related are the ethical problems of one's free will, how behaviour is motivated and how to influence motivation. There is an ongoing discussion among philosophers about the importance of such questions for the understanding of ethics. Such questions are obviously important in the context of ethical problems and occupational exposure limits and may relate, among other factors, to the contextual bias previously mentioned.

It has been argued that it is theoretically impossible to logically deduct normative moral statements on valid and true premises. The consequence of this is that moral values are always subjective and can neither be true nor false, neither good nor bad, neither correct nor incorrect. Examples, which indicate that this is, however, probably not true, are the so-called applied ethics, which seems to unfold in medicine, in biomedical research and recently in biotechnology and molecular biology. The decisions and statements seem to reflect a set of moral virtues and principles based on generally accepted human value judgements.

Applied ethics also seems to gain momentum as an increasing number of individuals or groups understand that all "reasonable" and "rational" human activity; political, economical, cultural or scientific, and even the use and understanding of human language, necessarily presumes accepted norms and human values. The interest in ethical and normative processes increases and promotes discussion also among others than groups of professional philosophers.

The purpose of such discussion is not necessarily consensus on moral values. Increased attention and mutual understanding based on a better communication to others of the background of one's own moral values, of what seems to be right or wrong, are important. According to ethical theories it is possible by such argument to move towards an agreement that is not based on a utilitaristic principle, but towards an agreement which represents the universally correct moral truth, the so called reflective equilibrium (Rawls's theory). With mutual distrust and condemnation, this discussion is impossible. The universe in such cases should be defined as those taking part, or being represented by the participants in the discussion.

A question - and a possible model for moral reasoning

Finally, let us try to apply ethical theories for discussing a basic conceptual problem of occupational exposure limits: *Should we (the society) accept that some workers are exposed to hazardous chemicals and possibly to a higher risk than others?*

Moral reasoning – or ethical analysis – may be based on the following four important requirements:

1. Issues or points of conflict
2. Interested parties – stakeholders
3. Consequences
4. Obligations

I will not go into details on the description of all the requirements in this specific case. The four points can be used as a framework for analysis of this and similar problems. Each of us will probably answer the question by a combined deontological and teleological ethical approach. We (the society) accept that some workers are exposed to a higher health risk than others because of the consequences to the economy and the development of our society not doing so. This is the teleological model implying an utilitaristic approach based on cost-benefit. It must be noted that this is not a scientific assessment. It is a value judgement based on consequences.

A warning must be given at this stage. Decision makers in politics and administration may try to interpret obvious value judgements as scientific facts. This is specifically important to be aware of by scientists involved in the risk assessment procedure. It is important to remember that scientific truths or facts should always be based on scientific conventions only, and never on the consequences of the truths or facts. The fact that taking consequences into consideration often may offer an easy way out of difficult ethical problems makes this important requirement of science even more important to remember. If scientific truths or laws are changed according to consequences, important principles of the philosophy of science are violated. Such behaviour may even in general threaten the scientific foundations of our societies.

Most of us would, however, probably claim that there is a limit of the utilitarian approach to the ethical dilemma in question suggested above. Based on our intuition there is a limit, which cannot be exceeded whatever the consequences might turn out to be. This is based on a deontological ethical model, which presupposes values that cannot be discussed, values without rational explanation. These may of course relate to one's obligation as a scientist – or as a medical doctor. And who are the stakeholders in a case like this. Why cannot the worker decide for himself? It seems to me that discussions about exposure limits are often confused because the structure of moral reasoning is not clear to everyone.

I have previously discussed the concepts of scientific truths and legal truths. Whether it is possible to define a moral truth in the context of the exposure limit paradigm is very interesting. According to the ethical theories (Rawls's theory) it is possible by continuous individual reflective reasoning and argumentation to reach a morally correct solution to all problems as a limit function. I am not in the position to discuss this postulate in depth, but I feel that the theory is applicable to solve ethical problems in the process of setting exposure limits. To reach an answer to the questions on acceptable risk we should all start out with our own set of values trying to reach this rational reflective equilibrium by open-minded exchanging and interpreting our own values and knowledge with others. This process presupposes awareness of the ethical model used for us, mutual respect for individual values, and organizational structures for discussion. The goal is not necessarily consensus or persuasion, but rather conviction in the group that the decision reached is morally fair and just. Taken universally this would constitute the moral and juridical truth, but not necessarily the scientific fact.

Summary

The exposure limit paradigm differentiates between the scientific approach of risk assessment and the value judgements of risk management. It is important that the concepts of both risk assessment and of risk management are visible.

Experts involved in the risk assessment process are familiar with toxicology, but often unfamiliar with ethics as a methodological approach to moral problems inherent also in science. Utilitarism seems to be the most common approach to the ethical dilemmas of the occupational limits paradigm, but deontological principles applied in professional ethics seem to function as a limitation of the utilitaristic principle in practice.

Dermal exposure

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In several occupations and work situations skin exposure to chemicals is frequent. It may be deliberate or unintentional, recognized or unknown in any combination. It may occur as direct handling of contaminated goods or objects or indirect by touching contaminated surfaces or coming from diffusion through working clothes and protective gloves. Examples are handling manufactured goods soiled with cutting fluid, cleaning the hands with organic solvents after they are heavily soiled or spreading of toxic, allergenic or carcinogenic compounds to the skin in so small amounts that it is not noticeable. If this exposure will represent a health hazard to the exposed person will depend on the amount of chemical, length and intensity of exposure, and type of chemical or product the skin is exposed to.

The skin is the largest single organ of the body with a weight of about 4 kg and a surface area of about 1.8 m^2 on a man of approximately 90 kg. The skin consists of three distinct layers, the epidermis, the dermis and the subcutis. The physiologically most important properties are located in the outermost layer of the epidermis, stratum corneum, consisting of flattened enucleated keratinocytes with a structured intercellular lipid domain surrounding them. The skin is a barrier to our environment with properties to enclose and regulate the body homoeostasis regarding water and temperature. It also is a barrier against invasion of micro-organisms and physical injury. The skin is additionally involved in our behaviour functioning as a signalling system (10). The barrier properties of the skin does not only regulate water loss through diffusion but is in addition a barrier against absorption of chemicals in our environment. The skin is constantly exposed to our environment and all types of dermal exposures present there which makes it vulnerable to injury.

Dermal exposure to chemicals can lead to systemic and/or local reactions depending on the type of exposure. Dermal exposure is usually hard to determine and quantify and there are several methods to assess and visualize skin exposure. These methods include the use of fluorescent compounds, personal samplers, coveralls, tape stripping, and washing of exposed body parts (2, 3, 4, 10, 12). The methods can give qualitative or quantitative results depending on the situation and technique used.

Recently an attempt to make a structured view of dermal exposure has been published (11). This model takes into account the direct distribution of cont-aminant from the source to the skin and clothing. It also deals with several ways

of redistribution from clothing and contaminated skin to other surfaces that may become contaminate and act as secondary sources of contamination. This schematic view is a big step towards a better understanding, quantification and prediction of dermal exposure but needs further development to be the powerful tool it is expected to become.

The dermal exposure to chemicals can lead to various reactions systemically or locally in the skin. The primary step in this is the absorption of the chemical into the skin. The major route of absorption of chemicals through the skin is through the epidermis. In addition to that the skin appendages, hair shafts and sweat ducts, may contribute in a minor way. Skin absorption is influenced by a number of factors of which the physico-chemical properties of the penetrating chemical, the vehicle and the concentration of the chemical in the vehicle are important. The status of the skin, the area and location of exposure and whether the exposure is covered or not are other important and rate regulating factors. Skin absorption is a passive diffusion and follows Fick's law of diffusion (1). The theory of absorption is discussed further in the chapter "Dermal absorption and principles for skin notation", by Johanson G.

The result of dermal exposure, as was mentioned above, varies. The absorption of chemicals through the unprotected skin adds to the total body burden emanating from other routes of absorption. The systemic effect following skin absorption varies depending on the chemical and dose absorbed. It can either be a direct intoxication following absorption of high amounts of toxic chemicals such as pesticides, certain organic solvents and other systemically toxic chemicals. It may result in the induction of cancer following long term exposure to carcinogenic chemicals in low doses. Other direct target organ effects may also follow on systemic absorption at dermal exposure. Systemic intoxication is always at risk following dermal exposure to toxic chemicals but the lethal dermal dose is for most chemicals higher than the oral but several chemicals have a pronounced toxicity at skin exposure with doses equal to the oral dose.

However, the most commonly seen effects following dermal exposure are localized to the skin. Several chemicals are lipophilic and act as delipidizers, extracting the skin lipids and thus influencing the integrity of the skin barrier. Once or twice can easily be repaired by the skin itself but intense exposure over long time with neglecting the use of emollient creams may lead to an alteration of the skin barrier and a subsequent inflammation in the skin. This inflammation, irritant contact dermatitis, is together with its allergy based counterpart, allergic contact dermatitis, the cause of important skin diseases since they are of great economical consequence for the society and persons afflicted. Contact dermatitis, often located to the hands, affects large numbers of persons and often have a long duration which leads to sick leave for extended periods. Hand dermatitis may also be a serious functional handicap at work and may also be socially bothering. Irritant contact dermatitis is often seen in special risk groups where persons with an atopic disposition have the highest risk of developing hand eczema. The risk of developing irritant hand eczema is also associated with certain occupations

involving exposure of the hands to defatting agents such as organic solvents, oils, cutting fluids, detergents and water leads to dryness and often to development of irritant contact dermatitis. The prevalence of hand eczema is around 11% in a normal population (7). In the risk occupations it is considerably higher as a result of the exposure to food, wet work, irritant and defatting agents. Example of these risk occupations are nurses, nurses aids, cleaners, machine operators, dentists and dental nurses, mechanics, hairdressers and cooks.

Allergic contact dermatitis is a cell mediated allergy to low molecular weight (<500) chemicals. It is an acquired alteration of reaction in the immune system. Usually it is a chemical that has been handled and tolerated for a long time that suddenly gives rise to a dermatitis. During this period the sensitization takes place which gives rise to the allergy. Subsequent exposures will induce an allergic response, allergic contact eczema, at the site of contact. This dermatitis can be induced on the whole skin and the allergy usually lasts for the rest of the life. There is no predisposition known and contact allergy can be induce in all persons. The symptoms of the disease, the allergic contact eczema, can be treated and cured by local treatment with steroids and avoidance of exposure but the allergy will still be present and renewed contact will result in a relapse of the sickness and a new eczema.

Prevention of adverse effects from dermal exposure is acquired from avoidance of exposure. It is done with rigorous occupational hygienic measures often in combination with wearing the proper protective clothes (5, 13). Selection of proper protective gloves is important and has to take into account the exposing chemical, work situation and comfort of the worker (8). Proper skin care is also of great importance. Choosing mild soaps and using emollient creams on the hands after work will reduce the risk of local reactions from dermal exposure (6).

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Dermal absorption and principles for skin notation

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Introduction

Dermal exposure is a major route of systemic exposure at work. Along with reductions in OELs and occupational exposure via air, the dermal route has become even more important. In addition, there is a growing use of and interest in transdermal drug delivery, for example of nicotine as a help to quit smoking, and in using dermal permeation enhancers.

Many toxic effects occur only after systemic exposure (direct effects on the skin are treated in the previous charter "Dermal exposure", by Boman A). The steps between the presence of a chemical in the environment to systemic exposure may be divided in two phases (Figure 1). The first phase is the relation between the chemical's presence and the exposure of skin (amount, area, duration). This relation is affected by a number of factors, such as the properties of the chemical, the work process, the individual's behaviour and work practices, type of clothing and protective equipment, etc. The influence of some of these factors may be highly random and is often difficult to predict. The second phase is that from exposure of the skin to systemic exposure. This relation depends on the properties of the chemical and of the skin and is more easily described. It should, however, be remembered that the properties of the skin may also vary thus affecting the absorption rate and systemic exposure.

There is a wide range of absorption rates reported for the same chemical (Figure 2). This reflects the need for standardized approaches. In view of the many sources of variability that are not directly related to the chemical per se, it might be wise to focus on the intrinsic properties of the chemical, i.e. determine dermal absorption rates for a large number of chemicals using standardized methods.

Fick's law

The driving force for dermal absorption of chemicals is diffusion and Fick's law can be applied. The relation may be written as:

$$P = K_p \times (A_1 - A_2)$$

where P is the absorption rate, K_p is a permeability coefficient and A_1 and A_2 are the thermodynamic activities (or partial pressures) of the chemical outside and inside the skin, respectively. The absorption rate or net flux may be expressed either as amount per time unit (e.g. μmol/h) or as amount per time and area unit (e.g. μmol/h/cm^2).

At low concentrations, the molecules are dispersed and do not interact, and activity can be substituted by concentration. At high concentrations, the molecules begin to interact. This reduces the diffusivity and the activity (and partial pressure) becomes sublinear and approaches a plateau value-saturation concentration (Figure 3). In many cases, for instance if there is a spill or splash of solvent on the skin, the activity at the inner side may be approximated to zero. The value of K_p depends on the properties of both the skin and the chemical. The numerical value (and units) of K_p also depends on the units chosen for P and whether activity, partial pressure, or concentration is used.

In summary, the penetration rate is directly proportional to the:
- concentration (activity, partial pressure) of the chemical at the skin surface,
- area exposed,
- permeability of the skin.

The permeability is mainly determined by the
- properties of the chemical,
- properties of the vehicle (if present),
- thickness of the keratin layer in stratum corneum,
- condition of the skin.

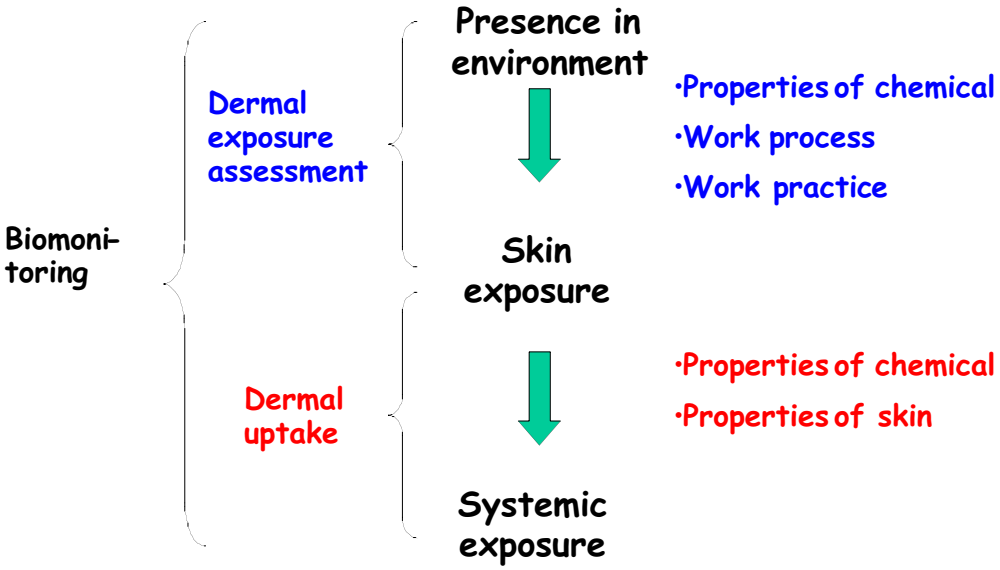

Figure 1. The relation between presence of chemical in the environment and systemic exposure via skin.

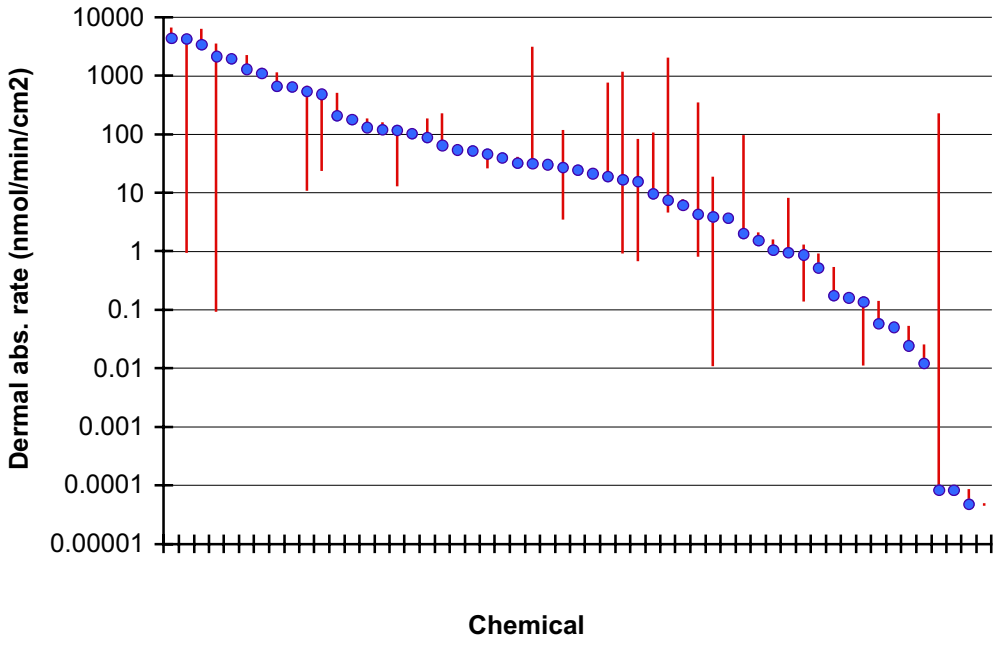

Figure 2. Reported dermal absorption rates vary by several orders of magnitude between different industrial chemicals. Each dot represents one chemical. Reported values for the same chemical may also vary greatly (vertical bars). Note the logarithmic scale. Adapted from (2).

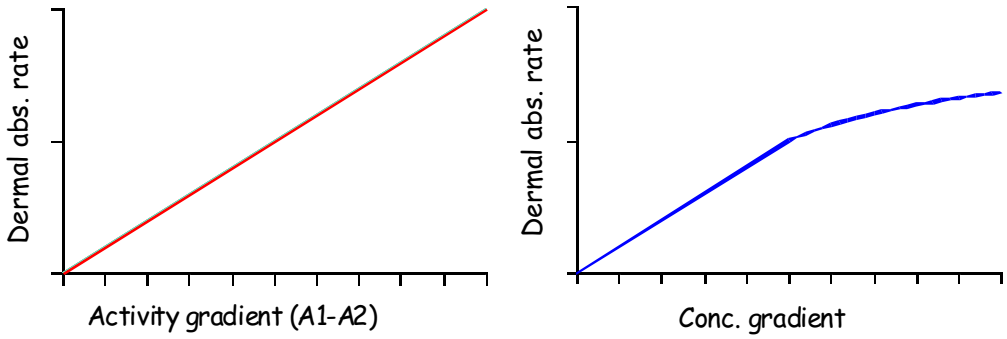

Figure 3. The dermal absorption rate is proportional to the activity and (at low concentrations) the concentration gradient over the skin.

The keratin layer varies considerably between species and between different parts of the body. It is therefore important to measure dermal absorption under standardized conditions, in order to obtain comparable results.

The activity (and partial pressure) depends not only on the concentration of the chemical but also on the properties of the vehicle. Thus, one chemical may express high dermal penetration when dissolved in water and low penetration when dissolved in vegetable oil. Another chemical may show the opposite behaviour. The vehicle (as well as the chemical itself) may also change the properties of the skin, thus affecting penetration via a change in the permeability coefficient.

Conditions of the skin that may affect the penetration include the:

– the degree of hydration,
– defatted skin,
– physical damage, wounds, cracks, and eczema.

Per cent absorbed dose and absorption rate at steady-state

The per cent dose absorbed is often used as a descriptor of a chemical's ability to penetrate the skin. The value obtained depends on a variety of factors, including: exposed area, exposure duration, applied dose, and occlusion. The per cent dose absorbed is therefore difficult to interpret. A better alternative is to apply chemical in excess on a defined area and then determine the lag time for penetration and the absorption rate at steady state. This can be done both *in vitro* and *in vivo*.

Dermal absorption *in vitro*

Dermal absorption may be measured *in vitro* using a Franz' cell (Figure 4). The cell is thermostatted to skin temperature and consists of a donor chamber containing the chemical and a receptor chamber with physiological saline or another suitable medium. The chemical has to penetrate a skin flap to reach the receptor chamber. The lag time and absorption rate at steady state is calculated by mass-balance from the concentration-time curve of chemical in the receptor medium. The shape of the curve will depend on whether a static or dynamic (flow-through) receptor chamber is used.

Dermal absorption *in vivo*

The lag time and absorption rate can be obtained in a similar way from *in vivo* experiments (Figure 5). In this case the dynamic receptor chamber corresponds to the whole body and, although the mass-balance over the skin is essentially the same, the toxicokinetic analysis becomes more complicated. Instead of volume

and receptor medium flow rate, the rates of redistribution and metabolism has to be known. It may be convenient to use a physiologically-based pharmacokinetic (pbpk) model in this kind of analysis.

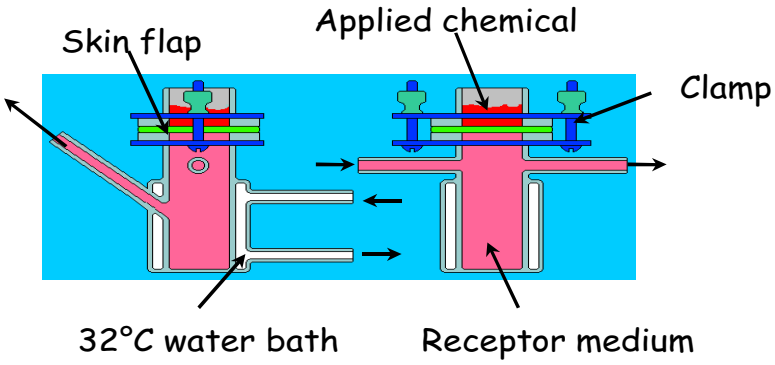

Figure 4. The Franz' cell for dermal absorption studies *in vitro*. *Left*: Static receptor chamber. *Right*: Dynamic receptor chamber.

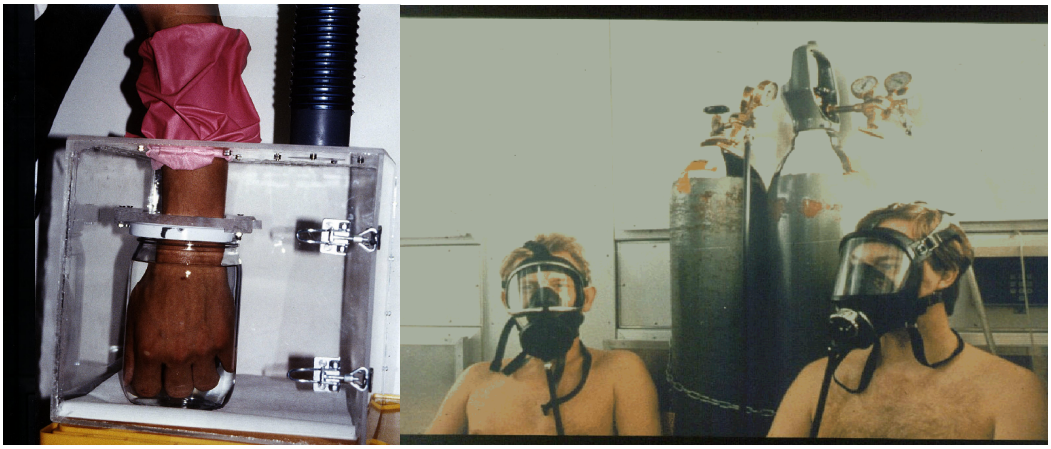

Figure 5. Dermal absorption experiments *in vivo*. *Left*: Exposure of one hand to liquid. A ventilated box is used to eliminate inhalation exposure to vapours. *Right*: Whole-body exposure to vapour. Air masks are used to eliminate inhalation exposure.

Dermal uptake of vapours

The skin is designed to protect from water losses and is relatively impermeable compared to the lung. The latter is designed for rapid gas exchange, has a large surface area, and is highly permeable. Dermal uptake of vapours and gases is therefore in most cases negligible (below a few per cent) compared to inhalation uptake. Important exceptions to this rule are organic solvents with low vapour pressure, good solubility in skin, and good penetration properties, such as nitro compounds and glycol ethers.

Calculation of dermal absorption rate by structure-activity analysis

For a given piece of skin, the absorption rate is largely determined by the polarity and diffusivity, i.e. the structure, of the molecule. Many structure-activity equations have been proposed, for example:

$$\log P = -6.3 + 0.71 \log K_{ow} - 0.0061 MW$$

where P is the absorption rate, K_{ow} the octanol:water partition coefficient, and MW the molar weight (1). Structure-activity equations generally give good predictions within a class of chemicals or homologous series (e.g. alcohols) but severely erroneous predictions may be obtained when moving from one group to another.

Criteria for skin notation

There are two useful criteria for skin notation:

1. a defined (area, duration, etc) skin exposure increases the systemic dose by a given percentage, compared to inhalation exposure at the OEL, and/or
2. realistic dermal exposure at the workplace has been shown to cause adverse effects.

Vague criteria (Table 1) and lack of good data have lead to different classifications for the same chemical by different authorities and organisations (Table 2). An additional problem is that substances, even those with a skin notation, vary by several orders of magnitude in their ability to penetrate the skin. Thus, there is a need to characterise chemicals in a more informative way than in the simple yes/no (skin notation or not) fashion presently used.

Table 1. Criteria for assigning a skin notation in different countries.

Denmark	"When known that the substance can be absorbed via skin"
Norway	"Substances that can be taken up via skin"
Finland	"Absorbed amounts and health risks cannot be evaluated only from air concentrations"
Sweden	"Substances easily taken up by the body via skin"
Germany (MAK)	"When dermal exposure increases the body burden"
European Union (SCOEL)	"Substantial contribution to total body burden via dermal exposure"
USA (ACGIH)	"Potential significant contribution to overall exposure..."
The Netherlands (DECOS)	"More than 10% contribution to total exposure..."
European industry (ECETOC)	"More than 10% contribution to total exposure..."

Table 2. The skin notation differs by country for several chemicals. Adapted from (2).

	SWE 2000	NL 2001	ACGIH 2001	GER 2000	UK 2001	NO 2000	DK 2000	FIN 1998	SCOEL 1998
Butanone 2-	no S	no S	no S	S	S	no S	S	no S	–
Benzyl acetate	–	–	no S	–	–	–	–	–	–
Butyl acetate	no S	no S	no S	no S	no S	no S	no S	no S	–
Cyanide	S	S	S	S	S	S	S	S	–
DEGBE	no S	S	–	no S	–	–	no S	–	–
DEGBEAc	no S	no S	–	–	–	–	–	–	–
DEGEE	S	S	–	–	–	–	–	–	–
Dichloromethane	S	no S	no S	no S	no S	no S	S	no S	–
Dimethylethylamine	no S	no S	–	no S	no S	no S	no S	no S	–
Dinitrobenzene	S	S	S	S	S	S	S	S	–
EGBE	S	S	S	S	S	S	S	S	S
EGEEAc	S	S	S	S	S	S	S	S	–
EGiPE	S	S	–	S	–	no S	no S	–	–
Ethanol	no S	no S	no S	no S	no S	no S	no S	no S	–
Ethylbenzene	no S	S	no S	S	no S	no S	no S	no S	S
Ethylene glycol	S	no S	no S	S	no S	no S	S	no S	S
Furfural	S	no S	S	S	S	S	S	S	–
Methanol	S	S	S	S	S	S	S	S	no S
n-Butanol	S	no S	S	no S	S	no S	S	S	–
PGME	S	no S	no S	S	S	no S	no S	no S	–
PGMEAc	S	no S	–	no S	no S	S	no S	S	S
Phenol	S	S	S	S	S	S	S	S	S
Propanol 1-	no S	–	no S	–	S	S	S	no S	–
Styrene	S	no S	no S	no S	no S	no S	S	no S	–
Tetrachloroethylene 1,1,1,2-	no S	S	no S	S	no S	S	S	no S	–
Tetrahydrofuran	no S	S	no S	no S	S	no S	S	no S	S
Thiourea	no S	S	–	no S	–	–	–	–	–
Toluene	S	no S	S	S	S	S	S	S	–
Trichloroethane 1,1,1-	no S	no S	no S	no S	no S	no S	no S	S	no S
Trichloroethane 1,1,2-	–	no S	S	S	–	S	S	no S	–
Trichloroethylene 1,1,2-	no S	no S	no S	no S	S	no S	no S	no S	–
Xylene	S	S	no S	S	S	S	S	S	S

S = skin notation.
no S = no skin notation.
– = not listed.

Dermal uptake index

One alternative to skin notation would be to use an index, i.e. the ratio between dermal and inhalation uptake under specified conditions.

$$Dermal\ Index = \frac{P_{skin}}{P_{inh}}$$

, where P_{skin} is the absorption rate via skin at steady-state, and P_{inh} is the absorption rate via inhalation during exposure at the OEL (3). The absolute value of the index will depend on chemical dependent factors (penetrating properties and OEL of the chemical) and chemical-independent factors (area and region of skin, pulmonary ventilation, and pulmonary retention), which have to be fixed. As seen in Figure 6, the dermal index varies by several orders of magnitude for different industrial chemicals. Thus, the index gives more quantitative information than a yes/no as in traditional skin notation.

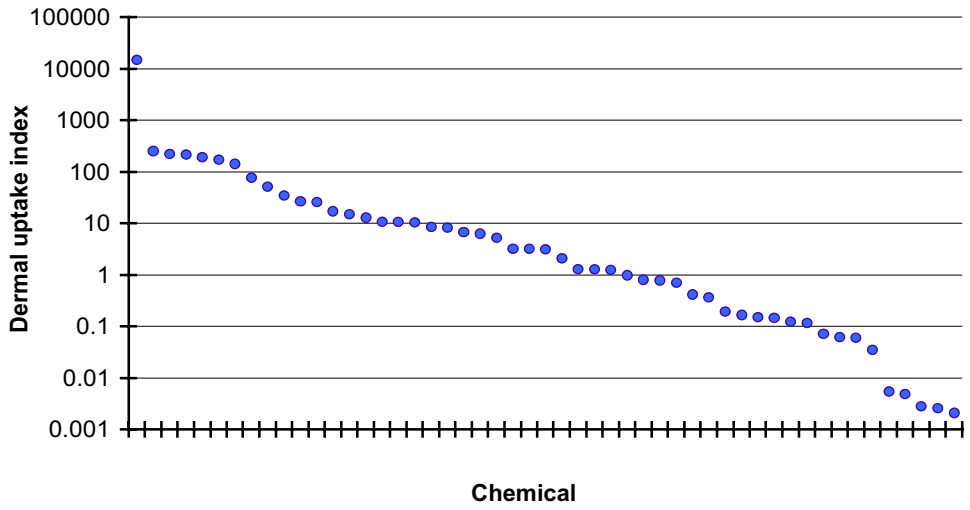

Figure 6. Dermal uptake indices calculated for industrial chemicals (same as in Figure 2). Each point represents one chemical. Note the logarithmic scale. Adapted from (2).

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Exposure to particles and lung disease

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Introduction

Particulate substances in the air at the workplace may be present as dust (fine particles of dry matter), mist (liquid droplets in gases) or as components of fumes (very fine dusts in gases, particularly air as a result of a chemical or thermal processes). If inhaled by the workers they may cause physiological, biochemical or histopathological abnormalities in the respiratory system. Other organ systems such as the cardiovascular system may also be affected if the particles or their components are translocated to sensitive receptor sites at other locations. There is growing interest for effects on the cardiovascular system from inhaled dust particles (11, 24). The purpose of this paper is to discuss some aspects of particle induced respiratory diseases in relation to risk assessment and occupational exposure limits.

Uncertain statistics for occupational exposures and lung disease

Occupational diseases are underestimated in Norway. Using pneumoconiosis as an example, only less than 10 cases of silicosis have been reported annually to the authorities since 1990. The corresponding notifications for asbestosis are 60-100, with no decreasing trend. Mineral particle induced lung diseases occur from a few years up to decades after onset of exposure, depending on the cumulative dose. For the last 10 years the occupational exposure limit (OEL) for respirable quartz dust and asbestos fibres have been 0.1 mg/m^3 and 0.1 fibres/ml, respectively. Earlier the limits were 0.2 mg/m^3 for quartz and 2 fibres/ml for asbestos. In this period, there has been change in technologies, automation of industrial processes and less dust at most, but not all workplaces, whereas many dusty industries have shut down. Although the database EXPO on occupational exposures at the National Institute of Occupational Health does not include representative nation-wide samples, it shows that the median quartz dust levels have been well below the OEL during the last decade. The highest exposures to respirable quarts dust today are found in construction industries during drilling in rocks.

OELs and inhaled particles

Health based OELs are generally based on responses observed in human volunteers, epidemiological studies or in laboratory animals. A major determinant for the toxic effects of particulate pollution is the size distribution of the particles in the air at the workplace, since size also determines deposition on to the airway surfaces, clearances from these sites, translocation to the underlying epithelium, and inherent toxicity to some extent. Other particle related factors for pulmonary toxicity and adverse affects are: chemical composition, durability in the lung tissues, the biological or mineralogical origin, whether natural or synthetic, amorphous or crystalline, surface characteristic, elemental composition and structure. Mineral particles presenting as mineral fibres have different biological properties compared to their non-fibrous counterpart. Impurities and absorbed pollutants should also be taken into account in the assessment of toxicity.

Sampling of airborne particulates for risk assessment and health surveillance

The proportion of particles at the workplace which is inhaled into the human body depends on the properties of the particles, on air movements near the body, and whether breathing is through the nose or mouth. Inhaled particles can deposit in different parts of the airways depending on the properties of the particles, the respiratory tract and breathing pattern. Since the deposition site is related to particle size, the adverse health effects may also be related to the deposition site. The European Standard defines standards and criteria for particle size-selective dust sampling to be used to for collecting airborne particles at the workplace (14). The sampling conventions are derived from experimental data in healthy adults, to be used for setting OELs to protect the mean worker. For comparisons of deposition probabilities for particles with various sizes, shapes and densities, the particles are characterized by their aerodynamic diameter (d_{ae}) which is defined as the diameter of a sphere with density 1 g/cm^3 which sediments at the same rate as the particle in calm air.

The Standard defines five size specific mass fractions of total airborne particles that can be sampled for health risk assessment and regulatory purposes; 1) particle mass fractions inhaled through the mouth and nose (inhalable fraction), 2) the fraction failing to penetrate beyond the larynx (extrathoracic fraction), 3) the fraction penetrating beyond the larynx (thoracic fraction), 4) beyond the larynx but failing to penetrate to the gas exchange region (tracheobronchial fraction), and lastly 5) penetrating to the gas exchange region of the lung (respirable fraction). The conventions are defined for inhalable, thoracic and respirable fractions. These conventions are illustrated in Figure 1. Extrathoracic and tracheobronchial fractions are calculated from these three defined conventions.

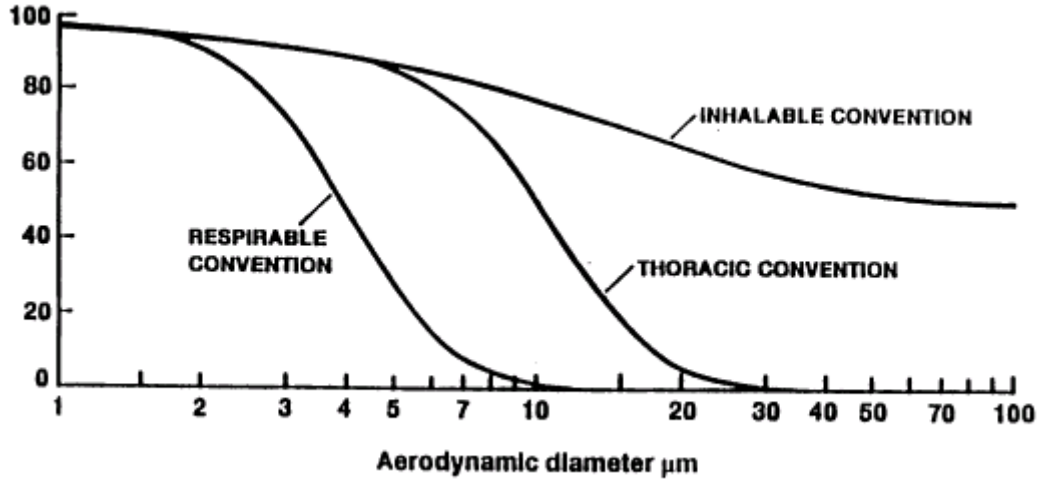

Figure 1. Conventions for size-specific mass fractions of total airborn particles.

Respirable dust particles

Respirable dust is thus airborne particulate material that is capable of penetrating to the gas-exchange region of the lungs. In occupational settings it is collected as PM_4 (the mass of particles present in the air having a 50% cut-off for particles with an aerodynamic diameter of 4 μm). Occupational exposures include particles such as asbestos and other silicates, silica, coal mine dust, cadmium and other metal fumes, organic particles and smaller particulate matter (PM) without clearly defined chemical composition.

PM_{10} and $PM_{2.5}$

These modes are used primarily for Ambient Air Quality Standards for particulate matter (13). PM_{10} is the mass of particles present in the air having a 50% cut-off for particles with an aerodynamic diameter of 10 μm. It is the standard measure for respirable particles used for ambient air particulates (10). They also occur at the workplace. There are two partly overlapping modes (13), with a sharp cut at 2.5 μm in order to be able to analyse the concentrations of fine and coarse particles separately.

The coarse mode, $PM_{2.5-10}$, is formed from large solids and/or droplets. In ambient air they may occur as mechanical disruption products from soil or soil like sources. In occupational settings they occur through grinding or crushing of solids, abrasion of surfaces or evaporation of sprays. They are produced during welding, sandblasting and mining. Other exposures occur during farming and work with bio aerosols.

The fine mode consists of smaller particles, measured as $PM_{2.5}$ (the mass of particles present in the air having a 50% cut-off for particles with an aerodynamic diameter of 2.5 μm). They are formed by chemical reactions predominantly from combustion sources, nucleation, and condensations of gases and coagulation of smaller particles. The particles are very numerous and represent large surface

areas, compared to mass. The chemical composition is less uniform. Typically it results from combustions of fossil fuels and high temperature industrial processes such as welding, soldering, and smelting. There is good correlation between $PM_{2.5}$ and particle dimensions found in the respiratory system of urban dwellers (4).

For some occupational exposures there are mixtures of respirable particles, such as coal particles from different sources. In coal mines a 0.8 μm cut-off is used, with almost all of the diesels exhaust particles laying below that cut size and almost all of the coal dust lying above it.

Ultrafine (Very very fine) particles

These are still finer particles within the respirable fraction. The term refers to particles less than 0.1 μm. They are constituents of ambient air and occur regularly in some occupational exposures such as metal fumes and polymer fumes. The number of particles and total surface area are large compared to mass.

Mixed exposures

Although lower than in the past, exposures today are generally more complex and mixed. Smoking lung cancer patients retain more mineral particles in the peripheral airways compared to non-smokers, thus increasing the risk for toxic effects in peripheral airways (5). Inversely, for quartz particles in cell cultures, the inflammatory effect is decreased in the presence of excess aluminium (12). The lower exposure levels of quarts today, often in conjunction with other particulates, notably aluminium silicates, induce less fibrosis in the airways, lung or pleura, and not the full-blown picture of silicosis.

Inhaled particles: airways defence and failure

The ciliated cells of the airway epithelium are covered by mucous which embeds deposited particles and clear them towards the pharynx and the gastrointestinal tract. This airway defence system is impaired by prolonged inhalation of pollutants. Irritation and cytotoxic effects may induce lesions in the cells of the respiratory epithelium which can slough off, followed by regeneration, squamous cell metaplasia thus further preventing the transport of particles upwards.

In the gas exchange region of the lung there are no ciliated cells. Phagocytosis and secretion by alveolar macrophages represents the primary defence line in these regions, and thereafter the phagocytic cells gain access to the mucociliary escalator. The phagocytic rate depends on size, morphology and surface characteristics of the particles. Mineral fibres longer than 15-20 μm are incompletely phagocytized. Many factors are involved in the phagocytic process. Highly cytotoxic particles such as quartz are less readily cleared through phagocytosis than less toxic particles. Ultrafine poorly soluble particles impair phagocytosis in cell cultures to a greater extent than fine particles on a mass basis (26). Human alveolar macrophage function is also impaired after exposure to ultrafine carbon particles (18). When the ultrafine particles escape phagocytosis, they can penetrate

the epithelial cells and induce toxicity or pass through the epithelial lining of the airways into the interstitial spaces and induce acute inflammation.

Particle overload

Ideally chronic exposures and subsequent dose levels results in lung burdens without adverse effects; the no-observed-effect-level (NOEL). This happens when the particle deposition rate is equal to or lower than the pulmonary clearance rate. However, when the clearance rate is exceeded, the particle burden may build up in the lung tissues. This overload is due mainly to impairment of the macrophage mediated clearance function (19). In chronic rat inhalation studies this overload has been shown to produce chronic inflammation in the airways and lung tissue, resulting in pulmonary fibrosis and tumours. Mice and hamsters also accumulate particles at the same exposure concentrations, but there is less inflammation and no tumours have been observed, due to more efficient protection towards inflammatory induced oxidative DNA-damage (17). The role of clearance impairment and overload in humans is not settled. There seems to be a good overall correlation between the fraction of dust deposited in the lung lobes and the frequency of lung cancer in the same lobes (28). On the other hand, coal workers chronically exposed to very high dust levels, rates of lung tumours are not significantly increased (16). Histological examination of lung tissues in general also indicates that they can accumulate a considerable burden of dust without adverse effect. Concurrent toxic exposures, such as smoking which impairs clearance, needs to be studied further.

Particle accumulation in the respiratory system

Respiratory bronchioles accumulate particularly high particle loads, typically 25-100 times the concentrations seen in the main stem bronchus. Similarly high concentrations are found in the large airway carina's, suggesting that these locations are likely sites for particle toxicity. Ultrafine particles, which are associated with toxicity of particulate matter in experimental situations, are present in small numbers as single particles and are largely metals. They represent perhaps combustion products, but carbonaceous chain aggregates are rarely found. Mean particle aerodynamic diameters vary from about 0.3 to 0.6 μm in different parts of the airways. Overall the airways retain $PM_{2.5}$ rather than PM_{10}, a finding supporting the observation that, in some studies, adverse health effects appear to correlate better with $PM_{2.5}$ than with PM_{10} (4).

Dust particles are found in alveolar and interstitial macrophages, the peribronchial perivascular, the subpleural connective tissues, in the lymphatic vessels, and lymph nodes. The major mineral species found in the normal lungs of urban dwellers are silicates and silica (29). Mineral fibres constitute less than 10% of the total mineral dust burden (5). The size distribution of non-fibrous minerals

extracted from the human lung is 0.6-0.73 μm (6, 7, 29). The dust load is positively correlated with age (29) and smoking (5).

Adverse health effects

Reflex responses from inhaled particles

Inhaled particles, with or without chemical irritants absorbed to the surface, may interact with the rich innervations of the airway linings. Depending on particle characteristics, this interaction produces reflex changes in breathing patterns, including coughing, sneezing and bronchial constriction. Other effects are reduction in ventilation rates and volumes, and excess secretion of mucus (1). Other effects such as intoxication, unpleasant smells or pain, may act to prevent further exposure of the respiratory tract.

Diseases of the respiratory tract and related to particle size

Some particles exert immediate local effects (irritation, corrosion) at the site of deposition, whereas others are translocated to other parts of the respiratory tract where they are absorbed or cause a biological effect. Although not always the case, particle size predicts the site and type of primary response. Examples are effects in the head airways region by particles within the inhalable fraction, such as rhinitis due to pollen allergens or fungi with large d_{ae} and carcinoma of the nose and nasal cavities due to wood dust. Particles within the thoracic fraction can be deposited in the conducting airways and contribute to exacerbations of asthma, the development or progression of chronic bronchitis and bronchial cancer. Even more distally, in the gas exchange region of the lung, pneumoconiosis or alveolitis is induced by particles within the respirable fraction.

Ambient air PM_{10} is associated with increased mortality in adults (9), a finding that is not consistent in all studies (27). In children, there is evidence of bronchitis (8) and decreased lung function (25). The fine particles $PM_{2.5}$ are well correlated with increased mortality among sensitive individuals in the population. The fine mode has not been considered for OELs since occupational exposures have not been sufficiently studied.

In animal experiments ultrafine particles like Teflon or titanium dioxide less than 0.05 μm produced much stronger inflammatory responses than 0.5 μm particles with the same mass concentrations (11, 21, 22). Also ultrafine polystyrene particles are more biological active compared to fine particles with the same mass. Oxidative stress can cause this enhanced activity (3). It has not been settled yet whether particle count is a more appropriate measure related to health effects than the particle mass used for larger particles (20). Solubility and uptake into pulmonary cells play an important role because of the small particles.

Asthma

Asthma is characterized by chronic inflammation of the airways, and intermittent airway obstruction as determined by reduced FEV_1. Particles within the thoracic fraction may act as inducers or as provokers of asthma. Allergens in animal houses are among the most potent inducers and provokers of asthma; levels around 1 ng/m^3 may cause asthma attacks. Exposure to flour proteins in the range 1-100 μg/m^3 is likely to cause IgE mediated respiratory symptoms. Once sensitized, inhalation of very low doses may cause an attack, but even when the dose is insufficient to cause an attack, it may worsen the airway inflammation and hypersensitivity.

For some low molecular weight chemicals at the work place such as anhydrides and isocyanates, where the mechanisms of sensitization are not solely IgE mediated exposures, exposures to 1-100 μg/m^3 cause respiratory symptoms.

It is not possible to set an OEL that fully protects already sensitized individuals. When scientifically justifiable an OEL could aim at avoiding new cases for defined allergens, when the mechanism of sensitization and dose-response relationships for these are known. In one study of asthma due to prepolymerized isocyanates in smoking spray painters, peak exposures and not mean exposures, were correlated with impairment in lung function (31). More research is needed on this important issue, as a basis for OEL setting.

Non-allergic particles worsen asthma at exposure concentrations often above 1000 mg/m^3. The non-allergic reactive airways dysfunction syndrome (RADS) may be caused by even higher concentrations. Epidemiological studies do not show that increases in PM_{10} elevated the risk for sensitization and induction of asthma (10). Mechanisms of diesel exhaust particle-induced allergy and asthma have been suggested form animal data (30), but it is not known whether these apply in humans (23).

Small Airways Disease

There are two major forms of small airways disease associated with inhalation of dusts and fumes, both are associated with chronic obstructive lung disease. The most common is respiratory bronchiolitis associated with cigarette smoking, in which there is chronic inflammation in the small airways associated with mild fibrosis, variable smooth muscle hyperplasia, accumulation of carbonaceous material and tan pigmented macrophages in the respiratory bronchioles and adjacent alveolar ducts. The other form is mineral dust-associated small airways disease. Typically deposits of mineral particles are found in the walls of small airways and alveolar ducts, particularly at their bifurcations. The fibrosis may be prominent and extend further into the alveoli (32). These adverse effects in the airways are also seen jointly with interstitial fibrosis due to fibrogenic dusts.

Pulmonary fibrosis

Weakly fibrogenic dusts, such as coal dust, carbon black and titanium dioxide, deposited in the walls of the respiratory bronchioles are associated with mild and predominantly reticulin fibrosis and centriacinar emphysema. There is little disruption of the normal tissue structures and scant interstitial fibrosis, in contrast to the collagen rich fibrosis due to highly fibrogenic dusts such as quarts and asbestos fibres. Pneumoconiotic nodules in the lungs are characteristic for the pulmonary response to silica and silicates, but also to the less fibrogenic dusts such as in coal workers pneumoconiosis. Diffuse interstitial fibrosis is the primary response to fibrous dusts (e.g. asbestos) but is also seen to some extent following exposure to silica, silicates and coal dust (2). There is a dose-effect relationship between exposure to the minerals and the degree of lung fibrosis, but not for the advanced stages complicated by super infections, progressive massive fibrosis or by end-stage lung.

Pulmonary fibrosis appears to involve complex interactions between proinflammatory and anti-inflammatory forces. Many studies have confirmed the role of endogenous and exogenous reactive oxygen species, other free radical species and proinflammatory cytokine releases, in particle induced chronic inflammatory processes and fibrosis.

The low OELs for quartz is not only due to the higher fibrogenic potential, but also because it is classified as a carcinogen. It is still a matter of debate whether pulmonary fibrosis is a mechanistic step in tumour induction by quartz and asbestos.

Carcinogenic effects

Inhaled poorly soluble fibrous and non-fibrous particles may interact with the cells in the respiratory epithelium and induce lung tumours by two different mechanisms. Firstly some particles are associated with primary genotoxic effects, and thus induce tumour formation through a non-threshold mechanism. Humans exposed to such particles are at increased risk, since any amount of these direct-acting carcinogens in theory can cause mutation. Secondly tumours may arise as a result of cytotoxicity, inflammation and increased cell proliferation. The particles may then act through a threshold mechanism. Humans exposed are not at increased risk when exposure concentrations do not induce inflammation and do not overcome the antioxidant and DNA repair capacity of the lung (15). Continuous animal inhalation studies with a variety of poorly soluble particles, TiO_2, quarts, or diesel exhaust particles, leading to overload and chronic inflammation of the lung and airways, have shown lung tumour induction (17). Inflammation is however not a prerequisite for mineral fibre carcinogenicity since all inhalable fibres seem to produce chronic inflammation at continuous inhalation over time beyond a certain level, but not all of them are carcinogens.

Standards for particles at the workplace and in ambient air

In occupational health the OELs are generally chemical specific, but not for particles with low toxicity (nuisance dusts). Particles at the workplace will not always have a homogeneous chemical composition, and there may be differences in size distributions for one dust in different occupational settings. The use of OELs for risk assessment and worker protection must be done knowing the pitfalls.

Opposite, for ambient air quality standards in the US there are only six defined chemical standards, whereas the standard for particulate matter is not specified in terms of chemical composition. For fine and ultrafine particles mass and chemical composition may thus be less important than the high particles numbers, for the health outcomes.

For ultrafine particles there are no regulatory standards neither for ambient air nor at the workplace, due to poor understanding of the adverse health effects in humans and that techniques for measuring them has not fully emerged. More clarification is needed on exposures and effects for these particle fractions.

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Occupational exposure limits and mixed exposures

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Abstract

In general, occupational exposure limits (OELs) are set for single chemicals and for more or less defined complex chemical mixtures such as, for instance, wood dust and welding fumes. To properly assess the potential health risks of chemical mixtures, it is essential to understand the basic concepts similar joint action, dissimilar joint action (with positive or negative correlation of susceptibility) and interaction of combinations of chemicals. It is equally important to distinguish between simple, defined mixtures at the one hand, and complex mixtures at the other hand.

In some countries, it has been recognised that in occupational standard setting consideration should be given to combined effects of simple, defined mixtures of two or more chemicals, using the appropriate formulas for assessing whether or not exposure to such mixtures at a given workplace is of health concern.

Recently, a scheme has been developed for the safety evaluation of complex mixtures. Two conspicuous elements of this scheme are the dichotomy of complex mixtures into mixtures that are virtually unavailable and mixtures that are readily available for testing in their entirety, and the identification of the *n* (say, ten) most risky chemicals or most risky classes of chemicals in the mixture. A workplace atmosphere is an excellent example of a complex mixture virtually unavailable for testing in its entirety. Once the (limited number of) most risky chemicals or classes of chemicals have been identified, a safety evaluation of the mixture of these selected chemicals (or pseudo chemicals each of which represents an identified class of chemicals) can be performed, using procedures suitable for hazard identification and risk assessment of simple, defined mixtures. In brief, the safety evaluation of a (complex) workplace atmosphere can be tackled by evaluating the safety of the defined mixture of its major (most risky) constituents.

Introduction

Humans are exposed concurrently and sequentially to hundred thousands of chemicals from very different sources such as food, drinking water, beverages, occupation, indoor and outdoor air, soil and consumer products. Thus, mixed exposures are everywhere and are the rule rather than the exception, indicating

hazard identification and risk assessment should focus on mixtures rather than on single chemicals (5, 12). However, until recently about 95% of the sources in toxicology were devoted to the exception, viz. single chemicals (22). Although all of this is true, there is another aspect of exposure to chemical mixtures that should not be overlooked: chemical mixtures are characteristic of life, and in a way our body can be regarded as a big reaction vessel with a complex, well structured, highly organised content. When we eat and breathe, we feed into this reaction vessel several hundred thousands of chemicals at the same time. As far as we can judge, as a rule (healthy) humans (and animals) apparently have learned to deal with simultaneous exposure to huge numbers of chemicals. In fact, exposure to certain chemical mixtures, for instance essential nutrients, drinking water and air are vital. Consequently, the focus in toxicology, including occupational toxicology should not be just on mixtures but on *priority* mixtures, priority being determined by (potential) risk rather than by toxicity (9).

The vast majority of occupational exposure limits (OELs) relates to single chemicals, and notes of warning for potential risks due to simultaneous exposure to certain other chemicals are generally lacking. However, OELs have been set for a small number of more or less defined complex mixtures such as e.g. wood dust, rubber solvent, stoddard solvent, welding fumes, asphalt fumes, coal dust and cotton dust. According to the American Conference of Governmental Industrial Hygienists (ACGIH), primary consideration should be given to the combined effects of mixed exposures to two or more chemicals which act on the same target organ (1). In the absence of information to the contrary, such effects should be considered as additive and the additivity rule should be applied to find out whether or not mixed exposure at a specific workplace is of health concern. The same rule is applied in Sweden (20). In the Netherlands, the same rule is also applied but only for chemicals with the same target organ *and* the same mechanism of action (21). The ACGIH (1) explicitly states that the additivity rule should not be used for mixtures of which the individual chemicals affect different organs, and ACGIH further explains that in such cases the formula for independent effects should be used to judge whether a specific mixed exposure situation is of health concern. Several countries recognise that synergistic action may occur with some combinations of chemicals, and observe that such cases must be dealt with on a case-by-case basis (1, 20). Awareness of the possibility of synergistic effects is, according to the Swedish National Board of Occupational Safety and Health (20), reason enough to keep occupational exposure concentrations as low as possible. The German "MAK-Kommission" refuses to use simple rules for calculating OELs (6). However, the German committee is willing to consider the recommendation of OELs for defined, specific mixtures of great practical importance on the basis of the committee's own studies. The Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Union (EU) does not derive OELs for such mixtures but when mixed exposure is of particular significance at the workplace the SCOEL will make a note to that effect in the documentation summarising the recommendations for the individual chemicals in question (8). For

details on the formulas to be used for assessing the potential health concern of the different types of mixed exposures, the reader is reffered to ACGIH (1).

To be able to properly assess the potential health risks of chemical mixtures, it is essential to understand the basic concepts of joint action and interaction of combinations of chemicals (18), and to distinguish between simple and complex chemical mixtures (10). These aspects will be briefly discussed in the present paper. Moreover, the major conclusions of a series of experimental studies relevant to safety evaluation of chemical mixtures will be presented.

Basic concepts

Some 50 years ago pioneers in the field of toxicology of chemical mixtures defined three basic types of action for combinations of chemicals that are still valid today (18):

Similar joint action

This form of action is also referred to as dose addition. Similar joint action is non-interactive, which means that the chemicals in the mixture do not influence each other's toxicity. Each chemical in the mixture contributes to the toxicity of the mixture in proportion to its dose, expressed as the percentage of the dose of that chemical alone which would be required to obtain the given effect of the mixture. All chemicals in the mixture act in the same way, by the same mechanism of action, and differ only in their potencies. This concept of joint action also serves as the basis for the use of toxic equivalency factors (TEFs).

Dissimilar joint action

This form of action is also non-interactive. Thus, the chemicals in the mixture do not affect the toxicity of one another. However, the modes of action and possibly but not necessarily, the nature and the site of the toxic effect differ among the chemicals in the mixture. This form of action is also referred to as independent joint action or response addition. For this mode of action it is important to understand the concept "correlated susceptibility". Two different concepts have been formulated: *complete positive correlation and complete negative correlation of susceptibility*. Assume a mixture consists of two chemicals X and Y. In case of *complete positive correlation,* individuals most susceptible to toxicant X are also most susceptible to toxicant Y. The toxicity of the mixture X + Y will be determined by the chemical with the highest concentration, and the proportion of individuals responding to the mixture will be equal to the response to the most toxic agent in the mixture. If, for instance doses of X and Y result in 15 and 25% deaths, respectively, the mixture of X + Y will result in 25% deaths. In case of *complete negative correlation*, individuals most susceptible to X are least susceptible to Y. The percentage of the individuals responding to the mixture will be

equal to the sum of the response to X and the response to Y. If, for instance the doses of X and Y result in 15 and 25% deaths, respectively, the mixture of X + Y will result in 40% deaths.

Interaction

All deviations from the former two concepts are defined as interactions. The term "interaction" describes the combined effect between chemicals resulting in a stronger effect (synergism, potentiation, supra-additivity) or weaker effect (antagonism, sub-additivity, inhibition) than expected on the basis of additivity.

These basic principles of joint action of chemicals and interaction between chemicals in a mixture are theoretical. In reality, however, one will most likely have to deal with these various concepts at the same time, especially when mixtures consist of more than two, say 10 or more compounds. For more details on these basic concepts and their application in safety evaluation of mixtures, the reader is referred to a review by Cassee *et al*.(5).

Simple and Complex Mixtures

A *simple* mixture consists of a relatively small number of chemicals, say ten or less, and its composition is qualitatively and quantitatively known. Examples are a cocktail of pesticides, a combination of medicines, and a combination of food additives. A *complex* mixture consists of tens, hundreds or thousands of chemicals and its composition is qualitatively and quantitatively not fully known. Examples are welding fumes, wood dust, drinking water, environmental tobacco smoke, and a workplace atmosphere.

Simple, Defined Mixtures

Lessons from studies with simple, defined mixtures.
During the past 15 years, at TNO we carried out a series of toxicity studies in rats with various types of simple, defined mixtures, ranging from mixtures of arbitrarily chosen chemicals to mixtures of chemicals with the same target organ (kidney, nose) and with the same or different mode of action, mixtures of mycotoxins, and mixtures of sensory irritants (3, 4, 5, 11, 12, 14, 15). One of the major objectives of this research programme on mixtures was to test the hypothesis that *as a rule* exposure to mixtures of chemicals at (low) non-toxic doses of the individual chemicals is of no health concern (11). Three main conclusions that could be drawn from these studies are:

- joint or interactive effects seen at clearly toxic-effect-levels of the individual chemicals do not predict the joint or interactive effects that might occur at or below the highest-no-toxic-effect-levels of the individual compounds,

- dose addition is appropriate for hazard and risk assessment of a mixture of chemicals with similar joint action,
- exposure to a mixture of chemicals with different modes of action does not constitute an evidently increased hazard compared to that of exposure to the individual chemicals, provided the exposure level of each chemical in the mixture is at most similar to its own "no observed adverse effect level". Expressed in terms of potential risk this conclusion reads: if the combined action of chemicals in a mixture meets the criteria of dissimilar joint action, the health risk of such a mixture is determined by the health risk associated with the "most risky chemical" (= the chemical with the highest risk quotient) in the mixture, provided the risk quotients of the other chemicals in the mixture are at most equal to unity.

In hazard identification and risk assessment, these lessons should be taken into account on a case-by-case basis.

Hazard identification and risk assessment
For hazard identification and risk assessment of simple, defined mixtures a wide variety of methods is available, ranging from whole mixture analysis (top-down approach) to component joint action or interaction analysis (bottom-up approach) (5, 12). A most promising method for quantitative risk assessment of defined mixtures is the so-called hazard index/weight of evidence (HI/WOE) approach (19). This method combines the HI (= exposure concentration divided by the OEL) of the individual compounds with weighing factors for aspects such as mechanistic understanding of binary joint actions or interactions, type and degree of toxicity, relevance of route of exposure, and availability of *in vitro* data. In its most recent version (2, 7), this method also takes into account the relative exposure levels of the chemicals in the mixture which is regarded as a major improvement of the original version (16).

Complex Mixtures

It is self-evident that for studying the toxicology of complex mixtures the bottom-up approach is virtually impossible. The top-down approach may be appropriate for some complex mixtures such as for instance welding fume and recycled drinking water, for others such as for instance the atmosphere at a hazardous waste site or a workplace atmosphere, whole mixture analysis seems to be impracticable and meaningless. A scheme for hazard identification and risk assessment of complex mixtures has been developed some years ago (10), and has recently been refined (13, 16). This scheme is depicted, in slightly modified form, in Figure 1. Two conspicuous elements of this scheme are the dichotomy of complex mixtures into mixtures that are virtually unavailable and mixtures that are readily available for testing in their entirety, and the "top-*n*" and "pseudo top-*n*" approaches. The

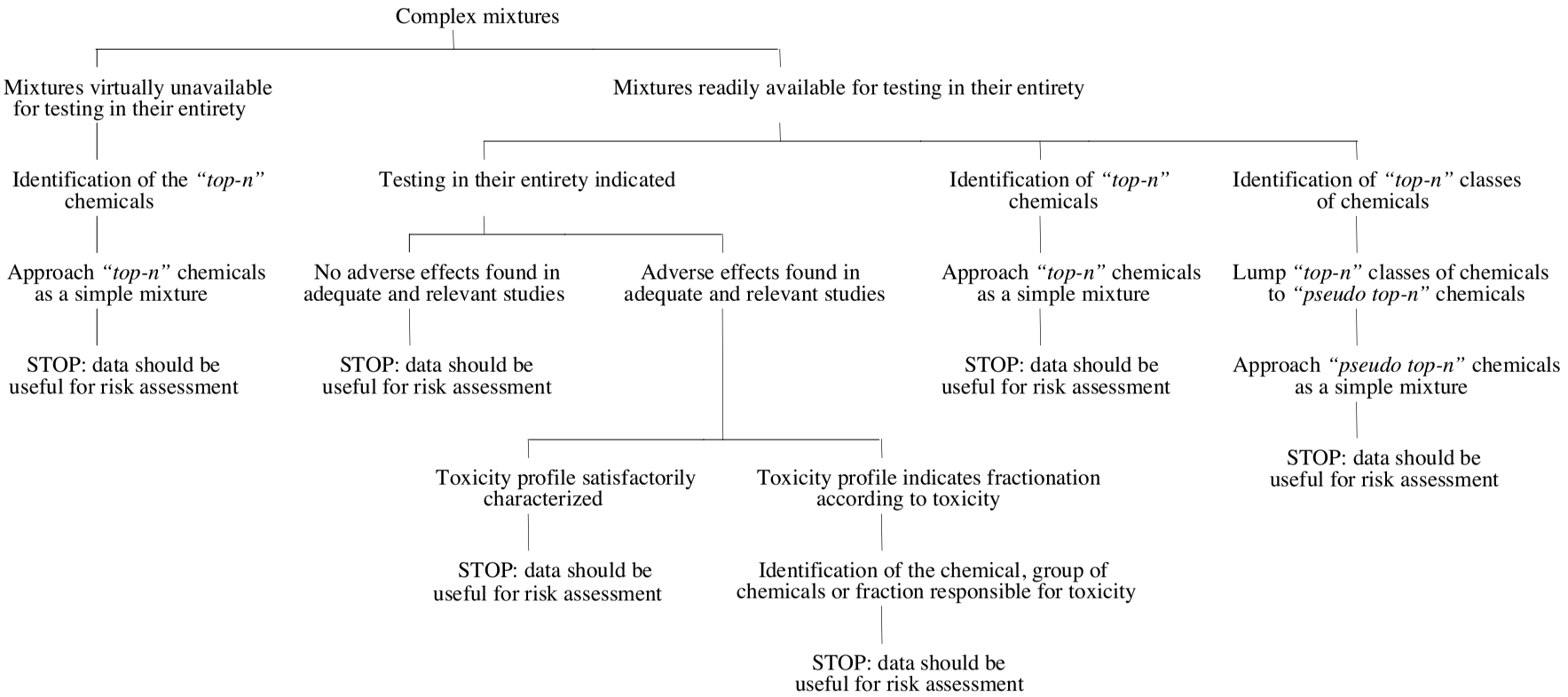

Figure 1. Scheme for toxicological evaluation of complex chemical mixtures.

"top-*n*" approach means identification in a complex mixture of the *n* (say, the ten) most risky (not most toxic!) chemicals, and the "pseudo top-*n*" approach means identification of the *n* most risky classes of chemicals (for each class a pseudo chemical is identified, using the so-called lumping technique). Once these chemicals or pseudo chemicals have been identified they will be approached as a simple, defined mixture, assuming that hazard and potential risk of the *n* selected chemicals or pseudo chemicals are representative for the hazard and risk of the entire complex mixture (10, 16). A comparable approach is successfully being used in the United States to identify the priority substances that are released from hazardous waste sites and that pose the greatest hazard to human health. Once the most risky chemicals have been identified, their potential health risk is assessed as a mixture, using a narrative weight-of-evidence approach incorporating mechanistic insights on possible joint actions or interactions (17). The "top-*n*" and "pseudo top-*n*" approaches seem to be particularly suitable for the toxicological evaluation of workplace atmospheres (11).

Concluding Remarks

When evaluating the safety of chemical mixtures, it is meaningful to distinguish between at the one hand simple, defined mixtures consisting of a relatively small number of chemicals, (say, ten or less) of which the quantitative composition is known, and on the other hand complex mixtures consisting of hundreds or many thousands of mostly unknown chemicals. For safety evaluation of simple mixtures a number of methods is available based on the basic principles dose addition, response addition or interaction (5, 12). For safety evaluation of complex mixtures a scheme has been developed, including a category of mixtures described as "virtually unavailable for testing in their entirety" (10, 13). Workplace atmospheres are examples of this type of complex mixtures. They can be approached by identifying the, say, ten or in more general terms the *n* most risky chemicals at a particular workplace (the top *n* identification). Once these priority chemicals have been identified, a safety evaluation of the mixture of these selected most risky chemicals can be performed, using procedures that have been described for hazard identification and risk assessment of simple, defined mixtures. Other than suggested by ACGIH (1), generally applicable OELs for such simple mixtures cannot be established. In brief, safety evaluation of a specific workplace atmosphere can be tackled by evaluating the safety of the defined mixture of the major (most risky) constituents (11). A similar approach is successfully being used in the United States for hazard identification and risk assessment of the mixture of chemicals that is released from hazardous waste sites (17).

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Summary

Johanson G (ed). *Occupational exposure limits – approaches and criteria*. Proceedings from a NIVA course held in Uppsala, Sweden, 24-28 September 2001. Arbete och Hälsa 2003;17:1-109.

This volume presents selected lectures given at the course *Occupational exposure limits – approaches and criteria, third international course*. The main objectives were to: describe and differentiate between the various approaches and criteria used to set an occupational exposure limit (OEL) identify the problems of comparing OELs from different countries, and analyse an OEL based on background information. The course was arranged by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) and the Nordic Institute for Advanced Training in Occupational Health (NIVA).

The presentations herein cover: basic concepts in toxicological risk assessment, information retrieval, criteria documents as basis for OELs, OEL setting by the European Union, the Netherlands, Sweden and the American Conference on Governmental Industrial Hygienists (ACGIH), scientific, socioeconomic, technological and ethical aspects, exposure to particles and lung disease, and mixed exposures. Several other topics were also addressed at the course.

Key words: chemical hazards, criteria document, dermal exposure, mixed exposure, occupational exposure limit, risk assessment, skin notation, toxicology, work environment.

Summary in Swedish

Johanson G (ed). *Occupational exposure limits – approaches and criteria*. Proceedings from a NIVA course held in Uppsala, Sweden, 24-28 September 2001. Arbete och Hälsa 2003;17:1-109.

Denna volym innehåller ett urval av de föredrag som hölls vid kursen *Occupational exposure limits – approaches and criteria, third international course*. Målsättningen med kursen var att beskriva och differentiera mellan olika tillvägagångssätt att sätta hygieniska gränsvärden (HGV) för arbetsmiljön, identifiera svårigheter med att jämföra HGV från olika länder samt att analysera ett HGV baserat på bakgrundsinformation. Kursen anordnades av Nordiska expertgruppen för kriteriedokument om kemiska hälsorisker (NEG) och Nordiska institutet för vidareutbildning i arbetsmiljö (NIVA).

Föreliggande presentationer täcker bland annat: grunderna i toxikologisk riskbedömning, informationssökning, kriteriedokument som underlag för HGV, gränsvärdessättning inom europeiska unionen, Nederländerna, Sverige och American Conference on Governmental Industrial Hygienists (ACGIH), vetenskapliga, socioekonomiska, tekniska och etiska aspekter, exponering för partiklar och lungsjukdom, samt blandexponering. Många andra ämnen behandlades också under kursen.

Nyckelord: arbetsmiljö, blandexponering, hudexponering, hudmärkning, hygieniskt gränsvärde, kemiska hälsorisker, kriteriedokument, riskbedömning, toxikologi.

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