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Scientific and Practical Considerations for the Development of Occupational Exposure Limits (OELs) for Chemical Substances[1]

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Occupational exposure limits (OELs) serve occupational health professionals as benchmarks for a healthy work environment. OELs are generally developed by manufacturers for substances which are not subject to governmental regulation or which have not been evaluated by consensus organizations such as the American Conference of Governmental Industrial Hygienists. This review is intended to serve as a practical guide to the standard-setting process. The discussion encompasses the evaluation of data, the different methods used for calculating limits, and the application of these limits to the workplace. The need for additional research to enhance the reliability of current methods is also discussed. © 1992 Academic Press, Inc.

I. INTRODUCTION

A great deal of progress has been made in the prevention of chemically induced occupational illness. The past 100 years have seen an increase in awareness for the potential hazards of exposure to chemical substances at work. Early investigations of occupational disease relied almost exclusively on anecdotal reports of working conditions. Evaluation of causality and significance was hampered by the subjective nature of the observations and by limited analytical capabilities, resulting in inadequate exposure information (for a review of the early literature on occupational disease, see Hunter, 1974). Advances in the areas of toxicology, industrial hygiene, and analytical chemistry permit a better evaluation of occupational exposures and provide objective biological data for analyzing and understanding the toxic effects of chemical substances. Through these developments and the institution of intensive testing programs, we have obtained a wealth of information to help understand the biological mechanisms underlying toxic responses and to better characterize the risks associated with occupational exposure to toxic substances (Paustenbach, 1989). Parallel to these devel-

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opments, government and industry have invested considerable resources and effort in managing those risks by implementing programs to prevent the adverse effects associated with these exposures. (OSHA, 1970/1989).

Among the programs credited for a substantial improvement in the incidence of occupational illness are those designed to reduce workers' exposure to toxic substances. With the development of the threshold limit values (TLVs) by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1942, a valuable tool was placed in the hands of industrial hygienists and occupational health professionals (Paull, 1984; Cook, 1987). The original list of TLVs contained 63 toxic substances. Currently, TLVs have been developed for well over 500 substances (ACGIH, 1990). Government agencies such as the Occupational Safety and Health Administration (OSHA) in the United States and the Occupational Safety and Health Branch of Labour Canada have adopted this approach to regulating exposure to toxic substances in the workplace. In the United States, OSHA has established its own permissible exposure limits (PELs), which now include limits for 600 substances (OSHA, 1970/1989). Similar approaches have been instituted by many other countries, such as the development of maximum allowable concentrations (MACs) in Germany (Henschler, 1991), the Union of Soviet Socialist Republics (Cook, 1987), and others (Spickett, 1990). The various approaches to the establishment of occupational exposure limits (OELs) by different countries and the compounds regulated by national standards have been reviewed extensively by Cook (1987).

Worldwide, Paustenbach and Langner (1986) estimated that as of 1986, fewer than 1700 OELs had been established. This is but a small fraction of the 65,000 chemicals on EPA's Toxic Substances Control Act Inventory list (EPA, 1985). There is clearly a need to establish OELs for those compounds not regulated by national or consensus standards. While this need has been recognized and has resulted in the publication of individual methods (Sargent and Kirk, 1988; Leung and Paustenbach, 1988), there is currently no consensus approach to such limit setting (Serocki, 1988; ABPI, 1984). The Occupational Toxicology Roundtable, an informal association dedicated to promoting open discussion of relevant issues and scientific advancement in this specialized area of toxicology, conducted a workshop on this topic at its inaugural meeting in 1988. As a result of this discussion, these authors recognized the need to establish a consistent and scientificially valid approach to the development of OELs. Recently, Zielhuis and Wibowo (1989) reviewed many of the philosophical issues attendant to this process. Agius (1990), in his review, considered the unique challenges to this process posed by therapeutic substances. The aim of this paper is to identify the specific criteria that must be considered in the development and application of OELs and to serve as a practical guide in establishing a standard-setting program. Without question, the issues and positions outlined here reflect the current knowledge and thought of the authors. However, it is also our aim to foster further scientific dialogue and research on these issues.

Central to our review is the recognition that OELs should not be viewed as an end by themselves. They are products of current scientific knowledge and methods and reflect the professional judgment of those developing them. There is considerable uncertainty inherent in the standard-setting process and any use of these standards must be undertaken in that light. OELs are valuable, if not essential, in evaluating the work environment and in relating exposure levels to medical surveillance data. As such, occupational exposure limits must be carefully developed, using all available

toxicological, clinical, and physicochemical data, and must be reviewed periodically to assure their appropriateness relative to current methods and data.

II. PARAMETERS TO CONSIDER WHEN SETTING OELs

Proper evaluation of the toxic potential of a chemical requires the collection and examination of all relevant toxicological data. The following paragraphs describe the types of data that should be considered when setting OELs.

A. Physicochemical Properties

The physicochemical properties of a substance often determine its potential for exposure, mode of entry, and ability to cross biological barriers. For example, properties such as physical state, boiling point, melting point, vapor pressure, density, and particle size may indicate whether, under ambient conditions, the chemical is a gas, vapor, mist, or inhalable dust and whether exposure will most likely be by inhalation and/or dermal absorption. The ability of a substance to cross biological barriers and damage tissue is often determined by parameters such as molecular weight, lipid solubility, water solubility, partition coefficient, dissociation constant, pH, and reactivity. Odor threshold is another property to consider, especially for particularly foul smelling substances.

B. Absorption, Distribution, Metabolism, and Elimination

Absorption of chemicals occurs when they come in contact with biological barriers they are able to cross. The ability to cross these barriers often depends upon solubility. For example, gases that are highly soluble in water tend to be absorbed from the upper airways of the lung, whereas gases that are less soluble can penetrate to the deeper, air exchange regions of the lung. Dermal absorption, on the other hand, is usually favored by lipophilic compounds. Often, the only toxicological data available are from studies in which the substance is administered orally. In these cases, assumptions about absorption by inhalation are made.

The distribution of a chemical is dependent on its partition coefficient, the perfusion rate to various organs, and the existence of specialized transport systems. The toxicity of a chemical is largely influenced by the target organ to which it is distributed. Plasma concentrations of a test substance can be extremely valuable in toxicology studies when used in a comparative manner within a species. However, plasma concentrations must be used with great caution for safety evaluation in that they may not represent either the concentration at the site of toxic action, or, in the case of most irreversible toxic phenomena, the relevant active molecular species (Monro, 1990).

Metabolic pathways are involved in toxifying and detoxifying exogenous chemicals. The enzyme systems that are responsible for these metabolic events may themselves be either inhibited or activated by chemical exposures. This action can cause a synergistic or antagonistic effect with other chemicals. For example, phenobarbital induces cytochrome P450, causing other chemicals to be metabolized more rapidly. As a result of different enzyme profiles, human metabolism of an exogenous chemical may be

different than that of the species used in a toxicological study. Any risk assessment must account for such differences.

The rate at which chemicals and their toxic metabolites are eliminated from the body is an important consideration when setting OELs. If the biological half-life is short (less than 3 hr), then the compound is considered to be cleared before the next day of exposure (Paustenbach, 1985). However, all chemicals are not eliminated so rapidly. Fat soluble compounds, such as PCB's or DDT, can accumulate in the body. Also, repeated exposure to slowly metabolized or eliminated substances may result in a progressive increase in total body burden. A factor is often entered into OEL calculations to account for this accumulation (Sargent and Kirk, 1988).

Pharmacokinetic data, if available, can be used to create physiologically based pharmacokinetic models (see Part III, Section B, iv) to attempt to account for interspecies differences. A fairly extensive pharmacokinetics database usually exists for pharmaceutical products; however, these data are rarely available for other types of industrial chemicals.

C. Toxicity Data

The amount of toxicological data available to conduct a chemical risk assessment varies. It can range from well-conducted and -controlled human and epidemiological studies supported by well-characterized chronic exposure studies in several animal species on one extreme to only structure–activity relationships (SAR) to guide the evaluation on the other. The nature and quality of the studies, relevance of the experimental routes of exposure, and nature and significance of the observed effects to human health must be evaluated. Only data considered to be of sufficient quality are used. Data of lesser quality are viewed as supportive (EPA, 1991).

i. Acute effects in animals. Acute effects include oral, dermal, and inhalation lethality data, pharmacotoxic signs, and dermal, eye, and respiratory irritation data. Acute dermal and inhalation studies provide information on the ability of a chemical to be absorbed during occupational exposures. Although acute lethality data are usually not very useful in setting OELs for chronic exposures, for some compounds these are the only data available. In this case, any pharmacotoxic responses observed and recorded during these acute studies are especially useful. Irritation data, especially sensory irritation, are very useful in setting OELs. Many of the ACGIH TLVs were set to protect from the irritant properties of chemicals (Kane *et al.*, 1979).

ii. Subacute/subchronic/chronic effects in animals. Repeated exposures of animals to toxic chemicals are more appropriate models for determining the effect of long-term exposure of humans to these chemicals than are acute studies. Subacute and subchronic studies include exposures for 14, 28, or 90 days or up to 6 months. For many non-cancer endpoints, 90-day studies are often sufficient for determining adverse effects from chemical exposures. Chronic studies include anything longer than 6 months. The most useful animal studies for setting OELs are multiple dose studies in which a NOEL (no observed effect level) or LOEL (lowest observed effect level) has been determined (see Appendix for more detailed definition). While lifetime bioassays are often the most useful, NOELs from subchronic or sometimes subacute studies may be used.

Repeated exposure to certain chemicals may induce a sensitization reaction in humans. Although recent research indicates that thresholds for sensitization effects may

exist (Nusair, 1989), it is not always practical to develop on OEL to protect individuals who have already been sensitized to industrial chemicals. For sensitizing compounds, it is more appropriate to set an OEL that will prevent an individual from becoming sensitized (De Silva, 1986).

iii. Reproductive effects in animals. The reproductive endpoints considered most serious in these types of evaluations are teratogenicity and loss of fertility. However, other endpoints that should be considered include embryotoxicity, fetotoxicity, maternal toxicity, and neurobehavioral changes in the offspring. These studies can involve one or more generations.

iv. Therapeutic data in humans. Clinical trials provide a well-controlled environment in which data on the response of humans to pharmaceuticals are collected. Voluntary human exposure data are usually unavailable for other types of industrial chemicals. Therapeutic responses as well as adverse events experienced during clinical trials are well documented. OELs for pharmaceutical products are often based on the lowest therapeutic dose determined by the clinical trials but may also be based on adverse events. Although the therapeutic effect of a drug is desired for the treatment of disease, it is considered an undesirable effect in a healthy worker population. Tranquilizers, antihypertensives, hormones, and antineoplastics are some examples of drugs that elicit these types of undesirable effects.

Other types of valuable information collected during clinical studies include pharmacokinetic data such as bioavailability, metabolism, and clearance.

v. Adverse effects from occupational exposures. All data collected in the workplace, ranging from anecdotal reports by workers to detailed epidemiological studies, may be of importance. An ideal epidemiological study would include a large database supported by the appropriate medical tests, medical histories, and industrial hygiene data. Anecdotal reports of adverse responses in the workplace should be verified by safety personnel and be supported by industrial hygiene surveys documenting exposures. Even though a "healthy worker" population is generally assumed, there may be individuals who are part of a subpopulation at greater risk (De Silva, 1986). For example, some employees may be receiving prescribed medications that could cause interactions with substances they are handling in the workplace.

vi. Genotoxicity data. The Ames bacterial mutagenicity test is often one of the first assays performed on a new chemical entity. Other mammalian genotoxicity assays include both *in vivo* and *in vitro* tests such as mouse micronucleus, sister-chromatid exchange, chromosome aberration, unscheduled DNA synthesis, and alkaline elution. Genotoxicity data should not be used as a substitute for carcinogenicity data. However, the ability of some mutagenicity tests to predict the carcinogenic potential of structurally similar compounds in animals and humans should be considered. For more information on the different types of genetic toxicology tests, refer to Brusick (1987).

vii. Biological relevance to humans. The initiation of disease in an animal species exposed to an exogenous chemical is certainly cause for initial alarm. However, the evaluation of the human relevance of the response will determine the study's inclusion in the subsequent risk analysis. Concerns have been raised regarding the relevance of tumors that are unique to certain animal species. For example, Zymbal gland tumors are formed in rats and mice exposed to benzene (Snyder *et al.*, 1984, 1988). Humans do not have Zymbal glands. Male rats exposed to certain hydrocarbons have developed nephropathies related to the deposition in their proximal tubules of α_{2u}-globulin (Borghoff *et al.*, 1990; Goldsworthy *et al.*, 1988). Neither female rats nor any other

animal tested, including humans, produces this protein. Similar concerns have been expressed toward chemical agents whose metabolic rates or pathways differ significantly in humans and animals (e.g., saturation of P450, leading to tumors in rats and mice exposed to methylene chloride) (NTP, 1986). In chronic bioassays, animals are routinely exposed to concentrations of chemicals much higher than would be observed in the occupational setting as a method to observe statistically significant responses (Ames and Gold, 1990; Infante, 1991). The relevance of these data needs to be addressed when reviewing all toxicological studies using a weight of evidence approach. While these studies cannot be ignored, in many cases they should not be the major factor driving the OEL.

viii. Hierarchial ordering of data. It is difficult to list an absolute hierarchy of toxicological endpoints. Selection of priority endpoints should be made on a case by case basis using the professional judgment of the toxicologist. If an extensive toxicological database exists for a chemical, the selection of a "reference level" or "dose for a given effect on which the OEL is based" must be made. The following criteria should be used when possible in order to minimize extrapolation to a level that will be safe for humans working a lifetime with this chemical.

Selection of a NOEL over a LOEL will eliminate the need to extrapolate to a dose at which no effect would be expected in that species. In the same way, studies performed by inhalation best simulate a primary route of exposure to workplace chemical agents. Therefore, selection of an inhalation study would not require the route to route extrapolation normally required for studies of oral or parenteral administration. Human data should, in general, take priority over animal data since no interspecies extrapolation would be necessary. Chronic studies are usually more appropriate than acute studies since the doses are lower and more accurately reflect the long-term exposure of the employee.

It is also important to consider the endpoint of the study. The most sensitive endpoint that is biologically relevant to man is usually selected. Irreversible changes such as teratogenesis or carcinogenesis are usually more of a concern than reversible changes such as irritation or elevated liver enzymes. Therefore, irreversible effects generally take priority over reversible effects, depending on their severity. However, if the LOEL of a reversible effect is much lower than the NOEL of an irreversible effect, the former might be selected as the reference level.

D. Nuisance Effects

Nuisance effects are important and should be considered when setting OELs but large safety factors may not be needed for protection. The kind of nuisance effects usually encountered (objectionable odor or taste, staining of the skin or clothes, etc.) can often be used as warning signs if they occur at levels lower than those where other effects occur. However, in order to provide a comfortable work environment, OELs need only be set just below nuisance levels.

E. Exposure and Population Parameters

Since exposure to chemical compounds can result in either acute or chronic health effects, the derivation of OELs must consider the total potential exposure to these

compounds. Exposure and population parameters involved in the derivation of OELs include the volume of air inhaled during a shift, the length of that shift, the duration and type of a handling operation, the number of years of continuous handling of the compound in question, and certain demographics of the target population.

A volume of 10 m^3 of inspired air per 8-hr shift has been most frequently used for exposure limit calculations. This volume was derived by assuming that a man engaging in "light" work has a tidal volume of 1000 cm^3 and is breathing at a rate of 20 breaths per minute for 8 hr (NAS/NRC, 1958). For an average woman performing "light" work, the average total volume is closer to 9 m^3. A resting man inhales approximately 5 m^3 during 8 hr. Therefore, 10 m^3 may be an overestimation for many operations. Although these calculations assume an 8-hr workday, many manufacturing operations employ extended shifts. For these operations the OELs may need to be adjusted to reflect the increased exposure potential. A conservative assumption often used is that a worker will be handling a chemical 8 hr a day, 5 days a week, for a 40-year working lifetime.

The reference level from an animal study may be expressed on the basis of body weight. To translate that level to a human dose, the standard body weight used for men and women is 70 and 50 kg, respectively. If the substance is a reproductive toxicant affecting women specifically over men, or a more conservative OEL is desired to protect the women in a workforce, the lower female body weight may be used.

Exposure to chemicals may also occur by absorption through the skin. For chemicals that may be dermally absorbed, a "skin" notation is usually added to the numerical OEL. The "skin" notation indicates that dermal exposure could result in absorption and contribute to the total dose.

OELs are designed to protect the healthy worker population. This differs from ambient air quality standard or "fence-line" standards that apply to the general population and must consider the most sensitive individuals in that population (e.g., children, the elderly, and hypersensitives). Less intrahuman variability is assumed in the workplace. However, it is recognized that subpopulations of otherwise healthy workers may be subject to idiosyncratic reactions to certain chemicals. OELs such as the TLVs are designed to protect "nearly all workers" (ACGIH, 1990). Additional protection or controls may be required to accommodate unusually sensitive individuals (De Silva, 1986).

III. METHODS FOR SETTING OCCUPATIONAL EXPOSURE LIMITS (OELs)

This section provides a general discussion of the various methods for setting OELs, including their suitability, inherent assumptions, and limitations. It is not possible to develop a step-by-step approach that can be applied to all substances.

The choice of any particular method depends greatly on the availability of data. In general, the simplest methods are used for chemicals with no or scanty toxicity data and are the least reliable. More complex methods are more suited for chemicals with a stronger database (see the decision logics in Fig. 1 for the choice of appropriate method for a chemical).

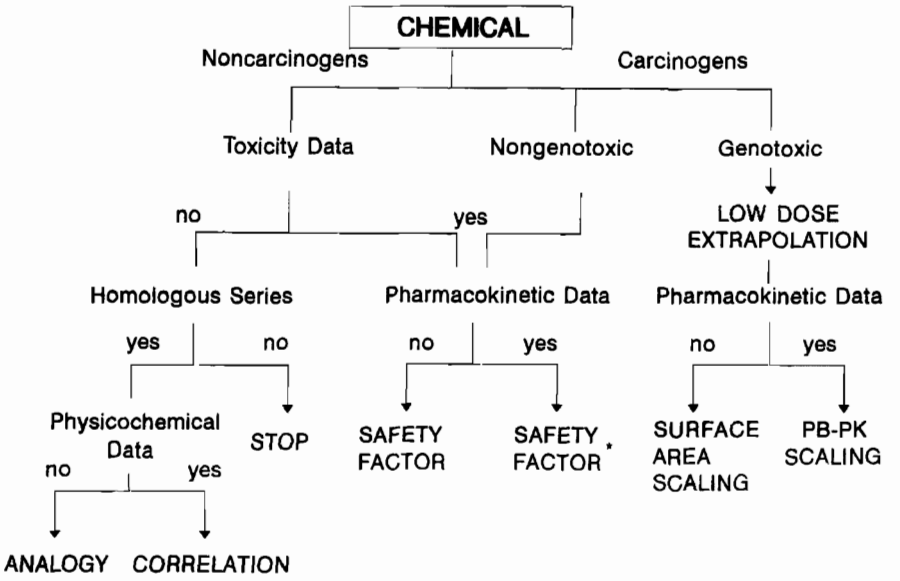

FIG. 1. Decision logic for OEL-setting methods. (*) Adjust for bioavailability, $t_{1/2}$, etc.

A. Selection of Endpoint and Reference Level

Generally, the selection of an endpoint should be based on the most sensitive adverse effect. The rationale is that by protecting against the most sensitive effect, all other less sensitive effects will also be automatically prevented. It is important to determine whether the most sensitive endpoint clearly presents an undesirable or injurious effect to the health of the workers. It may be worthwhile to determine and compare OELs based on two different endpoints. However, an OEL based on the most sensitive endpoint and developed by taking into consideration all potential adverse effects should be appropriate for preventing the most serious adverse effects. With many highly potent chemicals, especially those being developed as pharmaceuticals, the most sensitive biological outcome may be the intended therapeutic effect. Depending on the availability of data and the type of methodology used for the extrapolation, a reference level may be selected from the NOEL, LOEL, LD_{50}, or TLV for a related family of compounds, therapeutic dose, and endogenous production rate (for specific definitions of these terms, see Appendix).

B. Methods

i. Qualitative structure–activity relationships (analogy). This is the crudest method of setting OELs. It is best used for chemicals lacking toxicity data. In this method, a homologous chemical is assumed to have the same potential to cause a common biological effect as a reference chemical in the same family of compounds. The OEL of the chemical in question will take on an identical value as the reference chemical. This method has been used to set TLVs for the alkylamines and xylenes (ACGIH, 1986). One limitation of this method is that it is only applicable to chemicals in a

homologous series and isomers. It is the most unreliable method since the OEL of the reference chemical is also frequently established with limited data.

$$OEL_i = OEL_j.$$

ii. Quantitative structure–activity relationships (correlation). This is a variant of the analogy method described above. The correlation method is best suited to a chemical which has no toxicity data but has some physicochemical data that can be compared with chemicals in the homologous series. The choice of the physicochemical parameter (PP) will depend on the biological effect on which the OEL is based, e.g., vapor pressure, chemical fugacity, acid dissociation constant, partition coefficient, ionization potential, receptor affinity, bonding energy, and intermolecular interaction. Rather than assuming that all chemicals in the same homologous series have identical potency and therefore the same OEL as in the analogy method, the correlation method sets the OEL value proportional to the relative magnitude of the physicochemical parameter. This method has been used to set OELs for a series of alkylbenzenes (Nielsen and Alarie, 1982), and some organic acids and bases (Leung and Paustenbach, 1988). The limitation of this method is that the physicochemical parameter must be firmly established as a valid predictor of the biological effect on which the OEL is based.

$$OEL_i = (PP_i/PP_j) \times OEL_j.$$

iii. Uncertainty or safety factors. This method establishes OELs by applying an uncertainty factor (UF) and safety factor (SF) to the reference level. The rationale of this approach assumes that a chemical has threshold characteristics, and an acceptable level of exposure for humans can be derived by reducing the reference level with the appropriate safety and uncertainty factors. Sufficient toxicity data to identify a reference level are required. Since nongenotoxic carcinogens are believed to have threshold qualities, the uncertainty or safety factor approach can be used to set OELs for these compounds. Uncertainty factors are used to account for the uncertainties in extrapolating toxicity data. These exist when extrapolating from a high dose or LOEL to a low dose or NOEL. Other uncertainties exist in comparing data across species and from different routes of administration. Generally, these factors are small (1–10) and are selected based on an evaluation of the appropriateness or scientific validity of the data (Lewis *et al.*, 1990). The more that is known of the properties of the compound and the better the studies supporting the information, the smaller the uncertainty factors should be. Thus, good science is rewarded while larger uncertainty factors are used when data are incomplete or less relevant. This allows more flexibility to utilize the limited data available.

Safety factors are selected based on the level of protection deemed necessary to prevent adverse effects. Recently a range of safety factors has been used, providing for a greater margin of safety for more serious adverse effects (Lewis *et al.*, 1990; Dourson and Stara, 1983; EPA, 1991). Examples of OELs set with the safety factor approach include the majority of the TLVs established by ACGIH (1986).

$$OEL = \text{reference level}/(UF_1 \times UF_2 \times SF \times BR),$$

where SF is the safety factor (the size of this factor depends on the nature of effects); UF_1, the uncertainty in extrapolation to a chronic exposure NOEL; UF_2, the uncertainty from interspecies extrapolation; and BR, the breathing rate of a man performing

light duty work in an 8-hr workday (10 m^3). The composite factor ($UF_1 \times UF_2 \times SF$) may range from 1 to 10,000.

iv. Low dose extrapolation. This method applies to chemical carcinogens, especially genotoxic carcinogens which are believed to lack threshold characteristics. For these chemicals, since there is no one dose which does not produce a response, it will be necessary to set a level of response which is considered acceptable (de minimis). For workplace standards, such a level is traditionally 1 in a 1000 (10^{-3} or 0.1%) (see Rodricks *et al.*, 1987). In this method the dose–response curve in the observed range of the rodent cancer bioassay or epidemiological study is extrapolated downward to yield a dose corresponding to the 10^{-3} response level (risk specific dose, RSD). The most widely utilized extrapolation method is the linearized multistage (LMS) model (Crump *et al.*, 1976). There is no compelling scientific basis for the choice of the LMS over many others, other than to be consistent with that used by regulatory agencies including EPA and OSHA.

The limitation of the low dose extrapolation method is that it is purely mathematical and does not take into account biological or mechanistic data. The risk estimates provided by this method often vary widely with the choice of models and dose–response data, and hence have considerable uncertainties. If the RSD is derived from rodent dose–response data, it is necessary to perform an interspecies scaling to obtain the corresponding human RSD. When pharmacokinetic data are insufficient to allow for the construction of a physiologically based pharmacokinetic (PB-PK) model, interspecies scaling of the RSD is accomplished on the basis of surface area differences. This is consistent with the EPA Carcinogen Assessment Group Risk Assessment Guideline.

$$\text{OEL} = [\text{rodent RSD} \times (\text{human BW}/\text{rodent BW})^{-1/3}/\text{BR},$$

where BW is body weight.

This interspecies scaling method is based on the rationale that tissue burden and hence the sensitivity of a species to a chemical is correlated with the rates of metabolism and clearance of the chemical, which are approximately proportional to the body surface area. Obviously, such a universal correction, which presupposes a chemical's mode of action, will not apply to all chemicals. For instance, interspecies scaling based on surface area differences, which assumes that humans are more susceptible than rodents, is best applied for direct-acting carcinogens (Andersen, 1987).

PB-PK models may be used to overcome the shortcomings of universal interspecies scaling. PB-PK models achieve interspecies extrapolation by taking into account the anatomic, physiological, biochemical, and metabolic differences between species. Such models can provide a relationship between the external exposure concentration and the delivered dose to the target tissue. PB-PK models, however, require a large body of supporting data to construct and validate. Thus, this interspecies scaling approach is limited to chemicals that have a robust pharmacokinetic and pharmacodynamic database, e.g., new therapeutic drugs under development. (For example of how the PB-PK model is used in an OEL setting, see Andersen *et al.*, 1987).

$$\text{OEL} = (\text{human reference dose estimated by PB-PK model})/\text{BR}.$$

Examples of OELs established with the low dose extrapolation method include the PELs for asbestos (OSHA, 1986), and ethylene oxide (OSHA, 1984).

IV. APPLICATION

The preceding sections clearly illustrate that the development of occupational exposure levels is an evolving science. Setting occupational exposure levels requires considerable input of scientific data and judgment. The assumptions and uncertainties involved in the process are significant. Therefore, it is essential that occupational exposure limits be applied to the work environment appropriately and with full knowledge of their limitations. This section describes some of those issues to be considered.

A. Documentation

An OEL is only as valid as the data, method, and assumptions used in its development. These should be clearly documented for future reference and verification. In the case of litigation the validity of the data and methods used as well as the qualifications of those involved may be called into question. Appropriate documentation can be used to verify the appropriateness and currency of the data and methods used, and provide a reference point for review when new data or improved scientific methods become available. In addition, the documentation will be used to explain its development to those who must apply it or work within it. Thus, it will assure employees that a thorough evaluation has been performed.

B. Feasibility

The feasibility or ease of achieving exposures below the OEL should in no way drive the OEL setting process. Occupational exposure limits represent exposure levels that can be considered safe based on a scientific assessment of risk. The risk management side of the equation should be handled by the appropriate industrial hygiene, engineering, and production management personnel. In fact, it can be said that even the lowest OELs can be achieved through the application of appropriate engineering controls, personal protective equipment, administrative controls, isolation, and/or elimination.

c. Measurement

The principal application of OELs is as benchmarks for evaluating occupational exposures determined in industrial hygiene surveys. The measurement of occupational exposure levels requires the availability of sensitive and accurate sampling and analytical methods. While the ability to detect a compound at the OEL level is important, it should not drive the OEL-setting process. Rather, the OEL should be set based on principles outlined in the preceding sections even if those levels present a significant challenge to the analytical chemist. Advances in the analytical field allow detection of increasingly lower levels of most compounds through improved and new technologies.

Methods developed to support industrial hygiene measurements should be designed according to the length and type of exposure of concern, i.e., time-weighted averages or short-term exposures. In addition, where a compound presents an acute hazard,

continuous reading methods could be developed to warn of concentrations approaching dangerously high levels.

D. Controlling Exposure

OELs can be used in the design and implementation of manufacturing operations, such as in the selection of the appropriate machinery or ventilation. The OEL should be interpreted as a safe level of exposure without the use of respirator or other protective equipment.

Where engineering controls are not sufficient to meet established OELs, personal protective equipment can be used. However, OSHA regulations are expected to discourage, and possibly disallow, reliance on personal protective equipment to meet occupational exposure limits. An additional level of control may be effected by implementing administrative controls. These may take the form of restriction of sensitive individuals, such as those previously sensitized to an allergen, or those who are hypersusceptible to the effects of a toxicant, such as women in the first trimester of pregnancy whose fetuses may be at risk from exposure to teratogenic compounds. However, in light of the Supreme Court decision in Automobile Workers v. Johnson Controls (1991), exclusion of pregnant women should be considered only when exposure to a chemical is specifically linked to abnormal fetal development without affecting male reproductive capacity as well. Additional administrative controls may take the form of shorter or alternating shifts, job rotation, or enforced breaks.

E. Biological Exposure Indices

Biological exposure indices (BEIs) are developed to correlate occupational exposures to relevant levels of the toxicant or its metabolites in biological tissues or fluids. These levels have been developed for toxicants such as lead, for which serum levels can be correlated to biological effects and exposures. OELs developed using physiologically based pharmacokinetic models (see Part III, Section B iv) are particularly suited for the development of BEIs. In the pharmaceutical industry pharmacokinetic information is generally available for most drugs and correlation to therapeutic activity or adverse effects can thus be applied to evaluate levels found in the work environment. BEIs can be used as a backup to occupational monitoring to assure the adequacy of control measures or if sampling and analytical methods for the specific air contaminant are not available.

F. Medical Surveillance

It may be appropriate to implement a medical surveillance program for those employees involved in the handling of compounds deemed sufficiently hazardous to require an OEL. A medical surveillance program should focus on the most significant and relevant biological endpoint. In general this would be the same endpoint used for the development of the OEL, but may also include medical history, routine examinations, and diagnostic procedures. Medical surveillance programs can yield information specific to individual employees, but may also identify trends in a potentially

exposed population, and may serve to alert health professionals to unknown or unexpected hazards.

V. CONCLUSIONS AND RESEARCH NEEDS

OELs in conjunction with industrial hygiene surveys, biological monitoring, and medical surveillance programs can be used to evaluate thoroughly the health risks associated with occupational exposure to hazardous chemicals. However, even the most thoroughly researched and documented OELs cannot guarantee safety.

It is extremely important in the interpretation and application of occupational exposure limits that these not be used as indicators of toxicity. This type of misuse has occurred with the TLVs which have been applied to environmental contamination risk assessments as indices of toxicity. OELs represent the level considered to be safe in the work environment under specific conditions. They are not intrinsic properties of the chemicals and are developed by scientists using a good dose of professional judgment. Industrial hygienists and health professionals can provide a bridge between the development of OELs and their application by explaining the process and the significance of these values to those employees potentially exposed.

As the preceding discussion indicates, the process of setting OELs is a synthesis of scientific data and professional judgment. The skills and experience that a toxicologist uses in reviewing the scientific evidence of potential harm cannot be replaced by a "recipe" or formula. The toxicologist must make a weight-of-evidence analysis of the data to determine their relevance to the work environment. Furthermore, the toxicologist must evaluate the appropriateness of the different methods available.

In the case of the most frequently used method, the safety or uncertainty factor approach, one must also select the appropriate factors based on the credibility or relevance of the data and the severity of the adverse effects. This is an area that is of particular importance. Safety factors have traditionally been set with an eye to conservatism: protecting the employee from adverse effects using large safety factors multiplied by uncertainty factors to account for biological differences. Often the extrapolation from the reference no effect level reached thousands and even millions. The toxicologist must take a close look at the scientific validity of such large and multiplicative factors in light of the scientific evidence. Extremely large safety factors may not be appropriate for effects demonstrating a threshold dose or for compounds metabolized through different pathways in humans and animals. In selecting safety factors, the weight given to genetic toxicology tests must also be carefully considered. Rather than assigning safety factors to specific results, a more appropriate approach may be to select a safety factor on the basis of a thorough review and evaluation of the hazards represented by all the toxicological data.

Because it is data-driven process, if more information is available and is applied to the development of the OEL, less uncertainty will be involved. The OEL setting process would greatly benefit from additional research in several areas. Most significant would be studies to better relate available oral or parenteral toxicity data to the inhalation route. There is a paucity of inhalation toxicity information for the large majority of chemicals. While it is probably not practical to conduct acute or subacute inhalation toxicity tests on most compounds, it may be possible to develop methods to determine physiological levels that could result from inhalation exposure and relate these to oral

and parenteral doses. Pharmacokinetic and chronic toxicity data available following oral or parenteral doses could thus be related through appropriate models to the exposures of concern in the occupational environment. Occupational toxicologists would also benefit from additional work on *in vitro* and *in vivo* dermal absorption studies and models relating absorption potential to physical parameters. Low dose extrapolation methods, particularly for effects such as cancer, have been and probably will always be controversial. Resolution of the current dilemmas in this area of risk assessment is unlikely in the near future, although research in the area continues and should receive our support. In the meantime, it is incumbent on toxicologists to evaluate each case and each method on its merits, rather than accepting scientifically questionable risk assessments on the basis of conservatism and habit.

The process of setting occupational exposure limits represents a synthesis of all activities of the occupational toxicologist. This area of toxicology has recently taken on additional importance in both the industrial and the regulatory sectors. It is our hope that this discussion will serve as a guide to those who are beginning to develop or who have an active occupational toxicology program and will stimulate additional research and scientific evaluation to improve this important process.

APPENDIX: DEFINITIONS

NOEL (no observed effect level), Dose at which there is no statistically or biologically significant increase in the frequency or severity of effects between the exposed and the control groups.

LOEL (lowest observed effect level), Lowest dose tested at which there are statistically significant increases in the frequency or severity of adverse effects between the exposed and the control groups.

LD_{50} (median lethal dose), Dose that kills half the test group.

PEL (permissible exposure limit), Occupational exposure limit set by the United States Occupational Safety and Health Administration.

TLV (threshold limit value), Occupational exposure limit set by the American Conference of Governmental Industrial Hygienists.

Therapeutic dose, The recommended dose for an average adult for treating a disease or restoring an adverse physiological condition to normal.

Reference level, A measure for a given effect of a chemical on which the OEL is based. A reference level can be any of the above.

Endogenous production rate, For chemicals which are produced naturally in the human body, the endogenous production rate can be assumed to be a reference level for the purpose of setting OELs. The rationale is that if the body produces this much of the chemical to support normal physiological functions, then this level can be safely assumed to be at least a NOEL.

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