FEATURE

Application of Threshold Limit Values for chemical substances to employees in laboratories

By Philip L. Bigelow

As health and safety professionals, we have all responded to questions such as, "Will the chemicals I am exposed to cause me harm?" or "Will this chemical cause cancer?" To address such questions, we likely consult the scientific literature, evaluate exposures, compare exposure levels to regulated or recommended values, and finally use professional judgment to formulate our response. These questions become increasingly difficult to answer when asked by people who are not employed in traditional industrial settings. Laboratories have processes, practices, and potential exposures that differ substantially from what are found in traditional industries, and the application of occupational exposure values (OEVs) requires special consideration.

Although there are numerous agencies and organizations that regulate or recommend OEVs, the Threshold Limit Values® (TLVs) have become the most widely recognized and applied. In fact, when the Occupational Safety and Health Administration (OSHA) was established in 1972, it was able to incorporate into standards the approximately 400 chemicals on the 1968 TLV list. Many of the 1968 TLVs are still in use today as OSHA's permissible exposure limits (PELs).[1] Although OSHA's final rule, "Occupational Exposure to Hazardous Chemicals in Laboratories," requires that employers ensure that exposures do not exceed applicable PELs, many chemical hygiene plans also recommend compliance with the TLVs.

TLVs are intended for use in the practice of occupational hygiene as guidelines for the control of potential workplace hazards. The recommended values represent concentrations and conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effects.[2] The most common application of TLVs is for employees who are exposed to chemicals during manufacturing and other industrial processes; however, there is increasing use of the guidelines in nontraditional occupational environments. Laboratories represent a unique occupational environment in which employees have short-term, often low-level, exposures to a much wider variety of chemical agents as compared with industrial workers. The application of TLVs in the laboratory setting is an important part of the chemical hygiene plan, but it does require special consideration because of the nature of laboratory processes and exposures.

There are a number of fundamental concepts, discussed in the "Introduction to the Chemical Substances" section of the TLV and BEI book, related to TLVs and other OEVs that the occupational hygienist must consider to correctly apply such values in the protection of workers. A number of these concepts have direct relevance to the application of TLVs for workers in laboratories. First is the issue that TLVs will be protective for "nearly all" workers, and that at the TLV exposure concentration, a small percentage of the population may suffer adverse effects. A concept closely related to the issue of "nearly all" workers is the need to consider individual hypersusceptibility due to genetic factors, personal habits, or previous exposures. Multiple chemical exposures are commonplace in laboratories and have an impact on the application of TLVs and OEVs. Because chemical exposures in laboratories may be highly variable and intermittent, the application of the typical eight-hour time-weighted average TLV is an issue. "Notations" attached to specific chemical TLVs, such as sensitization, skin absorption, and carcinogenicity classification, are also crucial elements of TLVs. Finally, the listing of "TLV-Basis-Critical Effect(s)," which provides summary information on the adverse effects that may appear at the lowest levels of exposure, can be helpful in the successful application of TLVs in the laboratory setting.

TLV AND BEI BOOK AND DOCUMENTATION OF THE TLVS

We have all seen the book annually published by the American Conference of Governmental Industrial Hy-

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gienists (ACGIH) called TLV® and BEI® *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*[2] (also known as the TLV and BEI book). But how many of us have read the sections entitled "Introduction to the Chemical Substances," "Adopted Appendices—Appendix A: Carcinogenicity," or "Chemical Substances and Other Issues Under Study"? Most likely, we quickly flip to the "Adopted Values" section and go about our business. However, it is not only the color of the book's cover that changes every year; definitions of carcinogens, sensitizers, skin notations, excursion limits, or other information applicable to the interpretation and application of TLVs may also undergo revision.

So what are TLVs? They are, of course, numerical values based on the best available information to be used in the practice of industrial hygiene to protect workers. The values and notations that appear in the TLV and BEI book are summaries of the judgment of the TLV committee as ratified by the ACGIH Board of Directors; another publication, the *Documentation of the Threshold Limit Values for Chemical Substances and Physical Agent and Biological Exposure Indices*,[3] provides the pertinent information that supports these judgments. Although the TLV and BEI book is a useful tool for occupational health professionals, the importance of consulting the specific documentation must be emphasized. This is especially true when applying the TLVs to populations of workers who may have differing exposure scenarios or who are more diverse than the populations previously studied.

NEARLY ALL WORKERS: VARIATIONS IN SUSCEPTIBILITY

The "Introduction to the Chemical Substances" section of the TLV and BEI book states that "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."[2p3] This statement, explicit in the TLV and BEI book, is implicit for the application of all OEVs and reflects the wide variation in response in any population. Although it is clear that exposures at the TLV may not protect all employees in the laboratory setting, appropriate use of information within specific chemical TLV documentation can help protect workers who are unusually susceptible.

The TLV documentation often contains a summary of adverse effects in human populations if such data are available. This information can be helpful in identifying people who respond adversely at or below the TLV. The critical end points are those that drive the setting of the TLV and are often animal toxicology studies in which a no observed adverse effect level (NOAEL) or no observed effect level (NOEL) has been computed. The difference between the NOAEL or NOEL and the TLV gives an indication of the uncertainty of the estimate. Knowledge of both the end point of the NOAEL and the uncertainty factor provides the occupational hygienist with some indication of the relative risk faced by workers at given exposure levels.

Health surveillance of employees exposed to specific chemicals is often part of the laboratory's chemical hygiene plan, and information from this program can be useful in ensuring that all employees are protected from adverse effects of exposure. Even if health surveillance does not include biological monitoring, the information obtained by means of regular medical evaluations can identify symptoms that may be associated with chemical exposures. Linking symptomology data with information from workplace chemical hazard assessments has great value in ensuring the protection of employees who are unusually sensitive to specific chemicals.

Health studies conducted on employees may be biased as a result of what is known as the "healthy worker effect."[4] TLVs are based on data obtained from such studies, when they are available, and there is the concern that levels derived from these data would not be protective of nonindustrial workers. One would expect that the healthy worker effect would predominate for exposures that cause acute effects (e.g., sensory irritation), whereas less bias is introduced if effects are not noticed in the short term (e.g., chronic diseases). Although there is little published information regarding demographic differences between laboratory employees and industrial workers, one would expect that the proportion of women in laboratories is greater. Thus, sex-related differences in susceptibility should be considered when applying OEVs in the laboratory environment. Again, the importance of consulting the appropriate documentation must be emphasized, and any reference to reproductive end points should be highlighted.

HYPERSUSCEPTIBILITY DUE TO GENETIC FACTORS, PERSONAL HABITS, OR PREVIOUS EXPOSURES

From the discussion of "nearly all workers," it is clear that in addition to great variability of responses to chemical exposures (i.e., variation around the central tendency), there are often multiple distributions of individual susceptibility. These populations, referred to here as subpopulations, usually have an identifiable characteristic associated with an increase in susceptibility. In the past, such identifiable characteristics have been used to exclude individuals from certain employment. The TLV Committee's general practice is one of recognizing the differences in responses of sensitive subpopulations and considering such data in the TLV value to protect most, if not all, workers.

Unfortunately, data pertaining to the response characteristics of sensitive subpopulations are often lacking, and research on the health effects of chemicals should include an evaluation of risks for subpopulations. When workers exposed to 1,3-butadiene were studied to determine cancer mortality, black workers were often excluded.[5] Dr. Philip Landrigan noted that this was a missed opportunity to examine a subpopulation possibly at

risk, as blacks were historically assigned to high-exposure jobs and as a group have a greater leukemia rate than whites.[5] Current human health research in the United States strongly supports the inclusion of women and minorities; additionally, statistical analyses that assess risks to specific subpopulations are recommended.

It is well known that family history of allergy is strongly associated with the risk of developing sensitization from chemicals with such potential. With recent advances in genetic testing, it is now possible to identify workers who may be at increased risk of other adverse health effects due to exposure to a single chemical or groups of chemicals. This use of genetic information is controversial because it could lead to screening of workers from jobs and exposures for which they are at increased risk, and allowing exposures to be excessive for workers who are less susceptible. As genetic information that may affect the health of exposed workers becomes more widely available, it is most appropriate to consider it as confidential medical information. Health and safety professionals, in collaboration with the medical provider, have a moral and ethical obligation to use such information to protect the health of the worker while maintaining confidentiality.

Age, general health, illness, and pregnancy are factors that modify the distribution, metabolism, and elimination of chemicals. The relationships between these factors and the risks of adverse effects due to occupational exposures is complex, and consultation with an occupational physician may be appropriate. This information should be considered confidential in its use by the health and safety professional.

Personal habits such as smoking and consumption of alcohol or other drugs can influence the metabolism of xenobiotics; such recreational exposures may place individuals within the susceptible subpopulation when considering the adverse effects of occupational chemical exposures. In the "Introduction to the Chemical Substances" section of the TLV and BEI book, smoking is described both as acting "to enhance the biological effects of chemicals encountered in the workplace"[1p3] and is provided as an example of a cause of hypersusceptibility. Alcohol and other drugs, including medications, are also considered to be causes of hypersusceptibility. For workers with these exposures, the ACGIH recommends that an occupational physician be consulted to evaluate the additional protection that may be required.

Personal use of ethanol is widespread and is well known to have effects on general metabolism and, more specifically, the metabolism of organic solvents.

Smoking and exposure to asbestos is used as the traditional example of synergism. It is likely that smoking acts synergistically with other workplace chemical exposures, although such relationships have not been clearly elucidated because of the methodological difficulties inherent in human observational studies. Cigarette smoke contains more than 3700 constituents, and the mechanisms through which this mixture exerts possible synergistic or potentiating effects are largely unknown.[6] At least 200 microsomal enzyme inducers have been identified. Smoking, which provides exposure to multiple known enzyme inducers, has been demonstrated to interact with specific pharmaceuticals. By way of this induction, smoking can potentially increase the toxic effects of occupational chemical exposures.[7]

In the practice of industrial hygiene, smoking should be considered a coexposure, and smokers may not be protected by some specific chemical exposures at the TLV level. Workers exposed to chemicals should not smoke because contamination of cigarettes allows tobacco smoke to act as an exposure vehicle. Because exposure to tobacco smoke alone is associated with increased risks of cardiopulmonary disease, cancer, lung disease, and bronchial asthma, exposures to chemicals that also have such effects should be given special consideration.

Personal use of ethanol is widespread and is well known to have effects on general metabolism and, more specifically, the metabolism of organic solvents. The 1999 TLV documentation for xylene states, "Of note here is the competitive inhibition between ethyl benzene, ethanol, or toluene and xylene metabolism that occurs at the level of the hepatic enzymes responsible for their detoxification. This inhibition leads to increased blood concentrations of the respective solvents than would otherwise occur."[8] Ethanol's effect on increasing the activity of microsomal oxidative metabolism has also been shown to cause increased carbon tetrachloride toxicity.[9]

Similar routes and pathways of metabolism also may cause occupational exposures to chemicals to increase the toxicity of ethanol. For example, a metabolite of trichloroethylene, chloral hydrate, competes with ethanol for alcohol dehydrogenase (which catalyzes the oxidation reduction reaction between aldehydes and alcohols) and for acetaldehyde dehydrogenase (which catalyzes the irreversible oxidative reaction of aldehydes to acids). This interaction results in alcohol intolerance in workers exposed to trichloroethylene.[10]

An increasing number of employees hold second jobs where they may also be exposed to chemicals. Some employees may engage in activities off the job that result in exposures as well. These exposures may have a profound impact on the health of employees, even if exposures are at or below the applicable TLV. Thus, it is important to consider such exposures and possibly modify the application of TLVs for these workers. For example, if a laboratory worker who routinely uses acetone in cleaning glassware is exposed to irritants such as turpentine or glass wool fibers during home renovation, such exposures should be considered additive.

Whether it is a genetic factor, disease or ill health, personal habit, or previous or concurrent exposures, a

worker may be considered in the sensitive subpopulation when exposed to workplace chemicals. In applying TLVs to ensure sensitive workers are protected, the occupational health team must be proactive. Although accessing specific chemical TLV documentation is a good start, it is important to review the scientific literature to obtain all information possible regarding susceptible subpopulations. Even if the literature contains nothing to suggest that any group is especially sensitive, care should be taken ensure that employees are monitored to identify exposure-response relationships.

MULTIPLE CHEMICAL EXPOSURES (MIXTURES)

In many workplaces, employees are exposed to more than one chemical at a time. This is especially the case for laboratory workers, who work with a wide variety of chemicals, some of which may be of unknown toxicity. A review of Material Safety Data Sheets (MSDS) will indicate that many products contain more than one chemical, thus resulting in employees being exposed to the mixture. Multiple exposures may also result from exposures that occur off the job (at home or at a second job), because some chemicals may not be cleared from the body before work begins.

The general approach, regardless of the specific OEV, to evaluating exposure data for mixtures involves two steps. First, the identification of chemicals that cause similar kinds of toxic responses is required; and second, for those chemicals, implementation of the "mixture formula" as a means of assessing whether exposures are above or below recommended limits should be performed. A discussion of the application of the mixture formula for chemicals that have additive effects and those that have independent effects is contained in Appendix C in the TLV and BEI book. It should be noted that OSHA mandates the use of the mixture approach for all chemicals that have PELs, although the requirement is rarely enforced.[11]

A few years ago, the format of the TLV and BEI book was changed, in part to incorporate the listing of "TLV Basis—Critical Effect(s)" for each compound. In addition to providing information regarding the effects of concern, the listing is meant to provide guidance in the application of the mixture formula. For multiple chemical exposures, chemicals that have common critical effects should be considered as additive in the mixture formula.

Examples of the application of the mixture formula are given in the TLV and BEI book. In example A.1 in the book, exposures are to acetone, sec-butyl acetate, and methyl ethyl ketone, all of which list "irritation" as the critical effect (methyl ethyl ketone also has "CNS"[1] listed). Given that the basis for the respective TLVs are the same (similar toxicological effects), it is appropriate to apply the additive effects formula for the mixture. This example is unusually straightforward, and in many cases, multiple critical effects are listed for each compound. In more complex cases, it is important to consult each TLV documentation to determine how best to apply the mixture formula.

TIME-WEIGHTED AVERAGING (TWA)

The TLVs listed in the book are most often found under the "TWA" column, meaning that exposures should be evaluated over the course of eight hours and compared with this eight-hour TLV-TWA. Many chemicals have both a TLV-TWA and a listing under the short-term exposure limit ceiling (STEL/C; the "C" indicates that it is a ceiling value) column. The TLV-STEL is defined as a 15-minute TWA exposure that should not be exceeded at any time during the workday, even if the eight-hour TWA is within the TLV-TWA. The TLV-C refers to the concentration that should not be exceeded, even for a moment, during any part of the working exposure. The STELs represent concentrations "to which it is believed that workers can be exposed for a short period of time without suffering from 1) irritation, 2) chronic or irreversible tissue damage, or 3) narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue or materially reduce work efficiency."[2p4] Ceiling values are listed for chemicals that are very fast acting, such as some irritant gases.

The nature of laboratory work is such that exposures are of short duration and highly variable. When chemicals that are used in the laboratory have ceiling or STEL values, there is concern that short-term exposures to high concentrations of the substance may result in adverse effects. If there is potential for exposure to such chemicals, specific tasks for which exposure is likely the highest should be evaluated. Air monitoring should include evaluating exposures over the course of short periods (e.g., 15 minutes), and for chemicals with ceiling values direct reading instruments should be used. Because most chemicals with STELs or ceiling TLV values are sensory irritants, workers may experience eye and upper airway irritation when exposed.

Chemical exposures in laboratories have not been well investigated, but an investigation at the Massachusetts Institute of Technology (MIT) indicated that chemical exposures were minimal.[12] In this study, air samples were collected over a four-month period (winter) from both teaching and research laboratories in the departments of Material Sciences and Engineering, Chemical Engineering, and Biology. The most frequently sampled chemicals in these three departments were cobalt, styrene, and formaldehyde, respectively. A total of 23 different agents were measured. The ratio of measured concentrations to the appropriate ACGIH TLV was then calculated. The geometric mean of the ratio for the total samples was 0.34%.

Given the findings of the MIT investigation, we can assume that most laboratory employees are likely exposed to TWA concentrations that are less than the applicable TLV-TWAs. However, we should be aware that studies rarely consider the adverse effects of multiple chemical exposures. Also, some laboratory employees may be unusually susceptible to the adverse effects of specific agents. Additionally,

[1] CNS refers to central nervous system effects.

short-term exposures are difficult to evaluate, and for chemicals with STELs or ceiling values there may be risks of acute effects in exposed laboratory workers.

TLV NOTATIONS

The "Introduction to the Chemical Substances" section of the TLV and BEI book provides definitions and guidance in the application of TLV notations. When an agent of concern has a notation listed, it is prudent to review this section of the TLV and BEI book and consult the specific documentation. Any listing of a notation indicates concern about a specific adverse health effect, and this information should be provided to employees through appropriate mechanisms.

Skin Notation

The death of a Dartmouth College researcher in 1997 as a result of dermal exposure to a small quantity of dimethyl mercury shocked the academic community. This tragedy highlighted the need for laboratory workers to follow safety procedures that were once thought to overprotect those who use small quantities of chemicals. It also displayed the risks associated with toxic chemicals that can penetrate the skin.

Dimethyl mercury does have a TLV: it is listed as mercury, alkyl compounds, with a TLV-TWA of 0.01 mg/m^3 and a TLV-TWA of 0.03 mg/m^3, and it has a notation that it can penetrate the skin ("skin notation"). The PEL and other OEVs for alkyl mercury compounds all have skin notations as well. Although organometallics are well known for their characteristic high dermal penetration and toxicity, all chemicals with skin notation penetration deserve the same respect. Consulting the specific chemical documentation is important because it provides the basis for the skin notation and provides some information regarding the magnitude of the risk.

In traditional industrial hygiene practice, for skin notation chemicals, it is appropriate to ensure that dermal exposure be prevented. If dermal exposure to a compound cannot be eliminated, the dermal route of exposure must be quantitatively evaluated to apply the airborne TLV. Dermal exposure is most often evaluated or estimated by means of biological monitoring if a method is available. It should be noted that a listing of "BEI" as a notation indicates the availability of validated biomarkers of exposures. If biological monitoring is not an option, controls must be in place to ensure that the dermal route of exposure is eliminated.

Given the options that are available when dealing with chemicals that are absorbed dermally and can cause systemic toxicity, most health professionals agree that the complete elimination of the dermal route of exposure is the preferred approach. This is usually accomplished through a combination of administrative controls (such as training), engineering controls, and the use of personal protective equipment. MSOSs should be available and the appropriate gloves and personal protective equipment worn. Care should be taken to minimize the risks of injection of such chemicals because most are highly toxic.

It is also important to remember that just because a chemical does not have a specific skin notation does not mean that there is no risk related to dermal exposure. In atypical situations, it is appropriate to reduce skin exposure to the lowest levels feasible. Similarly, many chemicals used in laboratories have no skin notation because they have no TLV, PEL, or other OEV; these chemicals cannot be assumed to be without risk and should be treated as highly toxic and exposures via all routes minimized or eliminated.

Sensitizer Notation

The sensitizer notation is new for the TLVs. Compounds with this notation have the potential to cause sensitization in workers as a result of dermal contact, inhalation, or both. Although the numeric value for the TLV is meant to protect workers from all adverse effects, including sensitization, some workers may become sensitized at exposures below the TLV (this is true for any adverse health effect). Because studies involving sensitization are difficult to perform and difficult to interpret, chemicals currently without the sensitizer notation may later be assigned one. The sensitizer notation serves to heighten our awareness of this additional risk. However, without consulting the specific chemical documentation, it is impossible to determine if the sensitization risk is related to dermal or inhalation exposures (although there are some chemicals that cause sensitization by both routes).

Carcinogenicity Notation

The definitions of the categories for carcinogenicity, A1 to A5, are contained in the "Adopted Appendices" section of the TLV and BEI book (Appendix A, entitled "Carcinogenicity"). For substances that have a carcinogenicity category designated, the precise definition should be consulted to appropriately interpret the notation. It is important to be aware that a lack of any carcinogenicity notation only indicates that no studies that have assessed cancer risk were available when documentation was written.

For laboratory and all other workers, exposure to chemicals that are potential or known human carcinogens should be minimized. Any exposure to A1 carcinogens (confirmed to cause cancer in humans) should be eliminated or highly controlled. In many workplaces, chemicals with the A1 designation are not allowed on site. For A2 and A3 carcinogens (suspected human and confirmed animal carcinogens, respectively), exposures should be carefully controlled.

TLV BASIS: CRITICAL EFFECTS

This listing of critical effects is useful because it provides a summary of the adverse effects that appear at the lowest levels of exposure. As discussed previously, these end points provide guidance in the application of the mixture formula when workers are exposed to multiple chemicals. Additionally, the end points listed provide us with a reminder of the health effects and symptoms we may see in exposed workers, although, it is always best to consult the documentation to gain a more in-depth understanding of the potential risks.

Although there are a multitude of critical effects that drive the setting of

TLVs, a few deserve special mention here. The effect "irritation" appears frequently, so is important to consider; the listing of "reproductive" is important because this effect is of great concern to all workers.

Irritation

Almost two-thirds of all TLVs are based on sensory irritation. As noted in the "Introduction to the Chemical Substances" section of the TLV and BEI book, most workers who experience adverse effects at or below the TLV will display an irritation response. Although no adverse effect is desired, an employee's report of sensory irritation usually can be alleviated by removal from exposure or the use of protective equipment. There are usually no long-term adverse effects of sensory irritation if the exposure is reduced. Additionally, recent research indicates that workers become inured to the irritant effects of exposure because they are better able to determine the true level of sensory irritation, as compared with workers who were never exposed to the irritant.[13]

If irritation is listed as a critical effect, the data underlying the TLV (see the documentation) may provide an indication of the level of exposure that may result in irritation. The uncertainty factor for the outcome of sensory irritation and for other adverse outcomes should be noted. Uncertainty factors for irritation are often much smaller then those for more severe effects; thus, the presence of irritation in exposed workers should be taken as a warning that exposures should be reduced to prevent other, more serious health effects.

Reproductive

Very few hazard warnings elicit the type of response that one gets from identifying an agent that affects reproduction. Reproductive toxins, such as lead, originally spawned the controversy over fetal protection and reproductive rights. Given this background and the sensitivity of reproductive issues in society, chemicals that may cause reproductive effects must be identified and incorporated into a reproductive health program.

The documentation of the TLVs can be an important source of information for the reproductive health program. Although numerous publications, books, and other literature are available for determining the reproductive risks of chemicals, the TLV documentations are unique in that they have direct application. Although other sources also describe the findings of reproduction studies, the TLV documentation considers such research in the context of occupational exposures. Reading the TLV documentation provides an indication, which is based on the weight of scientific evidence, of the risks faced by workers when exposed to levels close to the TLV. It should be noted that the German MAK Commission[14] has developed notations for reproductive effects that provide assessment of risks of workplace chemical exposures during pregnancy.

CONCLUSION

TLVs are an essential tool in programs designed to protect laboratory employees from the potential hazards associated with the many chemicals they work with. Laboratories represent a unique occupational environment that makes the application of TLVs and other OEVs challenging. We have considered some of the concepts related to the use of TLVs that deserve special consideration when applied to laboratory work; however, TLVs are never clear lines between what it safe and unsafe, and it is important for the individual to be open to all kinds of information before formulating a professional recommendation.

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