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Threshold Limit Values for Chemical Substances Committee (TLV[®]-CS) Handbook

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Chemical Substance Subcommittee Procedures

Generally, no voting takes place in the TLV-CS chemical substance subcommittees. Decisions are made by consensus, if possible. However, a subcommittee chair may ask for a vote of the subcommittee members if consensus is not reached. In this case, a quorum of the subcommittee must be present and a simple majority vote will be required to bring TLV Documentation to the full committee. The subcommittee chair must seek subcommittee consensus for all substances currently on the NIC and the Under Study list. In a case where the subcommittee could not reach a consensus or majority vote, the subcommittee chair may bring the discussion of the particular substance to all members of the full TLV-CS Committee with approval from the committee chair.

Administrative Subcommittees

Steering Subcommittee

Method of Selection and Appointment

The Steering Subcommittee consists of the TLV-CS Committee Chair and Vice Chair, the technical subcommittee chairs and vice chairs, and the administrative subcommittee chairs. The committee chair also chairs the Steering Subcommittee.

Duties

The Steering Subcommittee:

- Advises the committee chair on issues.
- Reviews committee productivity, progress toward goals and mission, and spending and budget.
- Recommends specific annual goals and an annual committee work plan to the committee chair to be submitted to the board of directors for approval.
- Reviews, changes, and updates committee policies, for full committee approval.
- Recruits, reviews, and recommends member candidates or new members.
- Monitors the progress of member candidates.
- Assures the committee resources are reviewed and properly allocated.
- Identifies and uses external resources, as necessary.
- Reviews special projects and requests from subcommittees, as necessary.
- Reviews the progress of the TLV-CS subcommittees.
- Assists the committee chair and vice chair in organizing an annual education session.

The Steering Subcommittee will serve as the nominating group for the TLV-CS Committee Chair, with a member of the subcommittee serving as the chair for nominations. See the ACGIH Committee Operations Manual for specific information.

Notations Subcommittee

Method of Selection

The Notations Subcommittee will consist of at least one member from each of the three TLV-CS Technical Subcommittees. Members will be designated by the TLV-CS Committee Chair. The TLV-CS Committee Chair, in consultation with the subcommittee members, will select the subcommittee chair. Other ACGIH committees or task groups (e.g. BEI[®], Physical Agents, Air Sampling Instruments) may also be identified and asked to participate in the subcommittee's activities, as the need arises.

Duties

The Notations Subcommittee has as its mission to:

- Determine the appropriate types of notations for TLVs.
- Facilitate consistent use of all notations.
- Respond to emerging issues as they arise.
- Specific responsibilities of the subcommittee include:

- Reviewing current notations and recommending changes and modifications as necessary in their definitions.
- Developing criteria that guide authors in determining which notations are appropriate and how they should be applied.
- Identifying experts (internal and external to the TLV-CS Committee) that can be consulted for specific notations.
- Recommending workshops, seminars, webinars, or tutorials to provide input to the committee on emerging issues.
- Establishing ad hoc groups, where necessary, to consider special issues.
- Developing standard language that can be used in Documentation development and in the TLVs and BEIs book to describe notations and special issues.
- Providing attention to the consistent application of notations across the three TLV-CS technical subcommittees.
- Creating and revising appendices and other related documents.

It is the responsibility of the TLV-CS subcommittees and individual authors to ensure that notations are both considered and applied for specific substances. The Notations Subcommittee will serve as a consultant concerning the applicability of a notation to a specific substance. The Documentation author is responsible for the initial decisions about notations.

At this time, the types of notations that should be addressed by an author and on which they might consult with the Notations Subcommittee include:

- TWA
- TLV Basis
- STEL
- Ceiling
- Surface Limit
- Peak Exposures
- BEI
- Carcinogenicity
- Skin
- Dermal Sensitizer (DSEN)
- Respiratory Sensitizer (RSEN)
- Ototoxicant (OTO)
- Mixtures
- Inhalable Fraction and Vapor (IFV)
- Particulate Not Otherwise Specified (PNOS)
- Unusual ambient conditions
- Unusual work schedules
- Particle size-selective sampling criteria
- Minimal oxygen content
- Reciprocal calculation method for hydrocarbons

In the case of the adoption of a new notation, the Notations Subcommittee will be responsible for developing a written definition and assuring adequate review within the Committee.

Reporting

The chair of the Notations Subcommittee reports to the TLV-CS Committee Chair and will regularly report activities and progress to the TLV-CS Committee Chair, TLV-CS Committee Vice Chair, and Steering Subcommittee.

Chemical Selection Subcommittee

Method of Selection

The Chemical Selection Subcommittee will consist of at least one member from each of the TLV-CS technical subcommittees. Members will be designated by the TLV-CS Committee Chair. The TLV-CS Committee Chair, in consultation with the subcommittee members, will select the subcommittee chair. Other ACGIH Committees or task groups (e.g. BEI, Physical Agents, Air Sampling Instruments) may also be identified and asked to participate in the subcommittee's activities, as the need arises.

Duties

The Chemical Selection Subcommittee has as its mission to:

- Determine the chemicals for which the committee will establish new or revised TLVs.
- Optimize the deliberations of the committee by providing recommendations on the most important chemicals concerning occupational exposure, i.e., to ensure that efforts will have the greatest positive impact on worker health.
- Respond to emerging issues related to specific chemicals as they arise.
- Monitoring key information sources and organizations that prioritize their activities based on the greatest risk to human health due to their inherent hazards and exposure potential. Examples include the Agency for Toxic Substances Disease Registry (ATSDR), Environment Protection Agency (EPA), European Chemicals Agency (ECHA), International Agency for Research on Cancer (IARC), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA).
- Developing criteria that guide the chemical selection subcommittee members in determining which chemicals are appropriate to consider and how they should be identified.
- Preparing an annual report with specific recommendations on chemical substances for consideration by the chairs and vice chairs of each technical subcommittee. Each annual report will provide background on why the recommendation was made and provide links to useful data summaries.

Reporting

The chair of the Chemical Selection Subcommittee reports to the TLV-CS Committee Chair and will regularly report activities and progress to the TLV-CS Committee Chair, TLV-CS Committee Vice Chair, and Steering Subcommittee.

Technical Subcommittees

The TLV-CS Committee consists of three technical subcommittees:

- Particulate and Inorganic Compounds (PIC).
- Hydrogen, Oxygen, and Carbon Compounds (HOC).
- Miscellaneous Compounds (MISCO).

TLV Production Guide

The TLV-CS Committee follows the [TLV/BEI Development Process](#) posted on the ACGIH website. Specific details relating to TLV development in the TLV-CS Committee are listed below.

Under Study

The [Under Study list](#) is published on the ACGIH website, updated continuously, and in the TLVs and BEIs book, which is current as of December 1 of the prior year.

Substances are initially assigned to the Under Study list by a consensus of the respective subcommittee and can be added to or removed throughout the year as needed, by the TLV-CS Subcommittee Chairs. Changes are posted on the ACGIH website.

Draft Documentation on Under Study

An author is assigned by the TLV-CS Subcommittee Chairs to prepare the draft Documentation. Draft Documentation is not available to the public during this stage of the development process and is not released until it is at the NIC stage.

The draft Documentation is reviewed by the responsible TLV-CS subcommittee. Subsequently, a decision is made by consensus of the subcommittee to bring the TLV value(s), any notations, and draft Documentation to the TLV-CS Committee for review.

The subcommittee chair, vice chair, or subcommittee member summarizes the draft Documentation and proposes a motion to place it on the NIC. If the motion is seconded, the TLV-CS Committee will discuss and then vote on the proposed action, which requires a quorum.

Draft Documentation on the Notice of Intended Change (NIC)

A substance is held on the NIC for at least one comment period before adoption. The period for public review and correspondence is defined in the [TLV/BEI Development Process](#). Correspondence will be forwarded by staff to the TLV-CS Committee Chair, Vice Chair, and the subcommittees. At a minimum, the subcommittee chair and vice chair must ensure that all correspondence is reviewed in detail to ensure that the discussion at the subcommittee level includes full consideration of the points raised therein. During the subcommittee meetings, correspondence is reviewed by the subcommittee, and the draft Documentation is amended if necessary.

After subcommittee review and approval of the draft Documentation, it is brought to the TLV-CS Committee for review.

The subcommittee chair, vice chair, or a subcommittee member will summarize the draft Documentation and propose a motion for one of the following actions:

- Retain the draft Documentation on the NIC for an additional comment period.
- Change the draft Documentation and retain it on the NIC for an additional comment period.
- Adopt the draft Documentation.
- Withdraw draft Documentation.

If the motion is seconded, the committee will discuss and subsequently vote on the proposed action. Recommendations to adopt, withdraw, or retain NIC Documentation may be made at any meeting or teleconference if a quorum is present.

Documentation Guidelines

The purpose of the TLV Documentation is to clearly describe, present, and interpret the appropriate scientific information supporting the derivation of the TLV and its associated notations for a given chemical substance. In general, the entire Documentation should be no longer than 10 pages in length excluding references; however, exceptions will be made where circumstances warrant it. Documentation should be formatted as designated by the Documentation template. The [Guidelines and Services for ACGIH Authors](#) page on the ACGIH website provides more information, including the Technical Style Guide, Documentation template, and additional resources.

It should be kept in mind that TLV Documentation is not a complete review of all the literature available on a particular substance. It has as its purpose the derivation of a number from references and the identification of notations, to protect employees in occupational settings. The primary user of the TLV Documentation is intended to be the industrial hygiene professional.

Background

This guideline provides general instructions for preparing the main body of the TLV Documentation. It provides the TLV Documentation authors with a compendium of tools to efficiently and effectively update or create new TLV Documentation.

The primary purpose of the TLV Documentation is to describe and analyze the scientific literature that specifically supports the derivation of a TLV and any associated notations. The Documentation is not intended to be a comprehensive review of the literature on a substance, but it should describe the key studies that define the range of exposure information and animal and human health effects associated with exposure to a substance. To facilitate an organized description of this literature, the TLV Documentation Guidelines are divided into appropriate sections for description and analysis of the relevant studies. The review of the literature should not be just a recitation of the findings and conclusions of individual reports but also must provide appropriate integrated analyses as to which study(s) are most appropriate for consideration in derivations of the TLV. When a study seems to suggest the recommended TLV or any of its notations should be different from that selected, the study should be included and discussed.

In developing a written Documentation, the committee gives precedence to human studies, including case reports and epidemiologic evaluations. Animal studies with endpoints and routes of exposure and in relevant species are also considered. Genotoxicity and metabolic data are also considered and may inform the choice of TLV. The threshold concept guides the committee's decision-making. The ACGIH process for establishing occupational exposure guidelines relies on risk assessment whose basic elements are: 1) a priority of human over animal data; 2) the use of a threshold approach; and 3) reliance on good science and expert judgment.

In arriving at a TLV, the committee may consider various uncertainty factors (also known as adjustment or

safety factors) to address sources of variability and uncertainty. However, there are no rigid rules for their application and professional judgment is used to determine the overall margin of safety reflected in the TLV recommendation. Also, the committee does not develop values associated with specific levels of risk; however, modeling approaches (e.g. benchmark dose calculations) may be used to inform the TLV value. Rather, the scientific data are examined to identify the critical effect (worst-case health endpoints), no-observed- or lowest-observed-adverse-effect levels, before selecting a TLV associated with the key health endpoint(s).

Definitions

To write or update a TLV Documentation, the most current definitions cited in the TLVs and BEIs book must be used (i.e., TLV–TWA, TLV–STEL, TLV–Ceiling, TLV–SL, Skin, RSEN/DSN, OTO, etc.). The ACGIH TLV-CS Committee periodically reviews, clarifies, updates, and adds new definitions that must be considered in the development of the TLV Documentation.

Procedures

To begin the process of writing Documentation, an author is assigned to substances by a TLV-CS technical subcommittee (PIC, MISCO, HOC). Next, the author may contact ACGIH Staff to conduct a literature search.

For each major heading and subheading, it is not necessary to describe all studies, but only those regarded as reliable and relevant to the TLV recommendation (adequate description of methodology, reported in peer-reviewed literature, comprehensiveness of robust summaries, and evidence or reproducibility). The text of each section should present the studies regarded as most relevant and reliable to the derivation of the TLV first, followed by descriptions of studies deemed of lesser, but corroborative value. For studies that describe differential or contradictory findings, a brief rationale should be presented for weighting the information of greatest value to the TLV evaluation (e.g. appropriateness of route of exposure; full characterization of dose-response, adequacy of elements of study design, adequacy of description of study methodologies and results, lack of consistency with other studies, etc.). However, if no studies are available for a major heading (e.g. Human Studies, Animal Studies, etc.) indicate this with the standard statement “No studies available.” If no data are available for a subheading (e.g. Oral, Dermal, Chronic, etc.), do not include the subheading in the outline.

Any comprehensive literature reviews relevant to a major heading should be cited first for reference, without providing details. The key studies will be discussed within the section. Summaries of cited papers and additional resources should be kept concise.

The use of unpublished information requires that the entire study or communication be on file at ACGIH headquarters and be available for public release if requested. Robust studies and registration dossiers, which provide comprehensive data summaries, can be used with appropriate peer-review by the subcommittee, and the full committee, as appropriate.

TLV Documentation Outline

Section	Comments and Common Boilerplate
Title Provide formal chemical name in all capitals.	Subcommittee may decide on most common name for document title
CAS Number(s) Provide CAS number(s) describing the substance.	
Synonyms Provide listing of other chemical synonym(s) for this substance.	PubChem is a good reference for this. Also include common trade names.
Chemical Formula Provide chemical equation. Provide chemical structure on separate line, if appropriate.	PubChem is a good reference for this information.
TLV–TWA List current TLV–TWA expressed in appropriate units. If particulate matter, describe appropriate size fraction.	For aerosols, use mg/m ³ For gases and vapors, use ppm
TLV–STEL List value in appropriate units.	For aerosols, use mg/m ³ For gases and vapors, use ppm

Section	Comments and Common Boilerplate
If no value assigned, do not list.	
TLV-C List value in appropriate units. If no value assigned, do not list.	For aerosols, use mg/m ³ For gases and vapors, use ppm
TLV-SL List value in appropriate units. If no value assigned, do not list.	For solids and liquids, use mg/100 cm ²
Inhalable Fraction and Vapor (IFV) Listed when Saturated Vapor Concentration (SVC)/TLV (in mg/m ³) ratio is between 0.1 and 10.	SVC $= \frac{\left(\left(\frac{Vapor\ Pressure}{760} \right) \times Molecular\ Weight \times 1000 \right)}{\left(\left(\frac{0.08206}{1000} \right) \times 298 \right)}$
Skin If no Skin notation assigned, do not list.	
Respiratory Sensitizer (RSEN) If no RSEN notation assigned do not list.	
Dermal Sensitizer (DSEN) If no DSEN notation assigned do not list.	
Ototoxicant (OTO) If no OTO notation assigned do not list.	
Carcinogenicity List notation as A1, A2, A3, A4, or A5, with summary definition. If no information, do not list cancer designation.	
TLV Recommendation Focus only on studies providing the rationale for deriving the TLV recommendation, including notations. For example: - human study(s). - animal study(s) expressing most relevant route of exposure, doses, and appropriate responses. Include the relevant bibliographic references (e.g. Smith, 1999). The results of these studies should not be repeated in detail; provide only the key details (doses/concentrations) and conclusion(s) as they support the rationale for the TLV recommendation. This section should have a clear explanation about each of the following items: a description of the key health effects, a discussion of why particle size fraction was selected for the TLV (for aerosols), and the reasoning for the selection of a value. Various sources uncertainty and variability do not need to be quantified, but rather explained. Notations and other relevant information should also be described and explained. Identify appropriate notations and explain reasoning for their selection. - Carcinogenicity designation (see Appendix A in the TLVs and BEIs book). - RSEN/DSEN (see Sensitization definition in the TLVs and BEIs book).	Look at the critical study for the basis. Has enough been said about it? Is it clear to the reader? Look for contradictions. - How do you select the appropriate TLV? – see the description below this outline. - Do not restate definition of a notation used. - When assigning a cancer designation, revisit the definition in the TLVs and BEIs book and make sure that the evidence supports the rationale. Some useful boilerplate language: - A TLV-TWA of ___ mg/m³, measured as inhalable particulate matter (or IFV, R, T), is recommended for occupational exposure to _____. - Sufficient data were not available to recommend a TLV-STEL. - A TLV-Ceiling of _____ is recommended to minimize the <i>acute irritation</i> associated with occupational exposure to _____. - A TLV-SL of ___ mg/100 cm² is recommended to minimize the potential for dermal sensitization associated with occupational exposure to _____. - Sufficient data were not available to recommend a Skin notation.

Section	Comments and Common Boilerplate
• Skin (see definition in the TLVs and BEIs book). • OTO (see definition in the TLVs and BEIs book). Refer to BEI, if available for substance.	• Sufficient data were not available to recommend a RSEN/DSEN notation. • Available data on sensitization from exposure to _____ warrants the addition of the RSEN/DSEN (sensitizer) notation (include refs). • Sufficient data were not available to recommend an OTO notation. • Available data on ototoxicity from exposure to _____ warrants the addition of the ototoxicant (OTO) notation (include refs). • _____ is a substance for which Biological Exposure Indices (BEIs) have been recommended (see BEI Documentation for _____).
TLV Basis This section should briefly list the critical health effects that support derivation of the TLV. This description will be used to complete the TLV Basis – Critical Effect(s) column in the TLVs and BEIs book. In general, the listed Basis (Bases) should only be those at or near the TLV (e.g. within a factor of 10). It is acceptable to introduce a new critical effect as it will be added to the TLV Basis table for future use upon adoption of the Documentation.	See TLV Basis Table Each TLV-CS Subcommittee will ensure that the TLV Basis is appropriate for each new or revised TLV Documentation. Consider the following rules of thumb in selecting the appropriate TLV Basis: • If a TLV Basis is not on the current list of TLV Basis, discuss new Basis with Committee and ACGIH Staff for addition to the Basis list. • Use Cancer as a TLV Basis only if it drives the TLV. In this case, the organ or type of cancer is usually specified. • The first TLV Basis listing should be the primary effect. • If there is already a Skin or SEN notation, use care in using as a TLV basis, unless it's the primary basis.
Chemical and Physical Properties Provide a brief text description of the chemical and physical forms of the substance (e.g. solid, liquid, color, composition, contaminants, decomposition products, and known odor properties). The text section is followed by a specific listing of properties, some examples of which are provided below. If some of the specific data are not available, do not list the subheading. • Molecular weight: ### g/mol • Specific gravity: ### g/mL • Melting point: ###°C (###°F) • Boiling point: ###°C (###°F) • Vapor pressure: ### mmHg • Saturated vapor concentration: ### ppm at ##°C • Flash point: ###°C (###°F) • Flammable limits: ###% (LEL); ###% (UEL) • Autoignition temperature: ###°C (###°F) • Solubility (water): ### mg/mL • Octanol/water partition coefficients: ### @ 25°C	Log octanol/water partition coefficients (sometimes called log K_{ow}) should be included, if available. When there is more than one partition coefficient use the middle of the range. The best reference is: Leo A; Hansch C; Elkins D: Partition Coefficients and Their Uses. Chem Rev 71(6):525-616 (1971). A combination of the Log K_{ow} and molecular weight of the chemical can be used to (very roughly) estimate skin permeability from an AQUEOUS solution. The best reference is: Potts RO; Guy RH: Predicting Skin Permeability. Pharm Res 9(5):663-669 (1992). Saturated Vapor Concentration (SVC) should be listed especially for those compounds which will have an IFV endnote. SVC can be calculated using the following equation: $SVC (mg/m^3) = 53.81 \times MM \times VP$ List odor threshold, if available. Useful references include: AIHA: Odor Thresholds for Chemicals with Established Occupational Health Standards (1989).

Section	Comments and Common Boilerplate
• Conversion factors at 25°C and 760 torr: ### ppm = ### mg/m³; ### mg/m³ = ### ppm	Amoore JE; Hautala E: Odor as an Aid to Chemical Safety: Odor Thresholds. J Appl Toxicol 3(6):272-90 (1983). Ruth JH: Odor Thresholds and Irritation Levels of Several Chemical Substances: A Review. Am Ind Hyg Assoc J 47:3, A-142 (1986). U.S. EPA: Reference Guide to Odor Thresholds for Hazardous Air Pollutants Listed in the Clean Air Act Amendments of 1990. U.S. Environmental Protection Agency, Washington, D.C., EPA/600/R-92/047.
Major Sources of Exposure Describe in text format where available- • How the substance is produced (e.g. methods of manufacture, by-product of...). • Uses. • Production volumes and estimated numbers of workers exposed. • Major routes of exposure associated with manufacture and use (what forms are encountered during use, e.g. vapor, dusts, aerosol, liquid, etc.). • Particle size issues and characterizations, if relevant.	Resources • Use EPA Section Interagency Testing Committee for estimated number of employees exposed. Include the date. • Trade Association websites • TSCA database – check for production volumes. • U.S. Geological Survey/Dept of Interior List tonnage and year, e.g. date from Department of Commerce via internet.
Animal Studies This major heading and its subheadings describe the relevant <i>in vivo</i> animal studies supporting assessment and derivation of the TLV-TWA.	Detailed descriptions of animal toxicology studies are generally not required. However, if known, the minimum information for each study should include: • Species, sex, route and mode of administration (inhalation, oral gavage, oral diet, dermal, etc.), duration of dosing, specific doses tested, relevant toxic effects, No-observed-adverse-effect levels (NOAELs), Lowest-observed-adverse-effect levels (LOAELs), and frank toxic responses at higher dose levels. • Mechanistic studies (e.g. animal model and pharmacokinetic relevance) that provide perspective for appropriate extrapolation of animal findings to humans. • Published expert reviews (IARC, WHO, U.S. EPA, U.S. NIOSH, etc.) that offer analysis of human relevance of animal studies.
Animal Studies Acute (less than 2 weeks duration) Inhalation • As available, incorporate minimum information noted above in the animal studies comments column. • Describe LC₅₀ value(s) or equivalent indicator(s) of toxicity. • Describe minimum lethal concentrations/doses (LC_{Lo}, LC₅₀) and any reported clinical signs.	For LD₅₀ and LC₅₀ studies, the results can usually be summarized in a single sentence such as: • The LC₅₀ for substance XXX ranged from 588 to 1004 mg/m³ in mice and rats with signs of wheezing and coughing. Schaper M: Development of a database for sensory irritants and its use in establishing occupational exposure limits. Am Ind Hyg Assoc J 54(9):488–544 (1993).

Section	Comments and Common Boilerplate
• If no lethality found, indicate full range of concentrations, clinical observations, and effect-level concentrations. • Include particle size characterization to assess the human relevance of particle deposition in the test animal. Dermal Same as inhalation above. Include description of nature of applied substance (neat, concentration of solutions and vehicles, formulations, etc.) • Describe systemic toxicity resulting from skin absorption. • Describe specific toxicity to skin (irritation, burns, etc.); include assessment (classification) of toxic response (non-irritant, type of irritant — corrosive). • As available, incorporate minimum information noted above. • Describe LD₅₀ value(s) or equivalent indicator(s) of toxicity. • Describe minimum lethal doses (LD_{Lo}) and any reported clinical signs. • If no lethality found, indicate full range of doses, clinical observations, and effect-level doses. Sensitization Include species, doses, routes of administration, protocol used (e.g. GPMT, LLNA), ancillary information (adjuvant used, etc.), end results (dose-response (e.g. number of responders at each challenge dose); severity of response, NOAEL, EC₃ value, ancillary skin irritation, skin, or respiratory sensitization. Other studies As available, include minimum information noted above for each of the relevant other studies described. Examples of potentially relevant other studies include: • Eye irritation. • Respiratory irritation RD₅₀ studies (measures sensory irritation).	
Animal Studies Subchronic (>2 weeks ≤ 3 months) • Same information as acute studies, organized by route of exposure.	Subchronic studies are often the driver of the TLV Basis, therefore more details may be needed than for acute studies. Give the strain and #s of animals if more than one similar study. Report studies low to high dose. Give LOAEL, NOAEL, if you can. NOELs/LOELs for non-adverse effects can be included if considered relevant. Summarize by kind of study, species, route, dose, # applications, and results.
Animal Studies Chronic/Carcinogenic (> 3 months ≤ animal lifetime) • Same information as above, organized by route of exposure.	Historically, the 2-year bioassay has been considered the gold standard. However, new tests including the 1-month Pig-A assay and the 6-month transgenic rat and mouse assays, are becoming more prevalent.

Section	Comments and Common Boilerplate
If you include any carcinogenicity classification determinations published by internationally recognized review bodies, make sure that the date is cited (IARC, U.S. NTP, U.S. EPA, MAK, etc.).	Non-neoplastic effects (e.g. target organ toxicity) should also be discussed since these could be the effects that actually drive the TLV.
Animal Studies Genotoxic The results should be described briefly and are becoming more useful in the selection of the carcinogenicity category. Therefore, the results of <i>in vitro</i> and <i>in vivo</i> studies should be described briefly.	Example: Several genotoxicity studies have been reported but were generally negative. Positive findings were noted only in <i>in vitro</i> studies using the Ames test, forward mutation assays, and only with metabolic activation. Negative findings were found in other <i>in vitro</i> studies and <i>in vivo</i> studies using the micronuclei test in mice and chromosomal aberrations in rats. The weight-of-evidence indicates that this substance does not represent a significant genotoxic risk.
Animal Studies Reproductive/Developmental Toxicity This section should briefly describe adverse changes, presenting reproductive studies first, followed by developmental toxicity studies. The studies should also be organized by route of exposure with relevant routes of exposure, such as inhalation and skin, described first.	Reproductive/developmental toxicity is important to consider and sometimes serves as the basis of the TLV.
Absorption, Distribution, Metabolism, and Excretion (including toxicokinetics and toxicodynamics) Describe the human studies first followed by animal studies within each section. - Absorption information may be available for oral, inhalation, or dermal exposures. - Distribution of the chemical or metabolites into blood fluids and various tissues should be described. - Metabolism of the chemical in the liver or at the route of entry should be described. Important metabolites and their relative toxicity should be described, if known. - Elimination of the chemical or metabolites via exhalation, urine, or feces should be described (half-lives or clearance values). - Discuss ADME for a related substance if it is a known metabolite of the compound under consideration. - If a PB-PK or classical compartmental model is available for the chemical it should be referenced. - Dose-response evaluations with relevance to the TLV should be included. - Include information on the mechanism of action for the critical effect(s) and interpretation of the ADME data provided from a toxicokinetic and toxicodynamic perspective.	Studies may address the amount of chemical absorbed when the chemical is given orally and an absorption fraction for inhalation. For dermal absorption studies, the order of preference for absorption information is 1) permeability coefficient (kp), 2) flux, and 3) percentage of applied dose absorbed. Distribution of the chemical should be described if known, the octanol/water partition is important information that helps understand distribution. Any tissues that act as a sink for the chemical (such as fat) could be identified. It may be important to identify types of metabolism the chemical undergoes, i.e., P₄₅₀ (with specific isozyme if known) or glutathione conjugation. If metabolism is significant, a diagram could be useful. Relative toxicities of the parent and metabolite may be important. Primary route of elimination should be identified, e.g. exhalation, urine, or feces. Relative amounts eliminated through each route may be important, if known. Elimination half-lives may be useful. References to published compartmental or physiologically based pharmacokinetic models (PB-PK) should be cited if known. Details are not necessary but number of compartments for classical and general type of model for PB-PK (stochastic, flow or diffusion limited) could be described). The exposure route(s) that the models have been validated for should also be described.

Section	Comments and Common Boilerplate
	Dose-response evaluations such as slope factors (for cancer) or model-based extrapolations of NOAELs may be available.
Human Studies Studies among occupationally exposed populations should be given priority for detailed description. • The organization of the human studies and the order in which they are presented will vary greatly between substances based on the critical effects and the amount of human data available. • If there are relatively few human studies, it may be appropriate to describe all in detail. However, if there are many studies only the key studies for deciding the TLV or the notations should be described in detail. • Where there are many epi studies, use the boilerplate which states that many studies exist, but only discuss those used in the derivation of the TLV. • Cite available process-related occupational exposure findings, even if dose-response data/results are not available.	Key studies are generally those which: 1. Evaluate health effects in relation to level of exposure (i.e., assess dose-response) 2. In the absence of #1, provide some information on the level of exposure 3. Cohort and case-control studies that contribute to assigning the cancer notation 4. Studies that evaluated respiratory and skin sensitization 5. Studies that demonstrate systemic toxicity following dermal exposure For key studies, include the following information: 1. Type of study (e.g. cross sectional, case control, cohort, experimental, or other); 2. Study population (include location of study, number of participants, and pertinent demographic information); 3. Measurements of disease or death (e.g. death certificates, physical examination, laboratory analyses, questionnaires, etc.); 4. Measurements of exposure (e.g. laboratory analyses, air measurements, questionnaires, etc.); 5. The results relevant to setting the TLV or assigning notations. Include the measure of health effect (i.e., odds ratio, relative risk, standardized mortality/morbidity ratio [SMR], cross-shift change in physiologic measurement, etc.) and the confidence intervals or p-values. Present the results for critical health effects regardless of the statistical significance 6. Other potential causes of the health effect or confounders considered (e.g. age, sex, smoking, and other exposures present) and whether the results were adjusted for these factors. Non-key studies are those that describe health effects without any indication of level of exposure, those that describe health effects that occur at levels well above the proposed TLV, and those that indirectly contribute to our understanding of the critical effects. For non-key studies, it is acceptable to briefly summarize the results of studies and to cite reviews from the peer-reviewed literature or those conducted by public agencies that are widely available (i.e., ATSDR, IARC). If there are many human studies with similar designs, make tables of the data where possible to summarize the key information listed above.

Section	Comments and Common Boilerplate
TLV Chronology The purpose of this section is to describe only the historical, pending, or actionable activities (dates) associated with the TLV Documentation. It is not intended to describe the detailed history of actions completed on the Documentation. Authors complete this section in collaboration with the ACGIH Technical Editor. For updated documents, authors should upload or submit documents with track changes so ACGIH Staff can see the new edits. 20XX: Proposed: TLV–TWA, ## ppm 20XX: TLV–TWA, ## ppm 20XX: Documentation revised. Describes current Documentation revision efforts; use only when Documentation is revised but TLV is not changed 20XX: Proposed: TLV–TWA, ## ppm, notation(s). If necessary, describe published (NIC) Proposed TLV values and associated notations that have not been adopted by ACGIH.	Example statements to insert in historical section of TLV Documentation when there are no changes to the TLV or Notations. Authors should include the appropriate language for the Documentation: • _____ (cite year of change): TLV Basis update to Documentation _____ (cite year), retaining adopted TLV(s) and notation(s). ▪ Example: 2004: TLV Basis update to Documentation 2001, retaining adopted TLV(s) and notation(s). • _____ (cite year of change): Editorial clarification made to Documentation _____ (cite year), retaining adopted TLV(s) and notations. • _____ (cite year of change): New information and reference(s) added to Documentation _____ (cite year), retaining adopted TLV(s) and notations. ▪ Example: 2004: New information and references added to Documentation 1996, retaining adopted TLV(s) and notation(s). • _____ (cite year of change): New section(s) and reference(s) added to Documentation _____ (cite year), retaining adopted TLV(s) and notations. • _____ (cite year of change): Comprehensive revision of Documentation _____ (cite year), retaining adopted TLV(s) and notations or • The TLV Documentation has been updated and revised to reflect new scientific data, but the TLV recommendation has not been changed. • _____ (cite year of change): Literature search and review completed with no updates for Documentation _____ (cite year), retaining adopted TLV(s) and notations.
References Use Council of Science Editors Scientific Style Refer to the ACGIH Technical Style Guide	

Selecting an Appropriate TLV

When selecting an appropriate TLV, decide what the critical health effects are, i.e., those adverse effects that occur at the lowest exposure levels and will drive the TLV value. Next, determine which type of TLV (TWA, STEL, C, SL) is warranted by reviewing the definitions to select the appropriate form of a TLV. Although the type of available data may affect this, in general:

- **Threshold Limit Value–Time-Weighted Average (TLV–TWA):** The TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect.
- **Threshold Limit Value–Short-Term Exposure Limit (TLV–STEL):** A 15-minute TWA exposure that should not be exceeded at any time during a workday, even if the 8-hour TWA is within the TLV–TWA. The TLV–STEL is the concentration to which it is believed that workers can be exposed continuously for a short period without suffering from 1) irritation, 2) chronic or irreversible tissue damage, 3) dose-rate-dependent toxic effects, or 4) narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue or materially reduced work efficiency. The TLV–

STEL may not protect against these effects if the 8-hour TLV–TWA is exceeded. The TLV–STEL usually supplements the TLV–TWA where there are recognized acute effects; however, the TLV–STEL may be a separate, independent exposure guideline.

- **Threshold Limit Value–Ceiling (TLV–C):** The concentration that should not be exceeded during any part of the working exposure. If instantaneous measurements are not available, sampling should be conducted for the minimum period sufficient to detect exposures at or above the ceiling value.
- **Threshold Limit Value–Surface Limit (TLV–SL):** The concentration on workplace equipment and facility surfaces that is not likely to result in adverse effects following dermal exposure or incidental ingestion. The TLV–SL is intended to supplement airborne TLVs especially those with Skin, DSEN, and RSEN notations, to provide quantitative criteria for establishing acceptable surface concentrations, expressed as mg/100 cm².

Next, decide the value of the TLVs by using the following methods:

- If sufficient studies are available, develop a summary table of key studies and findings as they relate to the TLV. From this information, select a point at which it appears no adverse health effects are likely to occur in nearly all workers.
- Describe the relationship of recommended TLV to known human or animal toxicity responses.
- Describe how the TLV reflects uncertainties in the available data. If the uncertainty in the available data is high, state so. Using professional judgment, adjust the TLV to reflect an appropriate degree of conservatism.
- When animal data are the primary source, uncertainty considerations include:
 - The quality of the studies
 - Available exposure information
 - Use language that avoids referring to these adjustments as factors.
 - The TLV number should have only one significant figure unless your data are very precise (extremely rare).
 - If route-to-route conversion factors are used, be explicit/transparent.
 - See conversion guides.

Consider whether a volatile substance may occur or be generated in the form of an aerosol. If so, it may be necessary to develop a TLV for an aerosol form in addition to the vapor form or to determine separate TLVs for these two forms. If the TLV value is the same for both forms, then a designation of both vapor and aerosol must be made. If the TLV refers to an aerosol, one of the three Particle Size Selective (PSS)–TLV designations must be selected. In general, the following relationship will determine which one:

In which part of the respiratory system can deposition or absorption lead to health effects?	PSS
Throughout respiratory system	Inhalable
Lung airways and gas exchange	Thoracic
Gas exchange areas	Respirable

Exposure data that include particle size distributions may be useful in helping identify the PSS.

Selecting Appropriate Notations

Identify appropriate notations and explain the reasoning for their selection.

- Carcinogenicity designation (see Appendix A in the TLVs and BEIs book)
- RSEN (see sensitization definition in TLVs and BEIs book)
- DSEN (see sensitization definition in TLVs and BEIs book)
- Skin (see definition in TLVs and BEIs book)
- OTO (see definition in TLVs and BEIs book)

Authors should insert the boilerplate language if and when particular TLV forms are not recommended or certain notations are not assigned. See the TLV Documentation Outline above for the recommended boilerplate.

TLV Basis

Terms used as the TLV Basis with abbreviations (last updated January 2023).

Group Listing

Basis Group	Effect Name	Abbreviation (if necessary)
Cancer	Bladder cancer	Bladder cancer
	Cancer	Cancer
	Kidney cancer	Kidney cancer
	Laryngeal cancer	Larynx cancer
	Leukemia	Leukemia
	Liver cancer	Liver cancer
	Lung cancer	Lung cancer
	Mesothelioma	Mesothelioma
	Nasal cancer	Nasal cancer
	Prostate cancer	Prostate cancer
	Sino-nasal cancer	Sino-nasal cancer
	Skin cancer	Skin cancer
	Testicular cancer	Testicular cancer
	Upper respiratory tract cancer	URT cancer
Entire Human Body	Body weight effects	Body weight
	Cytochrome oxidase inhibition	Cyto oxid inhib
	Fatigue	Fatigue
	Malaise	Malaise
	Metabolic acidosis	Metabolic acid
	Muscular stimulation	Muscular stim
	Nausea	Nausea
	Simple asphyxia	Asphyxia
	Stimulation of basal metabolism	Basal metab
Upper Respiratory Tract	Anosmia	Anosmia
	Halitosis	Halitosis
	Larynx metaplasia	Larynx metaplasia
	Upper respiratory tract damage	URT dam
	Upper respiratory tract inflammation	URT inflam
	Upper respiratory tract irritation	URT irr
Lower Respiratory Tract	Asthma	Asthma
	Berylliosis	Berylliosis
	Beryllium sensitization	Beryllium sens
	Bronchitis	Bronchitis
	Bronchopneumonia	Bronchopneumonia
	Lower respiratory tract irritation	LRT irr
	Lung damage	Lung dam
	Metal fume fever	Metal fume fever
	Pneumoconiosis	Pneumoconiosis
	Pulmonary edema	Pulm edema
	Pulmonary emphysema	Pulm emphysema
	Pulmonary fibrosis	Pulm fibrosis
	Respiratory sensitization	Resp sens

Basis Group	Effect Name	Abbreviation (if necessary)
Autonomic Nervous System	Pulmonary function	Pulm func
	Pneumonitis	Pneumonitis
	Autonomic nervous system impairment	ANS impair
	Cholinesterase inhibition	Cholinesterase inhib
Central Nervous System	Auditory nerve impairment	Audit nerve impair
	Central nervous system convulsion	CNS convul
	Central nervous system impairment	CNS impair
	Cochlear impairment	Cochlear impair
	Cognitive decrements	Cognitive decrement
	Dizziness	Dizziness
	Headache	Headache
	Neurotoxicity	Neurotoxicity
	Ocular nerve damage	Ocular nerve dam
	Vestibular impairment	Vestibular impair
	Visual impairment	Visual impair
Peripheral Nervous System	Peripheral nervous system impairment	PNS impair
	Peripheral neuropathy	Periph neuropathy
Gastrointestinal System	Gastrointestinal damage	GI dam
	Gastrointestinal irritation	GI irr
Cardiac System	Cardiac sensitization	Card sens
	Cardiac system impairment	Card impair
	Myocardial effect	Myocard
Vascular System	Vascular system impairment	Vasc sys impair
	Vasoconstriction	Vasoconstriction
	Vasodilation	Vasodilation
Hematopoietic System	Anemia	Anemia
	Carboxyhemoglobinemia	COHb-emia
	Coagulation problems	Coagulation
	Hematologic effects	Hematologic
	Hemolysis	Hemolysis
	Hemosiderosis	Hemosiderosis
	Hypoxia/Cyanosis	Hypoxia/Cyanosis
	Increased platelet count	Incr platelets
	Inhibition of heme synthesis	Inhib heme synth
	Leucopenia	Leucopenia
	Methemoglobinemia	MeHb-emia
	Nitrosylhemoglobin formation	Nitrosyl-Hb form
	Porphyria effects	Porphyria
Immune System	Immune system impairment	Immun impair
Reproductive System	Female reproductive system damage (excluding teratogenic effects and embryonic and fetal damage)	Female repro
	Male reproductive system damage	Male repro
	Pregnancy loss	Pregnancy loss
	Reproductive effects	Repro
	Testicular damage	Testicular dam

Basis Group	Effect Name	Abbreviation (if necessary)
Eye	Cataract	Cataract
	Corneal necrosis	Corneal necrosis
	Eye damage	Eye dam
	Eye irritation	Eye irr
	Eye photosensitization	Eye photosen
Skin	Alopecia	Alopecia
	Argyria	Argyria
	Chloracne	Chloracne
	Dermal sensitization	Derm sens
	Dermatitis	Dermatitis
	Skin damage	Skin dam
	Skin irritation	Skin irr
	Skin photosensitization	Skin photosen
	Skin sensitization	Skin sens
Teeth	Dental erosion	Dental erosion
	Dental fluorosis	Dental fluorosis
Bones	Bone damage	Bone dam
	Fluorosis	Fluorosis
Thyroid	Thyroid effect	Thyroid
Liver	Bile duct hyperplasia	Bile duct hyperplasia
	Hepatic necrosis	Hepatic necrosis
	Liver damage	Liver dam
	Liver Effects	Liver
Spleen	Spleen damage	Spleen dam
Kidney/Urinary tract	Bladder irritation	Bladder irr
	Glomerular damage	Glomerular dam
	Kidney damage	Kidney dam
	Kidney irritation	Kidney irr
	Tubular damage	Tubular dam
Embryo or fetus	Embryo/fetal damage	Embryo/fetal dam
	Teratogenic effect	Teratogenic
Genetic effects	Mutagenic effect	Mutagenic

Alphabetical Listing

Alphabetical Basis Listing
Alopecia
Anemia
Anosmia
Argyria
Asthma
Auditory nerve impairment
Autonomic nervous system impairment
Berylliosis
Beryllium sensitization
Bile duct hyperplasia

Alphabetical Basis Listing
Bladder cancer
Bladder irritation
Body weight effects
Bone damage
Bronchitis
Bronchopneumonia
Cancer
Carboxyhemoglobinemia
Cardiac sensitization
Cardiac system impairment
Cataract
Central nervous system convulsion
Central nervous system impairment
Chloracne
Cholinesterase inhibition
Coagulation problems
Cochlear impairment
Cognitive decrements
Corneal necrosis
Cytochrome oxidase inhibition
Dental erosion
Dental fluorosis
Dermal sensitization
Dermatitis
Dizziness
Embryo/fetal damage
Eye damage
Eye irritation
Eye photosensitization
Fatigue
Female reproductive system damage (excluding teratogenic effects and embryonic and fetal damage)
Fluorosis
Gastrointestinal damage
Gastrointestinal irritation
Glomerular damage
Halitosis
Headache
Hearing impairment
Hematologic effects
Hemolysis
Hemosiderosis
Hepatic necrosis
Hypoxia/Cyanosis
Immune system impairment
Increased platelet count

Alphabetical Basis Listing
Inflammation
Inhibition of heme synthesis
Kidney cancer
Kidney damage
Kidney irritation
Larynx cancer
Larynx metaplasia
Leucopenia
Leukemia
Liver
Liver cancer
Liver damage
Lower respiratory tract irritation
Lung cancer
Lung damage
Malaise
Male reproductive system damage
Mesothelioma
Metabolic acidosis
Metal fume fever
Methemoglobinemia
Muscular stimulation
Mutagenic effect
Myocardial effect
Nasal cancer
Nausea
Neurotoxicity
Nitrosylhemoglobin formation
Ocular nerve damage
Peripheral neuropathy
Peripheral nervous system impairment
Pneumoconiosis
Pneumonitis
Porphyria effects
Pregnancy loss
Prostate cancer
Pulmonary edema
Pulmonary emphysema
Pulmonary fibrosis
Pulmonary function
Reproductive effects
Respiratory sensitization
Simple asphyxia
Sino-nasal cancer
Skin cancer
Skin damage

Alphabetical Basis Listing
Skin irritation
Skin photosensitization
Skin sensitization
Spleen damage
Stimulation of basal metabolism
Teratogenic effect
Testicular cancer
Testicular damage
Thyroid effect
Tubular damage
Upper respiratory tract cancer
Upper respiratory tract inflammation
Upper respiratory tract irritation
Vascular system impairment
Vasoconstriction
Vasodilation
Vestibular impairment
Visual impairment

Conversion from Animal Dietary PPM to Animal mg/kg per Day

All calculations are for the author's use only and should not be included in the Documentation.

Assuming that a diet contains X ppm of a particular chemical substance (CS), this is then equivalent to X mg ingested per 1 kg diet.

Some useful normative values*	
Mouse	body weight (BW) is approximately 30 g; mouse consumes ~4 g diet per day
Hamster	BW is approximately 100 g; hamster consumes ~10 g diet per day
Rat	BW is approximately 350 g; rat consumes ~20 g diet per day
Dog	BW is approximately 10 kg; dog consumes ~300 g diet per day

*Data reported in primary literature should supersede the use of these normative values.

General Equation (mg CS/kg BW per day)

$$\frac{\text{concentration of CS in diet (mg/kg of food)} \times \text{amount of diet consumed per day (kg food per day)}}{\text{body weight (kg)}}$$

Examples using normative values, assuming 25 ppm of substance in diet.

Mouse	$\frac{25 \text{ mg CS/1 kg diet} \times 0.004 \text{ kg diet per day}}{0.030 \text{ kg BW}}$	3.3 mg/kg per day
Hamster	$\frac{25 \text{ mg CS/1 kg diet} \times 0.01 \text{ kg diet per day}}{0.100 \text{ kg BW}}$	2.5 mg/kg per day
Rat	$\frac{25 \text{ mg CS/1 kg diet} \times 0.02 \text{ kg diet per day}}{0.350 \text{ kg BW}}$	1.4 mg/kg per day
Dog	$\frac{25 \text{ mg CS/1 kg diet} \times 0.3 \text{ kg diet per day}}{10 \text{ kg BW}}$	0.75 mg/kg per day
Monkey	$\frac{25 \text{ mg CS/1 kg diet} \times 0.1 \text{ kg diet per day}}{3.5 \text{ kg BW}}$	0.71 mg/kg per day

Conversion from Animal Dietary PPM to Animal Inhalation Exposure

Assuming that a diet contains X ppm of a particular chemical substance, this is then equivalent to X mg ingested per 1 kg diet.

Scaling Factors (assuming normative values)				
Species	BW (g) ^a	Respiratory Rate ^b (breaths/min)	Tidal Volume ^b (mL/breath)	Food Consumption (g) ^c
Human	70,000	12 to 17	750 to 1000	720
Dog	10,000	20	100	178
Guinea Pig	500	90	2	20
Rat	350	160	1.4	15
Hamster	100	74	0.8	10
Mouse	30	180	0.25	3

^aBW: Chapter 22, Inhalation Toxicology by G.L. Kennedy and R. Valentine, In: Principles and Methods of Toxicology, Third Edition, Raven Press Ltd., NY (1994), A.W. Hayes (Editor)

^b Normative data, University of Wisconsin-Madison, Research Animal Resources and Compliance.
https://www.rarc.wisc.edu/animal_health/normative_data.html

^cFood Consumption (g): $0.234 \times BW^{0.72}$ where BW is in g (Nagy, 1987)

Step 1: How much of the CS is ingested by the animal each day?

concentration of the CS in diet x amount of diet consumed per day

Units: mg/kg x kg per day = mg per day

Example (for rat): 5.0 mg CS/1 kg diet x 0.015 kg diet per day = 0.075 mg per day

Step 2: How much air does the animal breathe during the exposure (day)?

Respiratory Rate x Tidal Volume x Duration of Exposure

Units: breaths/min x mL/breath x min = mL (or can convert to m³ by dividing by 106)

Example: (assume rat exposure for 6 hrs = 360 min)

160 breaths/min x 1.4 mL/breath x 360 min = 80,640 mL (~80 L) = 0.08 m³ inhaled air

Step 3: What is the equivalent airborne concentration of this CS (assuming 100% deposition in and absorption by the respiratory tract)?

$0.075 \text{ mg} / 0.08 \text{ m}^3 = 0.94 \text{ mg/m}^3$

Thus, a rat that eats a diet with 5.0 ppm of the CS per day receives the same dose as the rat that inhales 0.94 mg/m³ of the CS over a 6-hour exposure period.

Conversation from Animal Dietary PPM to Human Inhalation Exposure

Assuming that a diet contains X ppm of a particular chemical substance (CS), this is then equivalent to X mg ingested per 1 kg diet.

Scaling Factors (assuming normative values)				
Species	BW (g) ^a	Respiratory Rate ^b (breaths/min)	Tidal Volume ^b (mL/breath)	Food Consumption (g) ^c
Human	70,000	12 to 17	750 to 1000	720
Dog	10,000	20	100	178
Guinea Pig	500	90	2	20
Rat	350	160	1.4	15
Hamster	100	74	0.8	10
Mouse	30	180	0.25	3

^aBW: Chapter 22, Inhalation Toxicology by G.L. Kennedy and R. Valentine, In: Principles and Methods of Toxicology, Third Edition, Raven Press Ltd., NY (1994), A.W. Hayes (Editor)

^b Normative data, University of Wisconsin-Madison, Research Animal Resources and Compliance.
https://www.rarc.wisc.edu/animal_health/normative_data.html

^cFood Consumption (g): $0.234 \times BW^{0.72}$ where BW is in g (Nagy, 1987)

Step 1: How much of the CS is ingested by the animal each day (assume rat)?

concentration of CS in diet x amount of diet consumed per day

Units: mg/kg x kg per day = mg per day

Example for rat: 5.0 mg CS/1 kg diet x 0.015 kg diet per day = 0.075 mg per day

Step 2: On the basis of body weight, how much of the CS is ingested by the rat each day?

Daily mass of CS ingested by rat (from Step 1) ÷ Body weight of rat

Units: mg per day ÷ kg BW = mg/kg per day

Example: 0.075 mg per day ÷ 0.35 kg = 0.21 mg/kg per day

Step 3: If a human receives the same dose of the CS as the rat (i.e., equivalent mg/kg basis), how much of the CS would be ingested (each day)?

Mass of CS per Mass of Rat (from Step 2) x Mass of Human

Units: mg/kg per day x kg BW = mg per day

Example: 0.21 mg/kg per day x 70 kg = 15 mg per day

Step 4: What is the equivalent airborne concentration of this CS in a human (assuming 100% deposition in and absorption by the respiratory tract)?

$15 \text{ mg}/10 \text{ m}^3 = 1.5 \text{ mg}/\text{m}^3$

Thus, the person who inhales 1.5 mg/m³ of the CS over an 8-hour workshift (inhales ~10 m³) receives the same dose as the rat that eats a diet with 5.0 ppm of the CS each day.

References

Nagy KA: Field metabolic rate and food requirement scaling in mammals and birds. *Ecol Mono* 57(20: 111-128 (1987).

Normative data, University of Wisconsin-Madison Research Animal Resources and Compliance.
https://www.rarc.wisc.edu/animal_health/normative_data.html.

Suckow MA; Danneman P; Brayton C: The laboratory mouse. The Laboratory Animal Pocket Reference Series. CRC Press, Boca Raton (2001).

The laboratory rat. Baker HJ; Lindsey JR; Weisbroth SH, Eds. Academic Press, NY (1979).

Kennedy GL; Valentine R: Inhalation toxicology. In: Principles and Methods of Toxicology, 3rd edition, AW Hayes, Ed., Raven Press, Ltd., New York (1994).

Carcinogenicity

Introduction

ACGIH has been aware of public concern over chemicals or industrial processes that cause or contribute to an increased risk of cancer in workers. Testing methods to aid in the identification of carcinogenic chemicals have diversified beyond the traditionally used rodent life-time dosing testing protocols and epidemiological data. Test methodology now includes the use of in vitro cell culture assays, transgenic rodent models, and human and rodent genomic bioassays. In addition to these laboratory-based methods, the use of sophisticated mathematical models that extrapolate the levels of risk among workers has led to differing interpretations as to which chemicals or processes should be categorized as human carcinogens and what can be considered an exposure level that would not result in an increased risk of carcinogenicity. The goal of ACGIH has been to synthesize the available information in a manner that will be useful to practicing occupational hygienists without overburdening them with complex and intricate details. The ACGIH carcinogenicity classification scheme has evolved over the years as described by Spirtas et al. (1986, 2000). This section summarizes the current classification criteria for carcinogenicity.

Background

General. In evaluating potential occupational carcinogens, it is necessary to consider evidence obtained from human (primarily epidemiologic) and experimental animal (primarily carcinogenesis bioassay) studies, as well as mechanistic studies. ACGIH gives greater emphasis to human studies having measured or estimated exposure levels for the chemical substance or process under consideration. The usual order of preference is cohort studies (highest preference), case-control studies, cross-sectional studies, case histories from clinical records, and descriptive studies (usually from secondary data sources).

Types of Epidemiology Studies	
Cohort Study	
In a cohort study, a group of individuals exposed to a putative risk factor and a group who are unexposed to the risk factor are followed over time (often years) to determine the occurrence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group. The relative risk (incidence risk or incidence rate) is used to assess whether the exposure and disease are causally linked. Cohort studies may be prospective or retrospective. A prospective cohort study is also called a concurrent cohort study, where the subjects have been followed up for a period and the outcomes of interest are recorded. In a retrospective cohort study both the exposure and outcome have already occurred at the outset of the study. While this type of cohort study is less time-consuming and costly than a prospective cohort study, it is more susceptible to the effects of bias. For example, the exposure may have occurred some years previously and adequate reliable data on exposure may be unavailable or incomplete. In addition, information on confounding variables may be unavailable, inadequate, or difficult to collect.	
Case-Control Study	
Case-control studies start with the identification of a group of cases (individuals with a particular health outcome) in a given population and a group of controls (individuals without the health outcome) to be included in the study. In a case-control study, the prevalence of exposure to a potential risk factor(s) is compared between cases and controls. If the prevalence of exposure is more common among cases than controls, it may be a risk factor for the outcome under investigation. A major characteristic of case-control studies is that data on potential risk factors are collected retrospectively and as a result may give rise to bias. This is a particular problem associated with case-control studies and therefore needs to be carefully considered during the design and conduct of the study.	
Cross-Sectional Study	
A cross-sectional study examines the relationship between disease (or other health-related state) and other variables of interest as they exist in a defined population at a single point in time or over a short period (e.g. calendar year). Cross-sectional studies can be thought of as providing a snapshot of the frequency of a disease or other health-related characteristics (e.g. exposure variables) in a population at a given point in time. Cross-sectional studies are used to assess the burden of disease or health needs of a population and are particularly useful in informing the planning and allocation of health resources	

ACGIH uses the criteria for interpreting epidemiologic studies as listed by Hill (1965, 2015):

- Strength of statistical association.
- Consistency with other epidemiologic studies.
- Specificity of risk associated with work areas having high exposures.
- Temporality: Temporal relationship between exposure and disease.
- Biological gradient: Dose-response relationship.
- Plausibility: Biologically plausible.
- Coherence with known biological mechanisms.
- Experimental evidence: Statistical significance.
- Analogy: Similar evidence with another compound.

Statistical significance is based on the magnitude of the effect measured, the sample size, the power, and the level of significance (usually 0.05) chosen. It is possible in epidemiologic studies for there to be an observed biological effect, which may be real without reaching statistical significance at the chosen level.

Convincing clinical evidence for classification as a confirmed human carcinogen is: 1) the appearance of rare or uncommon tumor types, i.e., those not normally expected in a worker population; 2) a decrease in the time between exposure and appearance of a tumor (latency) among a group of exposed persons; or 3) an increase in the incidence of tumors when the exposed population is considered too small for formal epidemiologic studies. In addition to the above criteria for epidemiologic studies, ACGIH considers whether known confounding factors have been adequately considered.

Animal bioassays can be reasonable, but not infallible, predictors of the qualitative response in humans exposed under certain conditions. Species concordance between tumor type(s) is not necessarily anticipated or expected. It is not at all clear, however, whether the doses used in animal studies are predictors of the quantitative potency of such chemicals in their carcinogenic potential in humans. Maximum tolerated doses

(MTDs), often defined for purposes of animal studies based on elevated mortality, increased body weight loss, or other toxicological effects not related to carcinogenicity, are justified based on the low statistical sensitivity associated with animal studies. It is recognized, however, that extraordinarily large doses greatly exceeding those typical of human exposures are also associated with marked physiological and often bizarre pharmacokinetic consequences. For chemicals of relatively low carcinogenic potency, but high local or systemic toxicity, it may be difficult to detect a carcinogenic response using currently available animal bioassay protocols, and such agents could be overlooked. Nevertheless, human exposures to such highly toxic chemicals would probably be controlled by TLVs that are based on their acute and chronic toxicities, with an expected concomitant reduction in their carcinogenic potential.

It is the opinion of ACGIH that an ideally planned experimental carcinogenicity study should have at least three dose groups in addition to a concurrent vehicle control group and a concurrent untreated control group: a high dose (typically an MTD) which will produce an effect, a suitably selected no-effect dose, and an intermediate dose. The high dose effect need not necessarily induce death or elicit other marked acute toxicity, but it may include the agent's known pharmacologic or toxicologic manifestations. The most acceptable evidence of carcinogenicity is a dose-response gradient for the various experimental groups which correlates with the exposure levels. In this manner, using properly selected models, one may be able to estimate the lowest dose (exposure) associated with a neoplastic response and subsequently assess the risk associated with airborne exposure levels and excursions. Where the evidence indicates skin penetration as a significant route of exposure, this will be indicated by the TLV Skin notation. Replication of results in multiple species or confirmatory experiments enhance the overall weight of evidence given to study results. The importance of time-to-tumor and incidence of distant and multiple tumor sites is recognized since differences between the exposed and control groups can be an important factor in the estimation of carcinogenic potential.

Assays for mutagenicity, DNA adduct formation, clastogenesis, sister-chromatid exchange, and related biochemical endpoints, although perhaps indicative of the potential for carcinogenesis under specific conditions, are neither sufficiently reliable or well enough understood to provide evidence in and of themselves for the designation of a chemical as a carcinogen. However, the results of genotoxicity assays can provide important supporting information on the mechanism of carcinogenicity. Where there is conflicting evidence in several animal studies, the differential results must be approached on a weight-of-evidence basis considering: the species and strain studied, the location(s) and type(s) of tumors observed, the dose-dependent pharmacokinetic parameters of the agent in the species studied (preferably in light of published human pharmacokinetic and metabolic fate studies), and the statistical power of the test.

Wherever possible, the route of administration used in a laboratory carcinogenicity bioassay should be similar or identical to the anticipated route of human exposure. Obvious toxic effects (e.g. regenerative target organ hyperplasia) associated with site-specific induction of cancer must be taken into account. Results of carcinogenesis bioassays in experimental animals cannot be used to prove that an agent does not cause cancer in human beings. Although questions can arise when an agent shows carcinogenic activity in only one of two or more species studied, it is often possible to attribute the cause of such an apparent discrepancy to one or more of the following reasons:

- Differential absorption, distribution, metabolism, or excretion of the chemicals.
- Differences in the doses studied.
- Differences in the purity of the test substances.
- Different routes of administration.
- Differences in the statistical power of the cancer bioassays.
- Differences in the particular strains of animals and the historical incidence of the tumor type(s).
- Differences in the number and structure of chromosomes.
- Differences in anatomy and physiology, e.g. obligate nasal breathing in rodents.

Regarding studies involving experimental animals, ACGIH has historically preferred long-term bioassay studies in two mammalian species dosed by a route of administration relevant to the exposure of workers. Bioassay studies cited in TLV Documentation to support ACGIH's recommended TLVs are reviewed according to the following criteria:

- Two species of test animals (usually rats and mice) were tested at three dose levels; one a high level (typically the MTD) and the others some fraction of the high level (usually one-half the MTD) based on the results of a 90-day subchronic toxicity study wherein the chemical under study is administered preferably by a route relevant to worker exposure.

- Dosing and observation for the animal's lifetime (in the case of rodents, usually 2 years).
- At least 50 animals per sex per dose group with adequate concurrent controls.
- Adequate historical controls.
- Detailed, quality-controlled, histopathological examination of tissues.
- Appropriate statistical evaluation of the results.
- A study carried out under Good Laboratory Practice conditions.
- Evidence for the classification of an agent as an experimental (animal) carcinogen includes:
- Statistically significant dose-related increase in malignant tumors.
- An increase in the occurrence of very rare malignant tumors (for example, increases in tumors having a near zero incidence rate among the historical control data).
- The occurrence of neoplasms at sites distant from the initial chemical contact.
- Earlier onset of cancers among the treated animals.

Malignant tumors are of greatest concern, but the presence of benign tumors can be considered as supportive evidence for other findings of carcinogenicity; the presence of benign tumors is not taken as evidence for the carcinogenicity classification in and of itself. For example, other histologic alterations, such as the development of squamous metaplasia of the respiratory epithelium, may be a precursor of malignancy. Such changes by themselves, however, should not be taken as evidence for the classification as a carcinogen in experimental animals.

Some chemical substances cause cancer, not by directly acting with genetic material in the cell, but by what are termed epigenetic mechanisms. The methods for assessing epigenetic carcinogens should differ from those for genotoxic agents. In general, since the dose-response relationship for genotoxic carcinogens (linear) appears to differ from that of nongenotoxic carcinogens (non-linear) the former group requires extrapolation to an acceptable level of risk while the latter requires a sufficient margin of safety when establishing occupational exposure limits.

Various mathematical models have been proposed for the assessment of risk to humans, based on data derived from designed experiments on laboratory animals. These models involve extrapolation of risk from high doses used in experimental animals to generally much lower doses experienced by workers in an occupational setting. In general, these models are of two main types: linear one-hit models or multistage-multihit models. Models such as the Moolgavkar-Venzon-Knudson (MVK) two-stage model and related cell-kinetic multistage models, can be valuable for describing the complex, multistep process of carcinogenesis. Linearized or one-hit models are useful for describing those agents with biochemical mechanisms of action akin to radiation-induced carcinogenesis, from which the linearized dose-response models are derived. All of the models proposed to date are confounded by various levels of uncertainty, particularly when attempting to quantitatively extrapolate from relatively high doses used in experimental carcinogenicity bioassays to the lower levels typically experienced by workers in an occupational environment. The linearized one-hit models usually provide the most conservative estimates. Benchmark-dose modeling is commonly used today, with linear extrapolation from the BMDL10 for genotoxic carcinogens and applying appropriate adjustment factors to achieve an acceptable margin of safety for non-genotoxic carcinogens.

Theoretical estimates of excess cancer risk can be calculated using any of a variety of statistical models, but there is no current understanding of whether anyone or the other model is appropriate or accurate unless the biochemical toxicology and mechanism of action have been used to direct selection of such a model. In the absence of this knowledge, model selection is arbitrary and because of the different assumptions that must be made for the use of the different models, the theoretical estimates of risk for cancer that result can differ by orders of magnitude. Cell-kinetic multistage models, physiologically based pharmacokinetic models for interspecies dose scaling, uncertainty factors, safety factors, time-to-tumor models, or other selected interspecies extrapolation methodology are each appropriate, depending upon the validity of the underlying assumptions for the particular agent under consideration and its biochemical mechanism of action. A familiarity with quantitative risk assessment is becoming more important to occupational hygiene practice.

Consistent with the practices of IARC and NTP concerning evaluating carcinogens, ACGIH has revised its carcinogenicity classification criteria to include greater consideration of mechanistic data on key characteristics of carcinogens. It also overlays some additional practical aspects such as consideration of routes, exposure levels, etc.

Key Characteristics of Carcinogens	
Characteristic	Example of Relevant Evidence
Electrophile	Parent of metabolite with an electrophilic structure (e.g. epoxide), formation of DNA and protein adducts
Genotoxic	DNA damage (DNA strand breaks, DNA-protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g. chromosome aberrations, micronuclei formation)
Alters DNA repair induces genomic instability	Alteration of DNA replication or repair (e.g. topoisomerase II, base-excision, or double-strand break repair)
Epigenetic alterations	DNA methylation, histone modification, microRNA expression
Oxidative stress	Oxygen radicals and damage to macromolecules
Chronic inflammation	Increased WBC, myeloperoxidase activity, altered cytokine, or chemokine production
Immunosuppression	Decreased immunosurveillance, immune system dysfunction
Modulated receptor-mediated effects	Receptor (in)activation (e.g. Estrogen, AhR) or modulation of endogenous ligands
Induces Immortalization	Inhibition of senescence, cell transformation
Alters cell proliferation, cell death, or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Recommendation

Classification with notations A1-A5 is limited to substances for which evidence exists (either positive or negative) regarding carcinogenicity, e.g. carcinogenicity bioassay data, epidemiologic studies, supporting mechanistic data. It is believed that such a modification is more easily understood by practicing occupational hygienists and will avoid misinterpretation of the intent of ACGIH. ACGIH is most interested in the predictive relevance to human risk due to occupational exposures.

The following table describes the various levels of Strength of Evidence used to evaluate available human, animal, and mechanistic evidence when deciding on the appropriate carcinogen category to assign to a substance:

Strength of Evidence Descriptors			
Strength	Human Evidence	Experimental Animal Evidence	Mechanistic Evidence
Sufficient	A positive association has been observed in epidemiological studies in which bias, confounders, and coincidence are ruled out. A plausible mechanism of action can be attributed to the association.	A positive association has been observed in well-designed and conducted studies. A plausible mechanism of action can be attributed to the association.	Data from multiple experimental studies support a mechanism of carcinogenicity that is consistent with the findings in human or experimental animal studies
Limited	A positive correlation between an exposed population and exposure to an agent is demonstrated; however, bias, confounders, and coincidence provide low confidence that the observation of carcinogenicity can be attributed to exposure.	Tumors, neoplasms, or lesions are observed but the data are limited or confounded such that a definitive carcinogenic diagnosis is possible. For example, evidence of carcinogenicity is only observed in one of many studies, the study demonstrates benign lesions, or the agent decreases tumor latency but does not increase tumor incidence	The evidence from experimental studies suggests interactions with DNA, nuclear receptor binding, etc., but there are inconsistencies in study design such as a limited number of doses, cytotoxicity is present in the experiment, or there are unexplained inconsistencies between experimental systems.

Inadequate	No human data are available, or the available data lack statistical power, are of insufficient quality, or lack precision to make an association between exposure and carcinogenicity	There are limited or insufficient data with subchronic, chronic, or lifetime exposures or studies with too short of an exposure period to allow for toxicity and preneoplastic lesion determination.	The available studies are in cell lines or species not relevant or validated for assessing an agent's ability to interact with DNA and subsequently induce a preneoplastic or neoplastic event at the cellular or nuclear level.
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The following table provides guidance on the overall assessment of available data to determine the carcinogenicity category:

Decision Making for Carcinogenicity Notation			
Human Epidemiological Evidence*	Experimental Animal Evidence	Mechanistic Evidence (<i>In Vitro</i> and <i>In Vivo</i> data)	Carcinogenicity Category
Strong positive evidence	Not necessary	Not necessary	A1-Confirmed Human Carcinogen
Limited evidence of carcinogenicity in epidemiological studies	Weak or no evidence	Weak or no evidence	A2-Suspected Human Carcinogen
Inadequate evidence or no data are available	Strong evidence in animals; ADME and physiological response in animals is found in humans	Strong mechanistic evidence	
No evidence	Carcinogenicity is observed but tumor type/site is not relevant to humans, dosimetry indicates responses for routes or at doses sufficiently high that do not occur in the workplace	Weak or no evidence	A3-Confirmed Animal Carcinogen with Unknown Relevance to Humans
Inadequate evidence	Weak or no evidence	Weak or no evidence	A4-Not Classifiable as a Human Carcinogen
Strong negative evidence	Not necessary	Not necessary	A5-Not Suspected as a Human Carcinogen
Not necessary	Strong evidence of no carcinogenicity in well-conducted studies	Strong evidence of no genotoxicity	
No Evidence	No Evidence	No Evidence	No Notation

*Start with human evidence, then consider animal evidence and mechanistic evidence as indicated in the table.

The recommended definitions for Categories for Occupational Carcinogenicity are as follows:

- A1 – Confirmed Human Carcinogen
 - The agent is carcinogenic to humans based on the weight of evidence from epidemiologic studies.
- A2 – Suspected Human Carcinogen
 - Human data are accepted as adequate in quality but are conflicting or insufficient to classify the agent as a confirmed human carcinogen; or the agent is carcinogenic in experimental animals at dose(s), by route(s) of exposure, at site(s), of histologic types(s), or by mechanism(s) considered relevant to worker exposure. The A2 is used primarily when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals is supported by mechanistic evidence of key characteristics of carcinogens that are relevant to humans.
- A3 – Confirmed Animal Carcinogen with Unknown Relevance to Humans
 - The agent is carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), of histologic types(s), or by mechanism(s) that may not be relevant

to worker exposure. Available epidemiologic studies do not confirm an increased risk of cancer in exposed humans. Available experimental animal evidence suggests mechanisms or dosimetry that the agent is unlikely to cause cancer in humans except under improbable routes or levels of exposure.

- A4 – Not Classifiable as a Human Carcinogen
 - Agents which cause concern that they could be carcinogenic for humans, but which cannot be assessed conclusively because of a lack of human data. In vitro or animal studies do not provide mechanistic evidence of key characteristics of carcinogenicity which are sufficient to classify the agent into one of the other categories.
- A5 – Not Suspected as a Human Carcinogen
 - The agent is not suspected to be a human carcinogen based on properly conducted epidemiologic studies in humans. These studies have sufficiently long follow-ups, reliable exposure histories, sufficiently high doses, and adequate statistical power to conclude that exposure to the agent does not convey a significant risk of cancer to humans; or that the evidence suggesting a lack of carcinogenicity in experimental animals is supported by mechanistic data demonstrating a lack of the key characteristics of carcinogenicity.

Substances for which no human or experimental animal carcinogenicity data are available and no strong genotoxicity data have been reported are assigned no carcinogenicity designation.

Exposure to carcinogens must be kept to a minimum. Worker exposures to A1 carcinogens without a TLV should be eliminated to the fullest extent possible. For A1 carcinogens with a TLV and A2 and A3 carcinogens, worker exposure by all routes should be carefully controlled to levels as low as possible below the TLV as indicated by the (L) endnote in the TLV Table.

References

Hill, AB: The Environment and Disease: Association or Causation? Proc. Royal Soc. Med. 58 (5):295-300 (1965).

Hill, AB: The environment and disease: association or causation? J. Royal Soc. Med. 108(1):32–37 (2015).

Spirtas, R; Steinberg, M; Wands, RC; Weisburger, EK: Identification and classification of carcinogens: Procedures of the chemical substances threshold limit value committee, ACGIH. Am. J. Publ. Health 76(10): 1232-1235 (1986).

Spirtas, R; Fleming, LE; Demers, PA; Weisburger, EK: TLV carcinogenicity categories: Recent modifications. Appl. Occup. Environ. Hyg. 16(9): 8756-883 (2001).

Sensitization (DSEN/RSEN)

Introduction

This document is intended to provide guidance to authors on assigning SEN notations. Dermal (DSEN) and respiratory (RSEN) sensitization are complex toxicological endpoints and evaluation of the myriad of potential human and animal study designs and diversity of available data require significant professional judgment. In addition to the background information provided in the TLVs and BEIs book, sections are included to summarize the type of sensitization data that may be available and how to determine if a SEN notation is appropriate. The purpose of the SEN notation is to highlight the potential for sensitization in the hope that flagging this hazard will result in greater worker protection. As such, the criteria are designed to identify chemical substances that represent a real sensitization risk in the workplace. A strength-of-evidence approach is recommended that emphasizes the use of human evidence, but animal data are also considered. Information is also provided to help distinguish situations that do not warrant a SEN notation. Examples are given to illustrate when and when not to use the SEN notation. Finally, a grid is provided to assist in determining if a SEN notation should be used along with the preferred standard terminology to be used in the Documentation. A reference section is included with key papers and guidelines on dermal and respiratory sensitization.

Definition

The designation, DSEN or RSEN, in the Notations column in the TLVs and BEIs book refers to the potential for an agent to produce dermal or respiratory sensitization. RSEN and DSEN are used in place of the SEN notation when specific evidence of sensitization by that route is confirmed by human or animal data. The DSEN and RSEN notations do not imply that sensitization is the critical effect on which the TLV is based, nor does it imply that this effect is the sole basis for that agent's TLV. If sensitization data exist, they are carefully considered when recommending the TLV for the agent. TLVs that are based upon sensitization are meant to protect workers from induction of this effect. These TLVs are not intended to protect those workers who have already become sensitized.

In the workplace, respiratory, dermal, or conjunctival exposures to sensitizing agents may occur. Similarly, sensitizers may evoke respiratory, dermal, or conjunctival reactions. The notation does not distinguish between sensitization involving any of these tissues. The absence of a DSEN or RSEN notation does not signify that the agent cannot produce sensitization but may reflect the paucity or inconclusiveness of scientific evidence.

Sensitization often occurs via an immunologic mechanism and should not be confused hyperreactivity, susceptibility, or sensitivity. Initially, there may be little or no response to a sensitizing agent. However, after a person is sensitized, subsequent exposure may cause intense responses, even at low exposure concentrations (well below the TLV). These reactions may be life-threatening and may have an immediate or delayed onset. Workers who have become sensitized to a particular agent may also exhibit cross-reactivity to other agents that have similar chemical structures. A reduction in exposure to the sensitizer and its structural analogs generally reduces the frequency or severity of reactions among sensitized individuals. For some sensitized individuals, complete avoidance of exposure to the sensitizer and structural analogs provides the only means to prevent the specific immune response.

Agents that are potent sensitizers present special problems in the workplace. Respiratory, dermal, and conjunctival exposures should be significantly reduced or eliminated through process control measures and personal protective equipment. Education and training (e.g. review of potential health effects, safe handling procedures, emergency information) are also necessary for those who work with known sensitizing agents.

Respiratory Sensitization (RSEN)

It is thought that most respiratory sensitization occurs via an immunologic mechanism that involves an IgE (Type I, Immediate-onset reaction) response. For this reason, a respiratory sensitization study may evaluate IgE antibody levels or responses to the specific substance. However, it is now clear that there are multiple non-IgE immunologic responses that may mediate human respiratory sensitization. Respiratory sensitization may occur as a result of a single inhalation exposure, but more often occurs after repeated exposure. It may also occur following dermal contact. Bronchoconstriction may be evoked in workers or animals that have become sensitized. If severe enough to impede gas exchange this creates a potentially life-threatening situation.

In workers, respiratory sensitization may be assessed via various approaches such as controlled exposure to the suspected sensitizer (antigen) in a chamber, determination of specific antibodies (e.g. IgE by blood tests or skin testing), measurement of pulmonary function (e.g. FEV1, FVC) in the workplace, and assessment of airway reactivity (e.g. methacholine challenges). Workers who have become sensitized to a chemical substance (CS) may also react to other chemicals with similar chemical characteristics. A sensitized individual who continues to experience respiratory difficulties while performing their workplace duties may need to consider a change in position.

Dogs, guinea pigs, monkeys, rabbits, rats, and mice have been used to study respiratory sensitizers. In such studies, the animals are exposed one or more times in an attempt to induce sensitization. Subsequently, the animals are re-exposed (challenged) to the same CS or a related conjugate. The protocols for these studies vary greatly, concerning routes of exposure that are employed, concentrations of CS that are used for sensitization versus challenge periods, and length of exposure. For example, a group of rats may be injected intraperitoneally (IP) with a CS in an attempt to produce sensitization and later challenged via inhalation. These animal models for respiratory sensitization are considered experimental and have not been fully validated to predict human sensitization.

Dermal Sensitization (DSEN)

Two areas of evidence are sufficient alone to support a designation of DSEN notation. Human evidence, as described in the following section, is the primary and strongest criterion. Animal evidence alone can also support a designation of DSEN notation, provided it meets the criteria described in the applicable section below.

Evidence in humans that the agent can induce sensitization by skin contact in a substantial number of people in occupational settings is the primary criterion in assigning this notation. The following information sources could be considered either alone or in combination to base a conclusion that an agent may produce skin sensitization in the workplace: positive human repeat insult patch tests, positive controlled experimental human exposure studies, well-documented case reports of allergic contact dermatitis in more than one person that are reported from more than one clinic or investigator, or epidemiological studies showing allergic contact dermatitis caused by the substance. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small.

The following information may be considered supportive but should not be the sole basis for a notation: isolated episodes of allergic contact dermatitis, epidemiological studies with inconclusive findings (e.g. where

chance, bias, or confounding are likely to have resulted in a conclusion of sensitization), or a chemical with a structure related to that of known dermal allergens.

In the case of weak responses in human diagnostic patch testing, results will be interpreted in conjunction with reported clinical findings and history. Where data indicate that sensitization involves UV irradiation, the Documentation should highlight the potential for photoallergenicity.

Among the animal tests that may be considered are adjuvant and nonadjuvant methods. When an adjuvant type test method, such as the guinea pig maximization test (Magnusson and Kligman, 1969) is used, a response of $\geq 30\%$ is considered positive. For a non-adjuvant test method, such as the Buehler test (Buehler, 1965), a response of $\geq 15\%$ is considered positive. Positive results (i.e., a stimulation index ≥ 3) in the murine local lymph node assay (LLNA) may also be used as evidence of a dermal sensitization hazard (Kimber et al., 1989, 1991; Geberick et al., 1999).

The level of validation for individual predictive animal test methods varies. The Reference section includes information on validation, which should be considered in the interpretation of data. It is important to note that less potent allergens may yield false negative results in animal testing and sensitization potential may not be discovered until a large enough human population has been exposed. Therefore, negative results in animal models cannot be interpreted as definitive proof of a negative sensitization potential in humans.

The following information may be considered supportive but should not be the sole basis for a notation: borderline data from acceptable animal studies, data from non-standard methods, positive results in the mouse ear swelling test (MEST) (Gad et al, 1986), or a chemical structure related to that of known dermal allergens.

In Vitro or QSAR Studies

There is an important need for test methods that rapidly identify dermal and respiratory sensitizers and evaluate their relative potency. Some recent studies have proposed alternative approaches to sensitization testing, including the design of in vitro test methods and the development of quantitative structure-activity relationships (QSAR) (i.e., computational toxicology methods).

Several cell lines that have been used for in vitro testing include keratinocyte cells, dendritic cells, and human histiocytic lymphoma cells. Although in vitro assays are not a replacement for animal studies at this time, they may be useful for the initial screening of chemicals and for some mechanistic studies.

When human or animal sensitization data are lacking, it is a good practice to examine the structure of a chemical substance and to compare it with other recognized sensitizers. The structure of a chemical substance may provide information regarding its ability to covalently derivatize a larger molecule such as a protein and certain functionalities (e.g. RNCO, (RCO)₂O) may suggest that a CS is capable of producing sensitization.

Examples of Sensitizers

Respiratory.* An example of a chemical that should clearly have an RSEN notation because of its potential to cause respiratory sensitization is 2,4-toluene diisocyanate (2,4-TDI). In the scientific literature, there are numerous reports of TDI-induced occupational asthma (OA) among exposed workers. These reports have provided TDI exposure data and other information such as specific challenge tests, antibody titers, FEV1 measurements, and methacholine challenges. Human data are supported by similar, positive responses obtained in animals (e.g. guinea pigs, rats).

Tetryl is a compound for which possible respiratory sensitization was reported in 1950 and 1952. However, the evidence was insufficient to assign an RSEN notation. Some workers experienced itchy eyes, sore throats, nose bleeds, and coughing bouts, some of which were troublesome at night. This chemical substance is also highly irritating, causing yellow discoloration of the skin and hair. The descriptions are more consistent with irritation of the respiratory tract, rather than respiratory sensitization. No animal sensitization data were available.

*Note that possible dermal effects and dermal sensitization of the chemicals in these two examples, TDI and Tetryl, were not considered here (see below for dermal sensitization examples and further discussion).

Dermal. An example of a chemical that should clearly have a DSEN notation because of its potential to cause skin sensitization is p-phenylenediamine. p-Phenylenediamine is a potent skin sensitizer in guinea pigs with concentrations of 0.001 to 10% causing positive responses in 56 to 100% of the animals. In humans, diagnostic patch testing showed positive reactions in 1.1 to 84.5% of patients who had been previously exposed. There are also case reports of allergic asthma in p-phenylenediamine exposed workers and evidence that small quantities of p-phenylenediamine could cause asthma after three months to ten years of exposure.

Picric acid is a compound that has some evidence of skin sensitization in workers but the evidence was insufficient to assign a DSEN notation. One study published in 1944 reported that skin contact with the dry powder of picric acid and ammonium picrate powder during the manufacture of explosives causes sensitization dermatitis. In this case report, edema, papules, vesicles, and desquamation were observed on the face around the mouth and nose. These compounds were also highly irritating, causing yellow discoloration of the skin and strange visual effects (i.e., yellow-tinted vision). No animal sensitization data were available.

References

- Agius RM; Nee J; McGovern B; Robertson A: Structure activity hypotheses in occupational asthma caused by low molecular weight substances. *Ann Occup Hyg* 35(2):129-37 (1991).
- Basketter DA; Lea LJ; Cooper K; et al.: Threshold for classification as a skin sensitizer in the local lymph node assay: a statistical evaluation. *Food Chem Toxicol* 37:1167-1174 (1999).
- Basketter DA; Evans P; Fielder RJ; et al.: Local lymph node assay – validation, conduct and use in practice. *Food Chem Toxicol* 40:593-598 (2002).
- Basketter DA; Gilmour NJ; Briggs D; et al.: Utility of historical vehicle-control data in the interpretation of the local lymph node assay. *Contact Derm* 49:37-41 (2003).
- Bickis U; Nakatsu K: A Single Skin Contact with Toluene Diisocyanate (TDI) Causes a One-Year Persistence of Airway Sensitization, Demonstrable in Vivo and in Vitro. Abstract of platform presentation No. 310 presented at the 1996 American Industrial Hygiene Conference and Exposition (1996).
- Bickis U: Investigation of Dermal Induced Airway Hyperreactivity to Toluene Diisocyanate in Guinea Pigs. Ph.D. thesis, Department of Pharmacology and Toxicology, Queens University, Kingston, Canada (1994).
- Brooks SM; Weiss MA; Bernstein IL: Reactive airway dysfunction syndrome (RADS): Persistent asthma syndrome after high level irritant exposures. *Chest* 88:376-84 (1985).
- Brooks SM: Occupational asthma. *Toxicol Lett* 82/83:39-45 (1995).
- Buehler EV: Delayed contact hypersensitivity in the guinea pig. *Arch Dermatol* 91:171-177 (1965).
- Dearman RJ; Basketter DA; Kimber I: Local lymph node assay: use in hazard and risk assessment. *J Appl Toxicol* 19:299-306 (1999).
- Dearman RJ; Kimber I: Cytokine fingerprinting and hazard assessment of chemical respiratory allergy. *J Appl Toxicol* 21:153-163 (2001).
- Deutsche Forschungsgemeinschaft: List of MAK and BAT Values. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. Report No. 39 (2003).
- Ebino K; Ueda H; Kawakatsu H; et al.: Isolated airway exposure to toluene diisocyanate results in skin sensitization. *Toxicol Lett* 121:79-85 (2001).
- European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC): Respiratory Allergy (Monograph No. 19). Brussels, Belgium (1993).
- Gad SC; Dunn BJ; Dobbs DW; et al.: Development and validation of an alternative dermal sensitization test: The mouse ear swelling test (MEST). *Toxicol Appl Pharmacol* 84:93-114 (1986).
- Gauggel DL; Sarlo K; Asquith TN: A proposed screen for evaluating low-molecular weight chemicals as potential respiratory sensitizers. *J Appl Toxicol* 13(5):307-313 (1993).
- Gerberick GF; Basketter DA; Kimber I: Contact sensitization hazard identification. *Comments Toxicol* 7(1):31-41 (1999).
- Gerberick GF; Ryan CA; Kimber I; et al.: Local lymph node assay: validation assessment for regulatory purposes. *Am J Contact Dermat* 11:3-18 (2002).
- Gerberick GF; Robinson MK; Ryan CA; et al.: Contact allergenic potency: correlation of human and local lymph node assay data. *Am J Contact Dermat* 12:156-161 (2001).
- Heedrick D; Thorne PS; Doekes G: Health-based occupational exposure limits for high molecular weight sensitizers: how long is the road we must travel? *Ann Occup Hyg* 46(5):439-446 (2002).
- Health and Safety Executive (HSE): Respiratory Sensitisers and Control of Substances Hazardous to Health (COSHH). <http://www.hse.gov.uk/coshh/index.htm> (January 3, 2007).
- Kimber I; Hilton J; Weisenberger C: The murine local lymph node assay for identification of contact allergens: A preliminary evaluation of in situ measurement of lymphocyte proliferation. *Contact Dermatitis* 21:215-220 (1989).

- Kimber I; Hilton J; Botham PA: The murine local lymph node assay: Results of an inter-laboratory trial. *Toxicol Lett* 55:203-213 (1991).
- Kimber I; Bernstein IL; Karol M; et al.: Identification of respiratory allergens. *Fundam Appl Toxicol* 33:1-10 (1996).
- Kimber I: The Role of the Skin in Development of Chemical Respiratory Hypersensitivity. *Toxicol Lett* 86:89-92 (1996).
- Kimber I; Dearman RJ: Immune responses: adverse versus non-adverse effects. *Toxicol Pathol* 30:54-58 (2002).
- Kimber I; Dearman RJ: Chemical respiratory allergy: role of IgE antibody and relevance of route of exposure. *Toxicology* 181/182:311-315 (2002).
- Kimber I; Dearman RJ; Basketter DA; et al.: The local lymph node assay: past, present and future. *Contact Dermatitis* 47:315-328 (2002).
- Kimber I; Dearman RJ: What makes a chemical an allergen? *Ann Allergy Asthma Immunol* 90(5 Suppl 2):28-31 (2003).
- Kimber I; Dearman RJ; Gerberick GF; et al.: Designation of substances as skin sensitizing chemicals: a commentary. *Hum Exp Toxicol* 22:439-443 (2003).
- Magnusson B; Kligman AM: The identification of contact allergens by animal assay. The guinea pig maximization test. *J Invest Dermatol* 52:268-276 (1969).
- Organisation for Economic Co-operation and Development (OECD): Environment Directorate. Detailed review document on classification systems for sensitizing substances in OECD member countries. Series on Testing and Assessment No. 13. ENV/MC/CHEM(98)22 (1998).
- Perez C; Soderholm SC: Some chemicals requiring special consideration when deciding whether to sample the particle, vapor, or both phases of an atmosphere. *Appl Occup Environ Hyg* 6:859-864 (1991).
- Ryan CA; Gerberick GF; Cruse LW; et al.: Activity of human contact allergens in the murine local lymph node assay. *Contact Dermatitis* 43:95-102 (2000).
- Townley RJ; Hopp RJ: Inhalation methods for the study of airway responsiveness. *J Allergy Clin Immunol* 80(2):111-124 (1987).
- Warbrick EV; Dearman RJ; Kimber I: IgG and IgE antibody responses following exposure of Brown Norway rats to Trimellitic anhydride: comparison of inhalation and topical exposure. *Toxicology* 172:157-168 (2002).

Glossary

Adjuvant - This is a substance that increases the antigenic response of a concomitantly administered substance by modulating the immune system.

Atopy - This is a genetic predisposition toward the development of immediate (Type I) hypersensitivity reactions against common environmental antigens. Hay fever and asthma are two of the most commonly inherited allergies; contact dermatitis and gastrointestinal reactions are inherited less frequently.

Buehler test - Test animals are initially exposed to the test substance by topical application under occlusive patch conditions (induction exposure). Following a rest period of 10-14 days, during which an immune response may develop, the animals are exposed to a challenge dose to determine if the test population reacts in a hypersensitive manner. The extent and degree of skin reaction to the challenge exposure in the test population is compared with that of the control population, which did not receive the induction exposure.

Freund's adjuvant - This is a mixture of killed microorganisms, usually mycobacteria, in an oil and water emulsion that induces antibody formation. Because oil retards absorption of the mixture, the antibody response is much greater than if the killed microorganisms were administered alone. Freund's adjuvant is widely used in predictive animal studies for dermal sensitization.

Guinea pig maximization - This test is similar to the Buehler test, with the exception that animals are initially exposed to the test substance in addition to Freund's adjuvant by intradermal injection. Topical application is used for the challenge dose.

Local Lymph Node Assay - This test is based on the fact that topical exposure to contact allergens causes lymphocyte proliferation in the lymph nodes draining the site of application. A chemical is regarded as a sensitizer in the LLNA if at least one concentration results in a three-fold increase in lymphocyte proliferation (EC₃) in the auricular lymph nodes, a measure of induction, compared to controls following topical application to mouse ears. See the reference section for more information.

Mouse Ear Swelling Test - Animals are initially exposed to the test material by topical application to abdominal skin under an occlusive patch. Following the induction period, a challenge dose is applied to one ear of the test animal while the vehicle alone is applied to the contralateral ear. Mice are considered positive responders if the challenged ear thickness is $\geq 120\%$ that of the contralateral control ear thickness. Results can also be reported as group mean relative thickness of challenged ears. See the reference section for more information.

Photoallergy - This is a type IV delayed hypersensitivity reaction in which absorption of UV energy by a potential photosensitizing chemical in the skin is required to produce a hapten that elicits an allergic response.

Respiratory hypersensitivity - This is an allergic lung condition following inhalation exposure and rarely dermal exposure, characterized by bronchoconstriction and rhinitis (occupational asthma), resulting from the IgE-induced release of histamine from mast cells. Immediate (Type I) allergic reactions can be life-threatening.

Skin sensitization - This is a delayed contact hypersensitivity reaction following skin absorption and interaction with the immune system that is cell-mediated (Type IV) and generally not life-threatening. There are two phases: induction and elicitation.

Inhalable Fraction and Vapor (IFV)

The Inhalable Fraction and Vapor (IFV) endnote is used when a material exerts sufficient vapor pressure such that it may be present in both particle and vapor phases, with each contributing a significant portion of the dose at the TLV-TWA concentration. The ratio of the Saturated Vapor Concentration (SVC) to the TLV-TWA is considered when assigning the IFV (Perez and Soderholm, 1991). The SVC values are determined for pure substances, typically at or near room temperature, where the material has sufficient time to reach an equilibrium between the partition of the aerosol and vapor phases. In some situations, this time may be short, but in other instances, this equilibrium may not be realistically reached within the time frame of worker manipulation of a substance in a ventilated space.

The IFV endnote is typically used for substances with an SVC/TLV ratio between 0.1 and 10, as this is the region where work is being done at or near the saturated vapor concentration, however, there are other situations where the validity of recommending the IFV endnote needs to be evaluated separately. These situations are outlined below.

Other considerations

- Liquids with TLV reported in ppm with SVC/TLV ratios > 10
 - Liquids present in a closed environment will establish an equilibrium as determined by the temperature of the liquid and generate a vapor phase. This vapor component is reported as the vapor pressure of that liquid. Compounds that have high ratios have a high tendency to exist in the vapor phase at the operating temperature. When work is done with the atmosphere at the TLV, this atmosphere is unsaturated, with much liquid aerosol that would continue to evaporate. This strongly favors the presence of vapor over aerosol. Typically, these liquids are generally considered to be low boiling liquids, often this means the boiling temperature is below 150°C . It is appropriate to report the TLV for these compounds in ppm, indicating the industrial hygienist to pay particular attention to the vapor phase, the principal phase for worker exposure. Any aerosol generated is likely to quickly evaporate
- Liquids with TLV reported in ppm with SVC/TLV ratios < 10
 - Liquids where the vapor pressure of the liquid is lower such that the ratio is now below 10, indicates that work at the TLV is very close to, within an order of magnitude of, the saturation level for that substance. Where there is ventilation in the workplace that would reduce the total airborne concentration, this scenario would generally require having aerosol present as well as vapor phase material. In this situation, the inclusion of the IFV endnote serves as a reminder to examine both phases to determine total airborne concentration.
- Solids with TLV reported in mg/m^3 with SVC/TLV ratios > 10
 - Solids will also generate an equilibrium vapor component and should have vapor pressures at room temperature reported if they are known. As a compound in the solid requires significantly more energy to enter the vapor phase than does the liquid, this generally results in a greater time needed to establish this vapor equilibrium phase or saturated vapor concentration. It is difficult to estimate whether this SVC value can be reached in a workplace environment where there is both some degree of ventilation and perhaps variable temperatures of reagents.
 - A simple method to classify whether the solid may lead to the formation of the vapor phase to a significant degree during manipulation or use is to examine the melting temperature. The melting temperature provides as rough indication of the relative energy needed to promote

the sublimation of a compound to create the vapor phase material. Melting temperatures that are high, often higher than 150°C, generally have corresponding sampling methodologies that rely principally on the filtration of airborne aerosol onto a filter without any attempt to capture any generated vapor using an adsorbent tube. Such tested sampling methods suggest that this solid is then not likely to have a significant loss of sample due to failure to capture the vapor phase due to phase transfer of material from an aerosol. And so, if the vapor phase contribution is likely negligible, then this material would not qualify for the inclusion of the IFV notation, even though at first glance, the SVC/TLV is very high. The formation of that saturated vapor phase is simply much too slow, not impacting the worker within the time frame they are exposed to the solid aerosol.

- Solids with lower melting points, say just above room temperature, are much more likely to have material from the solid sublime to enter the vapor phase. This increases the importance of the vapor phase to the overall total airborne concentration. For these solids, the inclusion of the IFV notation would be seen as appropriate. This can be verified against a verified sampling methodology, where now the filtering of the solid is generally accompanied by an adsorbent tube that is used to capture any loss of this solid that has transferred to the vapor phase.
- Some solids have fairly high melting points, however typical uses are not as pure compounds as they are typically dissolved in highly volatile solvents for use in spraying operations. The potential exposure to the worker could be solid aerosol when dealing with the pure substance, or to aerosolized droplets of solution where there is worker potential for worker exposure.
- Temperature and composition variables
 - The industrial hygienist should also consider both particle and vapor phases to assess exposures from spraying operations, from processes involving temperature changes that may affect the physical state of matter, when a significant fraction of the vapor is dissolved into or adsorbed onto particles of another substance, such as water-soluble compounds in high humidity environments. It is important to remember that the above discussions of ratios from SVC/TLV stem from the analysis of how a compound behaves in the pure state, using that to predict what would be present in different phases at room temperature. Changing solvent or temperature directly affects how compounds partition between different phases, and as such the hygienist needs to evaluate these situations independently.

Skin

The designation Skin in the Notations column refers to the potentially significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids. Where dermal application studies have shown absorption that could cause systemic effects following exposure, a Skin notation would be considered. The Skin notation also alerts the industrial hygienist that overexposure may occur following dermal contact with liquid and aerosols, even when airborne exposures are at or below the TLV.

A Skin notation is not applied to chemicals that may cause dermal irritation. However, it may accompany a SEN notation for substances that cause respiratory sensitization following dermal exposure. Although not considered when assigning a Skin notation, the industrial hygienist should be aware that several factors may significantly enhance the potential skin absorption of a substance that otherwise has a low potential for the cutaneous route of entry. Certain vehicles can act as carriers, and when pretreated on the skin or mixed with a substance can promote the transfer of the substance into the skin. In addition, the existence of some dermatologic conditions can also significantly affect the entry of substances through the skin or wound.

While relatively limited quantitative data currently exist about skin absorption of gases, vapors, and liquids by workers, ACGIH recommends that the integration of data from acute dermal studies and repeated-dose dermal studies in animals and humans, along with the ability of the chemical to be absorbed, be used in deciding on the appropriateness of the Skin notation. In general, available data that suggest that the potential for absorption via the hands and forearms during the workday could be significant, especially for chemicals with lower TLVs, could justify a Skin notation. From acute animal toxicity data, materials having a relatively low dermal LD₅₀ (i.e., 1000 mg/kg of body weight or less) would be given a Skin notation. When chemicals penetrate the skin easily (i.e., higher octanol-water partition coefficients) and where extrapolations of systemic effects from other routes of exposure suggest dermal absorption may be important in the expressed toxicity, a Skin notation would be considered. A Skin notation is not applied to chemicals that cause irritation or corrosive effects in the absence of systemic toxicity.

Substances having a Skin notation and a low TLV may present special problems for operations involving high airborne concentrations of the material, particularly under conditions where significant areas of the skin

are exposed for a long period. Under these conditions, special precautions to significantly reduce or preclude skin contact may be required.

Biological monitoring should be considered to determine the relative contribution to the total dose from exposure via the dermal route. ACGIH recommends a number of adopted Biological Exposure Indices (BEIs) that provide an additional tool when assessing the total worker exposure to selected materials. For additional information, refer to Dermal Absorption in the Introduction to the Biological Exposure Indices, Documentation of the Biological Exposure Indices (2001), and to Leung and Paustenbach (1994). Other selected readings on skin absorption and skin notation include Sartorelli (2000), Schneider et al. (2000), Wester and Maibach (2000), Kennedy et al. (1993), Fiserova-Bergerova et al. (1990), and Scansetti et al. (1988).

The use of a Skin notation is intended to alert the reader that air sampling alone is insufficient to quantify exposure accurately and that measures to prevent significant cutaneous absorption may be required.

Examples illustrating the use of the skin notation

Acrylonitrile is an example of a chemical substance that requires a skin notation. It is acutely toxic to a variety of species through multiple routes of exposure. The data indicate rapid and extensive absorption following oral and dermal administration. The reported dermal LD₅₀ values in rats and rabbits are <200 and >200 mg/kg, respectively. It should also be noted that the acute dermal LD₅₀ values are roughly three times higher than the intravenous LD₅₀ values, indicating that acrylonitrile can readily penetrate the skin.

Thiodicarb should not receive a skin notation because the dermal LD₅₀ values of 2540 to 6310 mg/kg were reported in rabbits. There were no reports of systemic toxicity following dermal contact in humans.

References and Selected Reading

- American Conference of Governmental Industrial Hygienists: Dermal absorption. In: Documentation of the Biological Exposure Indices, 7th ed., pp. 21–26. ACGIH, Cincinnati, OH (2001).
- Fiserova-Bergerova V; Pierce JT; Droz PO: Dermal absorption potential of industrial chemicals: Criteria for skin notation. *Am J Ind Med* 17(5):617–635 (1990).
- Kennedy Jr GL; Brock WJ; Banerjee AK: Assignment of skin notation for threshold limit values chemicals based on acute dermal toxicity. *Appl Occup Environ Hyg* 8(1):26–30 (1993).
- Leung H; Paustenbach DJ: Techniques for estimating the percutaneous absorption of chemicals due to occupational and environmental exposure. *Appl Occup Environ Hyg* 9(3):187–197 (1994).
- Sartorelli P: Dermal risk assessment in occupational medicine. *Med Lav* 91(3):183–191 (2000).
- Scansetti G; Piolatto G; Rubino GF: Skin notation in the context of workplace exposure standards. *Am J Ind Med* 14(6):725–732 (1988).
- Schneider T; Cherrie JW; Vermeulen R; Kromhout H: Dermal exposure assessment. *Ann Occup Hyg* 44(7):493–499 (2000).
- Wester RC; Maibach HI: Understanding percutaneous absorption for occupational health and safety. *Int J Occup Environ Health* 6(2):86–92 (2000).

Ototoxicant Notation (OTO)

Introduction

This section is intended to guide authors in assigning an Ototoxicant (OTO) notation. Ototoxicity (hearing impairment) is a complex toxicological endpoint and evaluation of the myriad of potential human and animal study designs and diversity of available data require significant professional judgment. In addition to the background information provided in the TLV Book, sections are included to summarize the type of ototoxicity data that may be available and how to determine if an OTO notation is appropriate. A weight-of-evidence approach is recommended that emphasizes the use of human evidence, but positive animal data are also considered. Information is also provided to help distinguish situations that do not warrant an OTO notation. Examples are given to illustrate when and when not to use the OTO notation. Finally, a grid is provided to assist in determining if an OTO notation should be used along with the preferred boilerplate statements to be used in the Documentation. A reference section is provided with key papers for further information. A glossary of terms is also included at the end of the section.

Statement in Introduction to TLV Book

The designation OTO for ototoxicity in the Notations column highlights the potential for a chemical to cause hearing impairment alone or in combination with noise, even below 85 dB. The OTO notation is reserved for chemicals that have been shown, through animal studies or human experience, to adversely affect auditory capacity, usually manifested as a permanent threshold shift at specific frequencies. Certain solvents,

predominantly aromatic hydrocarbons, but also some halogenated solvents and chemicals that cause anoxia, have been shown to cause hearing loss. Some solvents appear to act synergistically with noise. The OTO notation is intended to focus attention, not only on engineering controls, administrative controls, and PPE needed to reduce airborne concentrations, but also on other means of preventing excessive combined exposures with noise to prevent hearing loss. Specifically, affected employees may need to be enrolled in hearing conservation and medical surveillance programs to more closely monitor auditory capacity.

Relationship to TLV and TLV Basis

The designation, OTO, in the Notations column in the TLV Book refers to the potential for an agent to produce ototoxicity, as confirmed by human or animal data. The OTO notation does not necessarily imply that hearing impairment is the critical effect on which the TLV is based, nor does it imply that this effect is the sole basis for that agent's TLV. If ototoxicity data exist, they are carefully considered when recommending the TLV for the agent.

In the workplace, exposures to potential ototoxicants may occur. The absence of an OTO notation does not signify that the agent cannot produce ototoxicity but may reflect the paucity or inconclusiveness of scientific evidence.

Assessment of Human and Animal Studies

Two areas of evidence are sufficient alone to support a designation of an OTO notation. Human evidence, as described in the following section, is the primary and strongest basis for assigning an OTO notation. Animal evidence alone can also support a designation of this notation, provided it gives sufficient justification based on the available data.

Evidence in humans that the agent can cause hearing impairment in a substantial number of people in occupational settings is the primary criterion in assigning an OTO notation. Results of the following common tests could be considered either alone or in combination to base a conclusion that an agent may produce ototoxicity in the workplace: pure tone audiometric testing, high-frequency audiometry, emittance audiometry, reflex modification audiometry (RMA), transient evoked otoacoustic emissions (TEOAE) testing, TEOAE suppression, acoustic reflex measurements, and distortion product otoacoustic emissions (DPOAE) testing. Other central auditory processing tests include electrocochleography, auditory brainstem response (ABR), cortical response audiometry, middle latency evoked function testing, and late latency evoked function testing. Other behavioral tests include behavioral audiometry (BA), conditioned avoidance response (CAR), psychoacoustic modulation transfer function, Random gap detection test (RGDT), interrupted speech, speech recognition in noise, Northwestern University auditory test No. 6, and dichotic digits test.

In animal experiments, ototoxic effects have been established using electrophysiological methods such as cochlear compound action potential (CAP) testing (showing a permanent loss of auditory sensitivity) and by morphological examination of the cochlea (e.g. showing loss of outer hair cells).

Other Considerations

Several factors influence whether a chemical substance will cause ototoxicity in workers, including the inherent potential for a chemical to impair cochlear function, latency, concentration, frequency and duration of exposure, and concurrent exposures to other chemicals and noise. A collective assessment of all available animal and human data, including exposure considerations, is required to determine if hearing impairment could be expected at levels that may approximate or exceed the TLV by a reasonable margin (e.g. perhaps a factor of 50). A weight-of-evidence evaluation should be used to determine if an OTO notation should be assigned. An OTO notation may not be appropriate if the only data suggesting a potential for ototoxicity are from animal studies conducted at very high levels, well over the TLV.

Examples of Ototoxicants and Non-Ototoxicants

Styrene (OTO Notation Assigned). TLV-TWA, 10 ppm; TLV-STEL, 20 ppm

High-frequency hearing loss has been reported in workers exposed to styrene, with or without concurrent excessive noise exposure (Morata et al. 2002; Sliwinska-Kowalska et al., 2003; Johnson et al., 2006; Mascagni et al., 2007; Morata et al., 2011). Since hearing loss can be irreversible, it is unclear whether prior or current exposures contributed to the ototoxicity reported by these investigators. More recent studies by Triebig et al. (2009) and Sisto et al. (2013) suggest the threshold for styrene-induced hearing loss is likely to be between 20 and 40 ppm, expressed as mean exposure concentrations, assuming peak exposures are properly managed. Ototoxicity was only reported at concentrations ≥ 300 ppm in animals, especially in active compared to sedentary animals (Pryor et al., 1987; Albee et al., 1992; Lataye et al., 2005). The animal data demonstrate synergistic effects with styrene and noise exposure and the importance of concurrent continuous vs. impulse noise exposures in causing ototoxicity (Makitie et al., 2003; Chen and Henderson 2009; Campo et al. 2014). Collectively, the increased response with combined noise and styrene exposures in these studies

rarely exceeded 2-fold. Based on the evidence for high-frequency hearing impairment in animals and humans discussed above, an Ototoxicant (OTO) notation is recommended.

Xylene (OTO Notation Assigned only to p-xylene and not the other isomers). TLV-TWA, 20 ppm

P-Xylene is ototoxic, causing irreversible hearing loss in animal studies (Gagnaire et al. 2001; Gagnaire et al. 2007; Maguin et al. 2006; Gagnaire et al. 2005). No effects on the auditory system have been found in rats after exposure to o- or m-xylene only. In male Sprague-Dawley rats exposed to p-xylene by inhalation (450, 900, and 1800 ppm, 6 hours per day, 6 days/week for 13 weeks), the LOAEL was 900 and the NOAEL was 450 ppm for outer hair cell loss (Gagnaire et al. 2001). Brainstem auditory-evoked responses demonstrated increased auditory thresholds at 2, 4, 8, and 16 kHz in rats exposed to 1800 ppm p-xylene (Gagnaire et al. 2001). Hearing loss was observed in male Fischer-344 rats after exposure to 800 ppm mixed xylenes for 14 hours per day for 6 weeks, and after exposure to 1700 ppm, 4 hours per day for 3 days (Pryor et al. 1987), and after exposure for 13 weeks to 250 ppm of a mixture (LOAEL) containing approximately 50 ppm p-xylene but also 50 ppm ethylbenzene (Gagnaire et al. 2007). The combined exposure caused enhanced ototoxicity compared to exposure to ethyl benzene alone (Gagnaire et al. 2007). The mechanism is probably chemical poisoning and death of cochlear hair cells. The effect is permanent because the organ of Corti cannot replace neurosensory cells (Campo et al. 1989). Guinea pigs appear less susceptible than rats (Gagnaire et al. 2007; Campo et al. 1989). A human study of laboratory workers exposed to mixed xylene isomers, but not to other solvents, nor occupational noise over 85BA, showed worse results for pure tone thresholds, pitch pattern sequence test, dichotic digit test, hearing in noise test, and auditory brainstem response (absolute and interpeak latencies). Compared to unexposed laboratory workers, there was a significant correlation between the concentrations of methyl hippuric acid in urine and pure-tone thresholds (2 to 8 kHz), and participants with a high cumulative dose of xylene exposure had poorer test results than participants with less xylene exposure (Fuente et al. 2013).

Weight-of-Evidence Assessment Grid

The following grid is provided to assist in determining if an OTO notation should be used along with the preferred boilerplate statements to be used in the Documentation.

Human → Animal ↓	+	+?	-?	-	No info
+	A	B	C	D	E
+?	F	G	H	I	J
-?	K	L	M	N	O
-	P	Q	R	S	T
No info	U	V	W	X	Y

Boilerplate Language to Use in the Documentation

A, B, F, G. An OTO notation is assigned based on both the reported ototoxicity in humans and a positive response in animals.

Rationale. Despite possible uncertainties regarding an animal or human study, there is general agreement between the two; the results point in the same direction (i.e., positive). Thus, such CSs should be flagged as ototoxicants.

C, D, E. An OTO notation is assigned based on the positive response in animals alone.

Rationale. For these CSs, the animal studies are well-conducted and yielded positive results. Human data are either missing or are considered negative or possibly negative. In this instance, such CS should be flagged as ototoxicants to protect workers.

K, P, U. An OTO notation is assigned based on the reported ototoxicity in humans alone.

Rationale. For these CSs, the human reports are well-documented and the results are positive. Animal data are either missing or are considered negative or possibly negative. In this instance, such CSs should be flagged as ototoxicants since the data directly pertain to human exposures, and no extrapolation is needed.

H, I, L, Q. An OTO notation is not proposed at this time based upon weak or equivocal responses in humans or animals.

Rationale. For these CSs, there are questions surrounding human reports or animal studies. In some cases, the data are conflicting, with human data pointing in one direction and animal data pointing in the opposite direction. In this instance, it is inappropriate to flag such CSs as ototoxicants.

M, N, R, S. An OTO notation is not proposed based on the lack of ototoxicity in humans and negative responses in animals.

Rationale. Despite possible uncertainties regarding an animal or human study, there is general agreement between the two; the results point in the same direction (i.e., negative). In this instance, it is inappropriate to flag such CSs as ototoxicants.

J, O, T, V, W, X, Y. An OTO notation is not proposed based upon inadequate data in humans or animals.

Rationale. For these CSs, there are many questions surrounding the human reports and animal studies. Data are missing. In this instance, it is inappropriate to flag such CSs as ototoxicants.

References

- Albee RR; Mattsson JL; Yano BL; et al.: Ototoxicologic and Neurotoxicologic Evaluation of Rats Exposed to Styrene Vapor for 13 Weeks. Dow Chemical Co, Midland, MI (1992).
- Campo P, Maguin K, Gabriel S, Möller A, Nies E, Gómez MDS, Toppila E, Members of the Topic Centre Risk Observatory. Combined exposure to noise and ototoxic substances: European Agency for Safety and Health at Work (2009).
- Campo, P., Morata, TC, Hong, O. Chemical exposure and hearing loss. *Disease-a-Month* 59:119-138 (2013).
- Campo P; Venet T; Thomas A; et al.: Neuropharmacological and cochleotoxic effects of styrene. Consequences on noise exposures. *Neurotoxicol Teratol* 44:113–120 (2014).
- Chen G-D; Henderson D: Cochlear injuries induced by the combined exposure to noise and styrene. *Hear Res* 254:25–33 (2009).
- Fuente A, McPherson B, Cardemil F. Xylene-induced auditory dysfunction in humans. *Ear & Hearing*. [Research Support, Non-U.S. Gov't] 34(5):651-60 (2013).
- Gagnaire F, Marignac B, Langlais C, Bonnet P. Ototoxicity in rats exposed to ortho-, meta- and para-xylene vapours for 13 weeks. *Pharmacology & Toxicology*. 89(1):6-14 (2001).
- Gagnaire F, Langlais C. Relative ototoxicity of 21 aromatic solvents. *Archives of Toxicology*. 79(6):346-54 (2005).
- Gagnaire F, Langlais C, Grossmann S, Wild P. Ototoxicity in rats exposed to ethylbenzene and to two technical xylene vapours for 13 weeks. *Archives of Toxicology*. 81(2):127-43 (2007).
- Gagnaire F, Marignac B, Blachere V, Grossmann S, Langlais C. The role of toxicokinetics in xylene-induced ototoxicity in the rat and guinea pig. *Toxicology*. 231(2-3):147-58 (2007).
- Johnson AC; Morata TC; Lindblad AC; et al.: Audiological findings in workers exposed to styrene alone or in concert with noise. *Noise Health* 8(30):45–57 (2006).
- Johnson, A.C. and Morata, T.C. Occupational exposure to chemicals and hearing impairment. No. 142. NR 2010;44(4). The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (2010).
- Hoet, P., Grosjean, M. Somaruga, C. Factors potentially affecting the hearing of petroleum industry workers. Prepared for CONCAWE's Health Management Group, Brussels, Report No. 5/05. www.concawe.org (2005).
- Lataye R; Campo P; Loquet G; et al: Combined effects of noise and styrene on hearing: comparison between active and sedentary rats. *Noise Health* Apr–Jun:7(27):49–64 (2005).
- Maguin K, Lataye R, Campo P, Cossec B, Burgart M, Waniusiow D. Ototoxicity of the three xylene isomers in the rat. *Neurotoxicology & Teratology*. 28(6):648-56 (2006).
- Makitie AA; Pirvola U; Pyrkko I; et al.: The ototoxic interaction of styrene and noise. *Hear Res* 179:9–20 (2003).
- Mascagni P; Formenti C; Pettazzoni M; et al.: Hearing function and solvent exposure: study of a worker population exposed to styrene. (in Italian) *G Ital Med Lav Ergon* 29(3):277–279 (2007).
- Morata TC; Campo P: Ototoxic effects of styrene alone or in concert with other agents: a review. *Noise Health* 4(14):15–24 (2002).
- Morata TC; Johnson AC; Nylen P; et al.: Audiometric findings in workers exposed to low levels of styrene and noise. *J Occup Environ Med* 44:806–814 (2002).
- Morata TC; Sliwinska-Kowalska M; Johnson AC: A multicenter study on the audiometric findings of styrene-exposed workers. *Int J Audiol* 50:652–660 (2011).
- Pryor GT; Rebert DC; Howd RA: Hearing loss in rats caused by inhalation of mixed xylenes and styrene. *J Appl Toxicol* 7:55–61 (1987).
- Sisto R; Cerini L; Gatto MP; et al.: Otoacoustic emission sensitivity to exposure to styrene and noise. *J Acoust Soc Am* 134(5):3739–3748 (2013).

Sliwinska-Kowalska M; Zamysłowska-Szmytko E; Szyrnczak W; et al.: Ototoxic effects of occupational exposure to styrene and co-exposure to styrene and noise. *J Occup Environ Med* 46(1):15–24 (2003).

Triebig G; Bruckner T; Seeber A: Occupational styrene exposure and hearing loss: a cohort study with repeated measurements. *Int Arch Occup Environ Health* 82(4):463–480 (2009).

Glossary (From Johnson and Morata 2010)

Action level - A guideline used by many international occupational health bodies to express the level of a harmful or toxic substance/activity that requires medical surveillance, increased industrial hygiene monitoring, or biological monitoring. For chemicals, it is usually 50 % of the occupational exposure limit. For noise, it indicates the sound level which, when reached or exceeded, necessitates implementation of activities to reduce the risk of noise-induced hearing loss. The new European noise directive has two exposure action levels (See Section 2.3).

Continuous noise - Noise of a constant level as measured over at least one second using the slow setting on a sound level meter. Note that an intermittent noise, e.g. on for over a second and then off for a period, would be both variable and continuous.

Decibel (dB) - A dimensionless unit expressing the relative loudness (intensity) of sound on a logarithmic scale. The decibel was named after Alexander Graham Bell. A-weighted decibels, dBA, or dB(A). A-weighting is the most commonly used of a family of curves defined in various standards relating to the measurement of perceived loudness, as opposed to actual sound intensity. The others are B, C, and D-weighting (for dBB, dBC and dBD). The A-weighting is the most used in noise measurements since its corrections are aimed at replicating the sensitivity of the average human ear to sound at different frequencies.

Equivalent sound pressure level (Leq) - The steady sound level that, over a specified period, would produce the same energy equivalence as the fluctuating sound level occurring. Occupational exposure limits for a hazard expressed as an 8-hour time-weighted average value include the total exposure during a shift exposure. For noise, a single number gives the value in decibels that represents the equivalent average level of the actual changing noise levels. When the exchange rate (see below) of 3 dB is used in this calculation, the average noise level is called the Leq.

Exchange rate - The amount of decrease (or increase) in noise level which would allow doubling (or require halving) of the exposure time to have the same risk. The 3-dB exchange rate is also known as the equal-energy exchange rate because the equivalent acoustic energy is preserved when the sound level changes by 3 dB and the exposure duration changes by a corresponding factor of 2. Most countries use a 3dB exchange rate, thus, if the intensity of an exposure increases by 3 dB, the dose doubles or the allowable time is halved.

Hazardous noise - Any sound for which any combination of frequency, intensity, or duration is capable of causing permanent hearing loss in a specified population.

Hazard Index (HI) - A single chemical hazard index (also called hygienic or additive effect) is the ratio of a hazardous air pollutant concentration divided by its reference concentration, or safe exposure level. If this hazard index exceeds one, people are exposed to levels of that substance that may pose health risks. A cumulative hazard index or total hazard index is the result of the summation of the hazard quotients for all chemicals to which an individual is exposed. It is calculated according to the formula $HI = C1/T1 + C2/T2 + C3/T3 \dots$ where C1, C2, C3, etc. are the measured exposure levels of the different agents, and T1, T2, T3, etc. are the individual occupational exposure limits of the corresponding agent. If the hazard index exceeds 1, the total exposure load is considered excessive.

Hearing loss - Hearing loss is often characterized by the area of the auditory system responsible for the loss. For example, when injury or a medical condition affects the outer or middle ear (i.e. from the pinna, ear canal, and eardrum to the cavity behind the ear drum - which includes the ossicles) the resulting hearing loss is referred to as a conductive hearing loss. When an injury or medical condition affects the inner ear or the auditory nerve that connects the inner ear to the brain (i.e. the cochlea and the vestibulo-cochlear nerve) the resulting hearing loss is referred to as a sensorineural loss. Because noise can damage the hair cells located in the cochlea, it causes sensorineural hearing loss (see also Section 3.1). Hearing loss that results from damage or impairment to the central nervous system, especially the brain itself, is called central hearing loss. Unless stated otherwise, hearing loss means sensorineural hearing loss in this document. Mid- and high-frequency hearing loss. Hearing loss can be defined by audiometric frequency bands, but these definitions are species-specific. In humans, the terms mid- and high-frequency hearing loss, refer to hearing losses affecting frequencies at 1-3 kHz and above 3 kHz, respectively. In rats, high-frequency hearing loss is usually defined as affecting frequencies above 16 kHz, whereas a hearing loss at 4 -12 kHz is considered as a mid-frequency hearing loss. Other animal models may have other definitions depending on the hearing frequency range of that particular species.

Hearing threshold level - The hearing level, above a reference value, at which a specified sound or tone is heard by an ear in a specified fraction of the trials. It corresponds to the minimum sound level of a pure tone that an ear can hear. The International Organization for Standardization (ISO) specifies in ISO 389 a standard reference zero dB for the scale of hearing threshold level applicable to air conduction audiometers, which corresponds to the threshold of hearing in the mid-frequencies for young adults. Audiometric zero was determined by the average hearing of young adults who have never been exposed to loud noise or suffered ear disease or injury. However, in the clinic, because people differ considerably in their hearing, hearing thresholds up to 25 dB are considered to be in the normal range.

Hertz (Hz) - The Hertz is a unit of frequency. One Hertz simply means one cycle per second (typically what is being counted is a complete cycle). Hertz can be prefixed and commonly used multiples are kHz (kilohertz), MHz (megahertz), etc. The frequency range for human hearing lies between approximately 20 and 20,000 Hz. The sensitivity of the human ear drops off sharply below about 500 Hz and above 4,000 Hz. Different animal species have different hearing frequency ranges. Guinea pigs have the same frequency range as humans (20 Hz-20 kHz), whereas rats hear between 500 Hz and 40 kHz. Bats can hear above 100 kHz.

Noise - Any unwanted sound.

Noise dose - The noise exposure expressed as a percentage of the allowable daily exposure. If 85 dBA is the maximum permissible level, an 8-hour exposure to a continuous 85-dBA noise would equal a 100 % dose. If a 3-dB exchange rate is used in conjunction with an 85-dBA maximum permissible level, a 50 % dose would equal a 2-hour exposure to 88 dBA or an 8-hour exposure to 82 dBA.

Noise-induced hearing loss - A sensorineural hearing loss attributed to noise exposure, bilaterally symmetrical and often irreversible. In humans, it has its onset in the frequency range between 3 and 6 kHz and for which no other etiology can be determined.

Ototoxic - A term typically associated with drugs or other substances that are toxic to auditory or vestibular systems, affecting the senses of hearing or balance.

Ototraumatic - A broader term than the term ototoxic. As used in hearing loss prevention, ototraumatic refers to the potential of an agent (e.g. noise, drugs, or industrial chemicals) to cause permanent hearing loss after acute or prolonged exposure.

Sound pressure level (SPL) - A measure of the ratio of the pressure of a sound wave relative to a reference sound pressure. The sound pressure level in decibels is typically referenced to 20 mPa. When used alone (e.g. 90 dB SPL), a given decibel level implies an unweighted sound pressure level.

Time-weighted average (TWA) concerning noise - A normalized 8-hour average sound level expressed in dBA which is computed so that the resulting average would be equivalent to an exposure resulting from a constant noise level over an 8-hour period.

Tinnitus - Tinnitus is a perception of sound that has no external source. It is normal for almost all people to perceive a transient noise in the ear either spontaneously or associated with temporary hearing loss after exposure to loud noise. These temporary auditory sensations are reversible and resolved after a few minutes. For a sound without an external source to be defined as tinnitus, it has to last at least 5 minutes per day more than once a week. For most patients with tinnitus, the internal sound is constantly present. The prevalence of tinnitus is 10-15 % in adult populations. Tinnitus is often associated with noise exposure and hearing loss and is usually of neurophysiological origin. Tinnitus can also be generated by vascular, muscular, or teeth disorders. Another underlying cause of tinnitus is depressive disorders. Whatever the cause of tinnitus is, signals are processed in the central auditory system and perceived as a sound.

Surface Limit (TLV-SL)

Introduction

This section is intended to provide guidance to authors when considering establishment of a surface limit. The TLV-SL should be considered for all chemical substances that have a Skin notation or a DSEN notation. Those chemical substances that have an RSEN notation will also have a Skin notation if dermal exposure is known or suspected to cause induction of respiratory hypersensitivity. Establishment of a TLV-SL will also be considered for substances with A1 or A2 carcinogenicity classifications since Appendix A states that exposure to these substances by all routes should be minimized. Despite the presence of these notations, a TLV-SL may not be recommended if the substance is highly volatile and may not remain on surfaces long enough to be quantified. The TLV-SL was introduced in 2019 and first applied to a skin and respiratory sensitizer (o-phthalaldehyde) based on an extrapolation from the EC3 value from the murine local lymph node assay (LLNA). An example calculation of a TLV-SL using the LLNA EC3 is provided below. Fundamentally, the methodology for basing the TLV-SL on systemic effects is similar to that for setting airborne limits. Basic considerations will be discussed and illustrated with a series of short examples.

Statement in Introduction to TLV Book

Threshold Limit Value-Surface Limit (TLV-SL): The concentration on workplace equipment and facility surfaces that is not likely to result in adverse effects following dermal exposure or incidental ingestion. The TLV-SL is intended to supplement airborne TLVs and especially those with Skin, DSEN and RSEN notations, to provide quantitative criteria for establishing acceptable surface concentrations, expressed as mg/100 cm². For systemic effects, consistent with the use of the Skin notation, the TLV-SL will often correspond to the dose permitted by the TLV-TWA over an 8-hour period, unless chemical-specific data are available linking adverse effects in dermal studies in animals or with surface sample results. For certain dermal sensitizers, the surface limit may be established using potency estimates from animal studies, such as the effective concentration causing a 3-fold increase in lymphocyte proliferation (EC3). For other sensitizers, including some respiratory sensitizers that cause induction of sensitization via dermal exposure, professional judgment may be required to supplement available surface and airborne monitoring results. The Committee acknowledges that surface sampling is not a common practice but hopes that establishment of a TLV-SL will encourage further development of sampling and analytical methods to facilitate assessment of surface levels for this selected subset of compounds. The Committee also acknowledges that the relative contribution to exposure by the dermal route or accidental ingestion to that by inhalation is scenario dependent. The TLV-SL is intended to be used by the practicing industrial hygienist within the context of an overall exposure assessment using a model that includes several compartments and transport processes as described by Schneider et al. 2000 (see Figure 1).

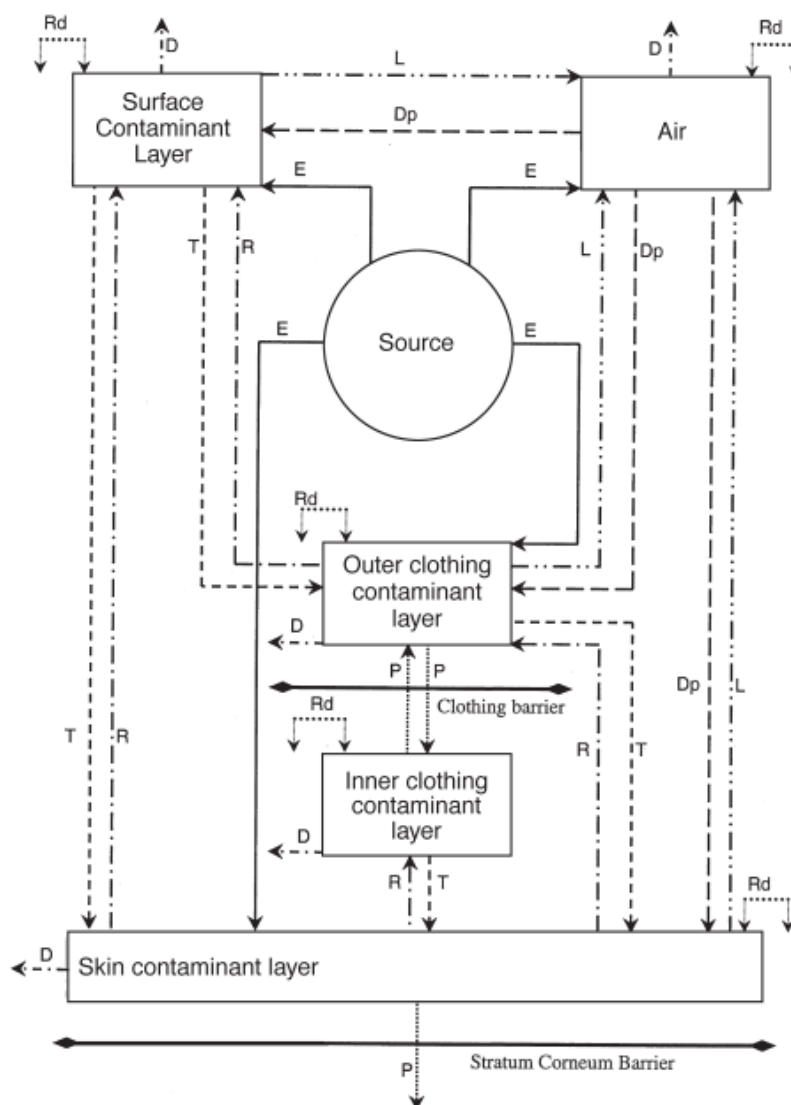


Fig. 1. The conceptual model. Adapted from Schneider *et al.* (1999). Overview of the conceptual model, compartments and transport processes. (E=Emission (—), Dp=Deposition (---), L=Resuspension/Evaporation (···), T=Transfer (- · -), R=Removal (---), Rd=Redistribution (· · ·), D=Decontamination (- · - ·), P=Penetration/Permeation (····)).

Physico-Chemical Considerations

When deciding whether to set a TLV-SL, in addition to various notations that may be assigned, the physico-chemical properties of the substance should also be taken into account. For example, the octanol/water partition coefficient and solubility data may help determine, along with dermal toxicity data, that a substance is likely to represent a significant health concern when coming into contact with, and absorbed through, the skin. Another key property is the volatility of the substance since this will determine how long it is likely to remain on contaminated surfaces or the skin and available for systemic absorption.

Specific criteria should be used to determine when to set (and when not to set) TLV Surface Limits based on VP and other physical properties, such as boiling point BP, MP and heat of vaporization. A simple rule of thumb is that a TLV-SL should be established, assuming the health-based criteria discussed above are satisfied, when the substance is less volatile than water (VP=20 mmHg at 25°C, BP=100°C). In the chemical selection report, there are often a few compounds that appear to be right on the edge with respect to these criteria. They all appear to be similar to water in terms of volatility. Water seems to “stick around” for a fair amount of time, especially under high %RH conditions, certainly long enough to represent a significant potential for exposure.

The recommendation to use water as a benchmark is based on the assumption that a TLV-SL would be most useful to the IH if a substance persisted for at least several/multiple minutes-to-hours. Water is a reasonable “moderately volatile” substance and VP is likely to be the most sensitive variable. BP is somewhat useful but is really just the temperature at which the VP has reached 760 torr. MP wouldn’t change as much and would be a weaker predictor, and heat of vaporization is really captured within both VP and BP values. With VP being the tendency to escape to the gas phase at the operating temperature, this is a quantitative measure of volatility in a workplace. The following examples support using water as a benchmark:

Water (VP~20 mmHg at room temperature (RT)) is a liquid that would persist on a surface for a few hours depending upon ventilation and relative humidity (RH).

Ethanol (VP~44 mmHg and BP~78°C) would also remain on a surface for 15-20 mins (tested as a thin coating from a spray).

Benzene (VP~95 mmHg and BP~80°C) is a more volatile liquid than ethanol, and more would escape liquid phase to lead to the higher observed vapor phase.

Acetone (VP~230 mmHg and BP~56°C) does not remain on a surface more than few minutes.

Use of water with a VP of 20 mmHg as our upper bound to capture low volatility liquids seems reasonable. This may be conservative because higher workplace ventilation will increase evaporation rates and lead to lower dermal exposures via liquid.

Therefore, as an example, if you examine 1,2,3-trichloropropane, with VP~2 mmHg and BP~150°C, you would consider this to be more persistent on a surface than water. This is consistent with reports of it behaving more like a heavy oil.

Deriving a TLV-SL for Skin Sensitizers

The murine local lymph node assay (LLNA) is a validated test for identifying potential skin sensitizers. The LLNA EC3 value, defining the effective concentration that results in a 3-fold increase in lymphocyte proliferation in draining lymph nodes of treated mice, provides quantitative dose-response information on induction of skin sensitization, including estimates of sensitization thresholds and potency. Building upon the previously established correlation between LLNA EC3 values and human repeat insult patch testing (HRIPT) no-effect levels, a quantitative method for setting surface wipe guidelines using the LLNA EC3 has been proposed (Naumann and Arnold 2019). The intent is that these limits can be used to assign compounds to occupational exposure bands (OEBs) and provide handling guidance for skin sensitizers of varying potency, supporting exposure assessment and control strategies. When used in conjunction with a comprehensive industrial hygiene program that includes hazard communication, engineering controls and personal protective equipment, skin exposure and consequent skin sensitization risks in the workplace can be minimized.

Example Calculation - Derivation of the TLV-SL for o-Phthalaldehyde

The following example illustrates how a surface (wipe) limit can be derived using the LLNA EC3 value of 0.051% determined by Anderson et al. for o-phthalaldehyde in which 25 µl was applied to 1 cm² surface area on both ears of the mouse.

Convert EC3 from volume percent to surface area concentration.

$$\text{EC3: } 0.051\% = 510 \text{ } \mu\text{g/ml} \times 0.025 \text{ ml/ear} \times 2 \text{ ears} \div 2 \text{ cm}^2 = 13 \text{ } \mu\text{g/cm}^2$$

Calculate Wipe Limit

$$\text{Wipe Limit} = (\text{EC3 } (\mu\text{g}/\text{cm}^2) \div \text{Adjustment Factor}) \times 100$$

$$\text{Wipe Limit} = 13 \mu\text{g}/\text{cm}^2 \div 50 = 0.25 \mu\text{g}/\text{cm}^2 \times 100 = 25 \mu\text{g}/100 \text{ cm}^2$$

$$\text{Wipe Limit} = 0.025 \text{ mg}/100 \text{ cm}^2 \text{ (in units used in the TLV Book).}$$

Deriving a TLV-SL for a Systemic Toxicant

Chemical substances that have been assigned a Skin notation are excellent candidates for establishing a TLV-SL. This is consistent with the fact that these substances have the potential to make a significant contribution to the overall exposure by the dermal route and contact with mucous membranes and the eyes. The practicing industrial hygienist may need to assess potential exposures via these routes in order to determine what the total dose might be for a worker also exposed by inhalation. While it is tempting to assume that the TLV-SL could simply be derived using the dose received by a worker when exposed by inhalation at the TLV-TWA for 8-hrs, there are a number of reasons why this may under- and over-estimate the absorbed dose following contact.

Dermal absorption depends on a number of factors, including physico-chemical characteristics of the chemical substance (e.g., MW, Kow, lipid solubility) and exposure-related considerations (e.g. frequency and duration of exposure, site of contact, occlusive conditions). All of these parameters must be evaluated in order to accurately develop appropriate and scientifically supportable limits.

The process of chemical migration from the surface of the skin to the systemic circulation is complex. According to Kimmel et al. (2011) There are many factors that contribute to the dermal absorption potential of a chemical, including the following:

1. The ability to penetrate the skin, determined by such factors as physical adherence to skin, the condition and thickness of the contacted skin, the number of sweat glands and hair follicles at the site of contact (even though these make very small contributions to the exposure), the ambient temperature in the work area, occlusion of the exposed area by clothing or other personal protective equipment (which might prolong the contact between the chemical and the skin), and inherent physicochemical properties such as the molecular size (smaller molecules are more likely to penetrate the skin) and lipophilicity (a log Pow between +1 and +2 is the most favorable for dermal absorption);
2. The amount of chemical that contacts the skin, referring to the chemical concentration on the surface;
3. The amount of skin that contacts the chemical, referring to the surface area of the skin that contacts the chemical;
4. The frequency and duration of the contact event;
5. Concomitant exposure to multiple chemicals which might include permeation-enhancers); and
6. The interindividual variability in rates of absorption between workers.

Within some industries (e.g., the pharmaceuticals industry), a common practice is to derive surface limits by performing a health-based risk assessment using readily available data and calculating an acceptable daily exposure (ADE) value as follows (Kimmel et al. 2011):

$$\text{ADE} = \frac{\text{NOAEL} \times \text{BW}}{\text{AF}_c \times \alpha}$$

where:

NOAEL = no-observed-adverse-effect level for the critical endpoint of concern (if a NOAEL is not identified, a lowest-observed-adverse-effect level or LOAEL may be selected instead).

BW = body weight (50 kg for an adult worker).

AF_c = composite adjustment factor reflecting various sources of uncertainty and variability such as inter-individual variability, interspecies extrapolation, pharmacokinetic variability, extrapolation from a LOAEL to a NOAEL, severity of adverse effects, consideration of sensitive subpopulations, and robustness (completeness) of the data set.

α = adjustment factor for differences in bioavailability via the route of administration by which the critical effect was observed and the route by which it will be applied (e.g. dermal or ocular).

The surface limit could therefore be calculated by dividing the ADE by the standard surface area used for the evaluation of contaminated surfaces (100 cm²):

$$\text{TLV-SL} = \text{ADE}/100 \text{ cm}^2$$

For some chemical substances, the TLV-SL may also be derived using the dose permitted over 8 hours at the TLV-TWA, expressed in mg per day. In its simplest form, the calculation could be as follows:

$$\text{TLV-SL} = (\text{TLV-TWA} \times V)/(\text{SA} \times \alpha)$$

where:

SA = surface area of the skin that comes into contact with the CS each day, and

α = adjustment factor for bioavailability via the dermal route of exposure.

In practice, the following equation could be used:

$$\text{TLV-SL} = (\text{TLV-TWA (mg/m}^3) \times 10 \text{ m}^3)/(100 \text{ cm}^2 \times \alpha)$$

For this approach, it is assumed that the average surface area of each palm is 100 cm² and, in the absence of data to suggest otherwise, dermal transfer (adherence and absorption) is complete (100%). These assumptions reflect the highly conservative and protective nature of this approach, which is needed given that the process of dermal absorption remains poorly characterized. The area that is typically sampled by the industrial hygienist when monitoring potential surface contamination is 100 cm². However, when the surface does not lend itself to using a 10 cm x 10 cm template (e.g. sampling a door handle or product vial), the surface area sampled is estimated. Surface limits can be expressed as mass units per square centimeter to account for this variability in sampled surfaces.

Example Calculation – Nitroglycerin (TLV-TWA, 0.05 ppm or 0.46 mg/m³)

Nitroglycerin is absorbed through intact skin in amounts sufficient to cause vasodilation. The human skin permeability coefficient is 1.1 x 10⁻² cm/hr. This value, along with other parameters and assumptions, could theoretically be used to derive a chemical-specific bioavailability adjustment factor. However, in this example, dermal absorption is assumed to be complete (100%).

$$\text{TLV-SL} = (\text{TLV-TWA (mg/m}^3) \times 10 \text{ m}^3)/100 \text{ cm}^2 \times \alpha$$

$$\text{TLV-SL} = (0.46 \text{ mg/m}^3 \times 10 \text{ m}^3)/100 \text{ cm}^2 \times 1 = 4.6 \text{ mg}/100 \text{ cm}^2, \text{ rounded to } 5 \text{ mg}/100 \text{ cm}^2$$

References

- Kimmel, TA, Sussman, RG, Ku RH, Ader, AW: Developing Acceptable Surface Limits for Occupational Exposure to Pharmaceutical Substances. J. ASTM Intl., published online August (2011).
- Naumann, BD and Arnold, SF: Setting surface wipe limits for skin sensitizers. Toxicol Ind Health 35(9):614-625. Published on-line 23-Sep-2019. SF (2019). <https://doi.org/10.1177/0748233719875365>.
- Schneider, T, Cherrie, J.W., Vermeulen, R. and Kromhout, H.: Dermal Exposure Assessment. Ann. Occup. Hyg., 44 (7):493–499 (2000).