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Defining the Science of Occupational and Environmental Health®

OPERATIONS MANUAL

THRESHOLD LIMIT VALUES FOR CHEMICAL SUBSTANCES COMMITTEE

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COMMITTEE MISSION

The Threshold Limit Value Chemical Substances (TLV®-CS) Committee is appointed by the Board of Directors of ACGIH® to develop occupational exposure guidelines for chemical substances. The issuance of Threshold Limit Values (TLVs®) and their supporting *Documentation* is the principal mechanism for the dissemination of these guidelines, although the Committee may also develop more general positions, instructional materials, educational media, or topical symposia to focus on issues of concern. This Committee's vision is to be a respected, worldwide leader in the development and dissemination of health-based occupational exposure guidelines.

Specifically, the mission of the TLV®-CS Committee is to recommend airborne concentrations of agents and exposure conditions for use in the practice of industrial hygiene and by other qualified professionals to protect worker health. The charge of the TLV®-CS Committee is to develop and disseminate occupational exposure guidelines (i.e., TLVs®). TLVs® are based on the best available data and, whenever possible, peer-reviewed literature on human health effects resulting from industrial, occupational or other exposure situations; from experimental human and animal studies; human epidemiological studies; and when possible, from a combination of all these sources. The goal of the Committee is to develop occupational exposure guidelines for chemical substances that are:

- Scientifically credible
- Leading edge
- Well-supported (i.e., TLVs® are based on ACGIH®'s review of "peer-reviewed scientific literature")
- Scientifically valid
- Reliable
- Understandable and clear
- Produced with a balanced, unbiased and clearly-defined process

The TLV®-CS Committee operates under the Bylaws of ACGIH® and the administrative policies and procedures approved by the ACGIH® Board of Directors.

MEMBERSHIP

Eligibility

Members of the TLV®-CS Committee must be members of ACGIH® or must join ACGIH® upon appointment as a Full Committee member. The Committee may have up to 30 members who should represent the four disciplines necessary to establishing TLVs® (industrial hygiene, occupational medicine, occupational epidemiology, and toxicology). The Committee will function within the guidelines and policies of the Board of Directors regarding the percentage of membership categories. Under current ACGIH® policy, a committee must maintain a simple majority of Regular members. The Committee may utilize consultants, as necessary, for additional specialized or temporary expertise. Consultants do not have voting privileges and attend meetings at the invitation of the Chair.

Member Selection

Individuals interested in joining the TLV®-CS Committee will be asked to complete a basic Application Form and provide a resumé or curriculum vitae. The Membership Subcommittee will review the application and determine whether the applicant is eligible and has qualifications that fit the needs of the Committee. This process is described in detail in the Membership Subcommittee section.

The following criteria will be used to evaluate an applicant for membership:

- Disciplinary training and education
- Professional background
- Past relevant experience
- Personal characteristics

The following criteria will be used to assess the overall membership of the Committee and whether a particular applicant fits with the Committee's activities:

- The Committee should have a mix and balance of persons who have expertise in one or more of the following: industrial hygiene, occupational medicine, epidemiology, toxicology or other related specialties (e.g., statistics, chemistry, etc.)
- Preference will be given to individuals with 10 or more years of professional experience and with advanced degrees in their field of expertise
- Individuals should demonstrate competence in writing and communication through publications, presentations or other activities
- The Membership should reflect the diversity of the industrial hygiene and occupational health field
- Preference will be given to individuals with multi-disciplinary backgrounds and experience or strength in a particular field

Member Responsibilities and Expectations

Each Member of the TLV®-CS Committee, with the exception of the Chair, will be affiliated with one of the TLV®-CS Subcommittees. TLV®-CS Committee Members are expected to prepare and review *Documentation* for TLV®-CS substances. The expected number of TLV® *Documentation* prepared and reviewed annually may vary for individual members, depending on other activities they undertake that serve the TLV®-CS Committee's priorities. In addition to TLV®-CS Subcommittee activities, each member of the Committee is encouraged to participate on at least one TLV®-CS Administrative Subcommittee, excluding the Steering Subcommittee. Individual members will arrange their activities with their respective Subcommittee Chairs, with review by the TLV®-CS Committee Chair.

TLV®-CS Committee Members are expected to contribute to the work of the Committee. This includes time spent attending up to three face-to-face meetings each year, preparing and reviewing TLV® *Documentation*, and participating in Administrative Subcommittee activities. More senior members are expected to provide guidance and to mentor new members.

Members are expected to comply with all Policies and Procedures of ACGIH®. Members are expected to interact at all times in a collegial fashion with other members of the TLV®-CS Committee and Staff.

Participation on the Committee is a privilege that must be continually earned, through on-going productivity, participation and collegial behavior. When considering re-appointment, the Chair will review a member's participation in light of membership expectations and length of tenure on the Committee. As members serve additional terms they are expected to take on a greater role in the Committee, which may include preparing additional *Documentation*, chairing a TLV®-CS or Administrative Subcommittee, and other activities as needed.

It is essential that Committee Members regularly attend Committee meetings, participate in all scheduled conference calls, and prepare and review *Documentation*.

Member Candidates

The TLV®-CS Committee may choose to invite potential members to participate in Committee activities as "Member Candidates" before recommending them for formal appointment to the Committee. This practice allows the potential member to understand the role of Committee members, and allows the Committee to evaluate the potential member. The Board of Directors must approve Committee Member Candidates. Member Candidates must follow all ACGIH® policies and procedures.

Consultants

When the TLV®-CS Committee needs specific technical expertise that is not available within the Committee, the Committee may request appointment of a Consultant.

Consultants should only be used when specific technical expertise is needed for a limited period of time. Consultants must be appointed by the Board of Directors. Consultants are not required to be members of ACGIH®, but must follow all ACGIH® policies and procedures.

Emeritus Members

Emeritus members are former, long-serving (20 years or more) members who are retired, but continue to contribute to the TLV®-CS Committee, although not as voting members. To remain as an Emeritus member, the former member must have contributed in some substantial manner, such as a written contribution or review of a draft TLV® *Documentation*, during the year. Emeritus Members are not required to be members of ACGIH®, but must follow all ACGIH® policies and procedures.

Conflict of Interest

The TLV®-CS Committee Members, Emeritus Members, Member Candidates and Consultants, hereafter referred to in this section as "Members", are required to follow the ACGIH® Policy and Process on Bias and Potential Conflicts of Interest (COI), published on the website at *www.acgih.org*. Any "Member" with a potential, real, or perceived conflict of interest with respect to a chemical substance or issue under consideration by the TLV®-CS Committee must orally disclose the conflict of interest to the full TLV®-CS Committee. In addition, a written declaration must be completed at the same time. It is essential that potential, real, or perceived conflicts of interest be identified before the TLV® process begins. Likewise, it is important that "Members" recognize and identify their particular technical or scientific biases, so that these differing perspectives can be balanced during Committee deliberations. Selected information of particular relevance to the TLV®-CS Committee and its conflict of interest process are described below.

All "Members" must complete an annual oral and written COI declaration at a full TLV®-CS Committee meeting that includes information about their sources of funding, including professional services and consultancies, professional affiliations, service on boards or committees, legal testimonies, and other activities that may represent a potential conflict of interest for participation in the affairs of the Committee. In addition, the individual should disclose their publications history and identify any technical biases. As part of this annual declaration process, the TLV®-CS Committee Chair will conduct a presentation and discussion of conflict of interest. This presentation will include a variety of scenarios and possible methods for resolving conflicts while maintaining participation. This declaration is required annually and when material changes in their status occur. Typically at the beginning of a TLV®-CS Subcommittee meeting the Subcommittee Chair will inquire about material changes in each member's COI and bias status.

- Bias is defined as "views stated or positions taken that are largely intellectually motivated or that arise from close identification or association of an individual with a particular point of view or the position or perspectives of a particular group." Conflict of interest means "any financial or other interest which conflicts with the service of an individual because it (1) could impair the individual's

objectivity or (2) could create an unfair competitive advantage for any person or organization."

- In the case of bias, the TLV®-CS Committee attempts to create a balance of opinions and views by maintaining a diversity of professional affiliations, disciplines and activities among its membership.

- In the case of conflict of interest, the TLV®-CS Committee has created a number of avenues for minimizing or eliminating the potential effects of conflict of interest while allowing a "Member" to participate as fully as possible in Committee activities. The Committee believes that it is the primary responsibility of the individual to identify his/her potential conflicts and to consider carefully the level of participation that is appropriate.

- Within a Subcommittee meeting, each TLV®-CS Subcommittee Chair will begin the review of new substances with a request for notification of conflict of interest from the "Members" present. In addition, any "Member" who develops a new conflict of interest for an ongoing chemical *Documentation* is required to notify the other members of the Subcommittee.

It may not always be in the best interests of the TLV®-CS Committee for a "Member" who has significant conflicts of interest to remove himself/herself entirely from the development of a TLV® because they may be very knowledgeable about that particular substance. In these cases, the TLV®-CS Subcommittee Chairs should work directly with the "Member" to assure these conflicts are minimized while allowing for as full participation as possible.

Open and free discussion of conflict of interest is key to this process. The classification of conflict and the selection of the appropriate action should not be left to the individual but is based on a consensus of the whole Subcommittee. If there is no consensus with the Subcommittee, the appropriate action is at the discretion of the Subcommittee Chair. The Committee Chair should be informed of all high levels of conflict and proposed action.

To assist in identifying levels of conflict and possible actions for mitigating conflict, the following definitions are offered as guidance.

<u>High Degree of Conflict</u>

A "high" level of conflict exists if a "Member" has been or currently is directly involved with the substance.

Examples of situations with a high level of conflict are:

a. A "Member" working with a regulatory agency who plays a role in developing regulations for the chemical substance.
b. A "Member" affiliated with an academic institution and who performs research central to the TLV®.
c. A "Member" who works for a company that is a major producer of a chemical substance under review by the TLV®-CS Committee.

d. A “Member” who performs consultation services for an associated trade organization or a producer of a chemical substance under review by the TLV®-CS Committee and plays a direct role in the development of internal exposure levels.

Where a high degree of conflict exists, the “Member” is not permitted to author or co-author *Documentation*, and must recuse themselves from discussions about the recommended TLV® value and notations. Full members with a high degree of conflict must also abstain from voting on the recommended TLV® and *Documentation*; although, the “Member” may discuss matters of science.

Medium Degree of Conflict

A “medium” level of conflict exists if a “Member” has been or is indirectly involved with the chemical substance.

Examples of situations with a medium level of conflict include:
a. A “Member” who works for a regulatory agency that regulates the chemical substance, does not have a direct role in developing regulations but may be concerned with enforcing regulations.
b. A “Member” who is an academic and whose present, past, or anticipated research may be concerned with the chemical substance but is not central to the determination of a TLV®.
c. A “Member” employed by a company that is a major producer of a chemical substance that is competing with a chemical substance under review by the TLV®-CS Committee.
d. A “Member” who performs consultation services for an associated trade organization or a producer of a chemical substance under review by the TLV®-CS Committee but who plays a minor role in the internal development of exposure levels.

When an intermediate level of conflict has been identified, the matter should be carefully discussed with the Subcommittee Chair and members, and appropriate steps taken to mitigate the conflict. Typically, this will mean assigning a co-author or a reviewer for the *Documentation*. In some cases, abstention from voting on the TLV® is also appropriate.

Low Degree of Conflict

A “low” level of conflict exists if the “Member” is affiliated with an organization that has a financial or other interest in the substance but has a very minor or nonexistent role with respect to the substance.

Examples of situations with a low level of conflict include:
a. A “Member” affiliated with an academic institution who does not conduct research relevant to the chemical substance but whose immediate colleagues have research that is directly concerned with the substance.
b. A “Member” working for a regulatory agency that regulates the substance but whose role is non-regulatory.
c. A “Member” working for a company that is a minor producer and has no role in the development of internal occupational exposure levels.

d. A "Member" who performs consultation services for an associated trade organization or a producer of a chemical substance under review by the TLV®-CS Committee but who has no role in the development of internal occupational exposure levels.

In most cases, simply informing the Subcommittee and Committee members about low-level conflicts is all that is needed.

All "Members" who have participated fully in the TLV®-CS Subcommittee and Committee discussions about conflict of interest and who have made their best effort to eliminate or minimize personal conflicts will be eligible to participate in all votes. In cases where there are high levels of conflict, "Members" must recuse themselves from any discussions, reviews, and votes related to that substance.

Failure by any "Member" to report a conflict of interest is grounds for immediate termination of that member's service on the Committee. The Chair will conduct a review with the Steering Subcommittee and make a recommendation to the Board. Depending on the status of the TLV® (under study, proposed, or adopted), it may be necessary to carry out a complete review of the decision-making process for the substance to determine appropriate action.

Terms

Members, who are annually appointed by the Board of Directors generally begin their term on January 1. The TLV®-CS Committee Chair will consult with the appropriate TLV®-CS Subcommittee Chair/Vice Chairs and other members of the Committee prior to recommending re-appointment.

Expectations for continuing membership include, at a minimum:

- Attending all meetings,
- Participating in all scheduled conference calls, and
- Preparing and reviewing *Documentation* each year.

Awards

The ACGIH® TLV®-CS Committee is a voluntary activity of extremely busy and competent professionals with expertise in a range of scientific areas who contribute to international worker health and safety and the development of OEVs.

The contributions over time of these TLV®-CS Committee members will be recognized by Membership Service Awards based on years of service to the TLV®-CS Committee. In particular, TLV®-CS Committee members will be recognized for 5, 10, and 20 years of service. This recognition will occur at a TLV®-CS Committee meeting. Awards will be presented by the TLV®-CS Committee Chair in consultation with the Membership Subcommittee. The funds to support the Membership Service Award will be included in the budget for the TLV®-CS Committee.

Every third year (starting with 2002) the TLV®-CS Committee will submit a recommendation to the Board of Directors for the William D. Wagner Award. The award

will be given to someone (not necessarily a member of the Committee) who has been an outstanding example of commitment and dedication to the creation and dissemination of OEVs. Funds to support the travel expenses for the recipient will be determined by the Board of Directors and managed through the ACGIH® awards program.

TLV® PRODUCTION GUIDE

TLV® Development Process

The TLV®-CS Committee follows the TLV®/BEI® Development Process: An Overview, posted on the ACGIH® website (http://www.acgih.org/TLV/DevProcess.htm). Specific details relating to TLV® Development in the TLV®-CS Committee are listed below. Note: Important dates are listed at the end of this section.

Under Study

List of substances/issues under study are published by February 1 in the Annual Reports of the Committees on TLVs® and BEIs® and on the ACGIH® website (www.acgih.org) to allow public review and to solicit comments and data. This list is current as of January 1.

Substances are initially assigned to the Under Study list by a consensus of the respective Subcommittee, and can be added to or removed from the list throughout the year as needed, by the TLV®-CS Subcommittee Chair(s) or Committee Chair. Changes are posted on the ACGIH® website.

In addition, the Under Study list is updated by July 31 into a two-tier list. Tier 1 indicates which substances/issues may move forward as an NIC in the upcoming year, based on their status in the development process. Tier 2 consists of those substances/issues that will not move forward, but will either remain on, or be removed from, the Under Study list for the next year. Once the tiered list has been released to the public, any substances/ issues added to the Under Study list must be placed on Tier 2. This updated list will remain in two-tiers for the balance of the year.

Draft *Documentation* on Under Study

An author is assigned by the TLV®-CS Subcommittee Chair(s) to prepare the draft *Documentation.* (Note: Draft *Documentation* is not available to the public through this stage of the development process and is not released until it is at the Notice of Intended Changes (NIC) stage.)

The draft *Documentation* is reviewed by the 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 Full Committee for review.

The Subcommittee Chair(s) or Subcommittee member summarizes the draft *Documentation* and proposes a motion to place it on NIC. If the motion is seconded, the Full Committee will discuss and then vote on the proposed action. Approval requires a majority of the voting members present at the Full Committee meeting. Recommendation to place a draft *Documentation* on the NIC can be done at the Spring or Fall TLV®-CS Committee meeting.

The Committee's recommendation is sent to the Board of Directors for review and ratification. If ratified by the Board of Directors, the TLV® value(s) and any notations are listed on the NIC and the *Documentation* is published and available as a "draft".

Draft *Documentation* on the Notice of Intended Change (NIC)

A substance must be held on the NIC for at least one year for public review and comment before adoption. The comment period is defined in the TLV®/BEI® Development Process. Comments are forwarded by Staff to the TLV-CS Committee Chair, Vice Chair, Subcommittee Chair(s), the author, and the reviewer. At a minimum, the author and co-author or reviewer of the *Documentation* must review all of the comments in detail to ensure that the discussion at the subcommittee level includes a full consideration of the points raised therein. During the Subcommittee meetings, comments are reviewed by the Subcommittee and the draft *Documentation* is amended if necessary.

After Subcommittee review and approval (by consensus) of the draft *Documentation*, the TLV® value(s), any notations, and draft *Documentation* are brought to the Full Committee for review.

The Subcommittee Chair(s) or Subcommittee member will summarize the draft *Documentation* and propose one of the following actions:
1) Retain the TLV® value(s)/notations and draft *Documentation* on the NIC for an additional year,
2) Change the TLV® value(s)/notations and draft *Documentation* and retain on the NIC for an additional year,
3) Adopt the NIC TLV® value(s)/notations and draft *Documentation*, or
4) Withdraw the NIC TLV® value(s)/notations and draft *Documentation*.

If the motion is seconded, the Committee will discuss and subsequently vote on the proposed action. Approval requires a majority of the voting members present at a Full Committee meeting. Recommendation to adopt, withdraw, or retain NIC *Documentation* are typically done at the Fall TLV®-CS Committee meeting.

The Committee's recommendation is sent to the Board of Directors for review and ratification. If ratified by the Board of Directors, the TLV® value(s), any notations and the *Documentation* are published.

Under Study Important Dates

Fall Meeting	Subcommittee establishes Under Study list (for upcoming year).
February 1	Under Study list is published in the Annual Report and posted on the web site.
Spring Meeting	Subcommittee updates Under Study list into two-tier list.
By July 31	Tier 1 and 2 lists released to the public.
Year Round	Under Study list can be updated, however, once the tiered list has been released to the public those substances/issues must be placed on Tier 2.

Notice of Intended Change (NIC) Important Dates

Spring Meeting	Committee votes to place a draft *Documentation* for an Under Study substance on the NIC.
	Committee votes to adopt, withdraw or retain NIC *Documentation*. (Note: Typically this will be done at the Fall meeting.)
Fall Meeting	Committee votes to place a draft *Documentation* for an Under Study substance on the NIC. (Note: Where practical, this will be done at the Spring meeting.)
	Committee votes to adopt, withdraw or retain NIC *Documentation*.

Voting Procedures

The Committee follows the TLV®/BEI® Committee Voting Procedure.

TLV® Documentation Guidelines

An outline of a TLV® *Documentation* is included in Appendix A.

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. In general, the entire *Documentation* should be no longer than 10 pages in length; however, exceptions will be made where circumstances warrant it. *Documentation* should be formatted as designated by the Documentation Template (included in Appendix A). 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 and the identification of notations, for the purpose of protecting employees in occupational settings. The primary user of the TLV® *Documentation* is intended to be the industrial hygiene professional.

Literature Search

For new TLVs®, the author of the *Documentation* or Assistant to the Chair shall conduct a full literature search using the appropriate online databases. ACGIH® Staff, Assistant to the Chair or other Committee members may provide assistance with those references to which a member does not have access. Basic toxicology and other references should also be consulted (see Appendix B).

For TLVs® requiring revision, the Committee member should request an electronic copy of the current TLV® *Documentation* from ACGIH®. Staff should provide copies of any references currently on file. A full literature search should then be conducted using on-line databases and references listed in Appendix B.

The TLV® *Documentation* is to rely on published, peer-reviewed information from scientific journals and books. Other types of information may be used, if necessary, to

provide a more complete picture of the substance and its health effects. However, care must be taken in the use of such information.

When unpublished information is used, it must meet the following criteria:

1. The information should have undergone some form of peer review. The importance of the information to the *Documentation* determines the degree of peer review necessary. For example, if the information is one of several reports in agreement about a particular aspect of the substance, then peer review by the Subcommittee may be adequate. If the information plays a larger or more important role (e.g., it is in disagreement with other information or it is the only information of its type), then a broader peer review may be necessary by the Full Committee. It will be up to the Subcommittee to determine the nature of peer review that is appropriate. When conducting such peer review, the Subcommittee should ensure that accepted scientific methods were used to obtain and analyze the data.
2. If unpublished data is used, a signed copy of permission to use, cite and release to a third party upon request must be filed with ACGIH® Staff before it can be used or referenced in a NIC or final *Documentation.*
3. Robust summaries can be used with some limitation for TLV® Development, keeping the following limitations in mind:
    a. Can be used as further information in the *Documentation*, if not deriving the TLV® or notation
    b. Can be used to support another source reference
    c. Can be used to support a TLV® or notation if they are the only data available upon which to base a TLV® or notation. Use of a robust summary in this manner is contingent upon review and approval of the Committee, and limited on a case by case basis.

If the information is contained in a "government" document it should not be assumed that it has undergone peer review.

Secondary sources may be used for an overview of the data. However, primary sources should be relied upon for discussion of specific studies. In particular, conflicting results require review of the original data (e.g., research paper).

In the case of translated information, care must be taken to ensure the information has been properly interpreted. Translation of non-English sources may be possible, if the study is critical to the TLV® recommendation. The need for such translation should be discussed with the Subcommittee Chair; such requests should then be sent by the Subcommittee Chair to the TLV®-CS Committee Chair for review and recommendation to the ACGIH® Staff for approval.

COMMITTEE STRUCTURE

Organization Chart

The Committee organization chart is shown in Appendix C.

Position Descriptions

TLV®-CS Committee Chair

Method of Selection and Appointment. Candidate(s) for the Chair of the Committee is/are recommended through an internal Committee nomination and vote process, the results of which are sent to the Board of Directors for final selection and approval. Prior to the expiration of the current Chair's appointment, the Membership Subcommittee will seek nominations from Committee members for candidates. Candidates may be drawn from current members of the Committee or may be people from outside the Committee. The latter must meet the criteria for Regular membership within ACGIH®, as well as the membership criteria of the TLV®-CS Committee. The Membership Subcommittee will screen nominees and present names to the Committee, accompanied by background information and a statement from each nominee. All Committee members will be asked to vote for one of the nominees. The Membership Subcommittee will tally votes (with assistance from Staff). The slate of nominees and number of votes received by each nominee will be sent to the Board of Directors for final selection and approval. The Chair of the TLV®-CS Committee will hold the position, contingent upon annual re-appointment by the Board of Directors.

Duties. The Chair leads the TLV®-CS Committee and works closely with the Vice Chair and Steering Subcommittee to ensure the Committee's progress toward fulfilling its mission and goals. The Chair:

- Assists and oversees TLV®-CS Subcommittee activities
- Monitors the annual selection of substances
- Oversees budget management, spending, meeting plans (with assistance from Staff)
- Monitors overall workload and makeup of the Committee
- Monitors and assists the activities of the Administrative Subcommittees
- Assures regular, clear communications with Staff and Board of Directors by interacting with the Board Liaison, Committee's Staff Persons, and other staff or Board members, as necessary
- Assures regular, clear communications with external parties by such processes as reviewing comments received, providing input to replies prepared by Staff, etc.
- Assures communication between all members of the Committee by consulting regularly with the Steering Subcommittee (Chair, Vice Chair and TLV®-CS Subcommittee Chairs)
- Consults regularly with the Vice Chair to assure proper functioning of internal Committee activities
- Works closely with the Chairs of the Administrative Subcommittees to assure their groups are functioning according to their guidelines and policies.

- Represents the TLV®-CS Committee to the public in accordance with ACGIH® Public Affairs and Communication Policy
- Represents the TLV®-CS Committee to the ACGIH® Board of Directors and communicates and consults regularly with the Committee's Board Liaison

Reporting. The Chair reports directly to the Board of Directors of ACGIH® and the Committee's Board Liaison.

Assistant to the Chair

Method of Selection and Compensation. The Assistant to the Chair will be selected by the Chair of the Committee after consultation with Staff. Compensation for the Assistant to the Chair must be approved by the Board of Directors.

Duties. The Assistant to the Chair will work directly with the Chair in providing support and assistance in assuring that the Chair's responsibilities and various activities are adequately addressed and managed. The job description of this Assistant may vary with the individual in the Chair position and will be defined and negotiated with the ACGIH® Executive Director.

Reporting. The Assistant to the Chair will report directly to the Chair. The Chair will report on activities and progress of the Assistant to the Board of Directors and Staff as requested.

Vice Chair

Method of Selection and Appointment. The Committee Chair recommends the Vice Chair to the Board of Directors, which approves the recommendation and appoints the Vice Chair for a one-year term. The Vice Chair may be re-nominated by the Chair and annually re-appointed by the Board.

Duties. The Vice Chair is responsible for assisting the Chair in assuring that internal Committee functions are adequately cared for. The Vice Chair will undertake the responsibilities of the Chair when s/he is unable or unavailable to do so. The Vice Chair may be a candidate for future appointment as Committee Chair.

The Vice Chair assists the Chair as necessary. In particular, the Vice Chair participates in the Steering Subcommittee and oversees internal Committee activities that support *Documentation* preparation and membership.

Specifically, the Vice Chair will:

- Assure the internal functioning of the Committee. As such, the Vice Chair is specifically responsible for overseeing the Administrative Subcommittees.
- Determine the make-up of all the Administrative Subcommittees, in consultation with the Chair. Members will be asked for their preferences and assigned to an Administrative Subcommittee. Every effort will be made to meet a member's preference, if possible. However, the Vice Chair will also ensure an appropriate

mix of members on the Administrative Subcommittees (by TLV®-CS Subcommittee affiliation, professional background and skills, etc.).
- Participate in decisions on Member Candidates recommended to the Board of Directors by consulting regularly with the Membership Subcommittee.

Reporting. The Vice Chair will report to the Chair of the Committee on his/her individual activities and the activities and make-up of the Administrative Subcommittees.

TLV®-CS Subcommittee Chairs

Method of Selection. The Committee consists of three TLV®-CS Subcommittees:
- Hydrogen, Oxygen and Carbon Compounds (HOC)
- Dusts and Inorganic Compounds (D&I), and
- Miscellaneous Compounds (MISCO).

Each of these Subcommittees is headed by a Chair, who is nominated by the Committee Chair in consultation with the Vice Chair. There is no established term for a TLV®-CS Subcommittee Chair. The TLV®-CS Committee Chair will review the activities of each TLV®-CS Subcommittee Chair on a regular basis, seeking input from members of the Subcommittee. While continuity is important in ensuring the on-going productivity of these Subcommittees, it is also important to build leadership skills among all Committee members who demonstrate skill and interest. Subcommittee Chairs shall select, in consultation with the Committee Chair, another individual within their Subcommittee to serve as a Vice Chair. This person should become versed in the management of the Subcommittee and should be given opportunities to play a leadership role within the Subcommittee. In case of the Subcommittee Chair's absence, this person should be prepared to chair meetings and ensure progress toward completion of the Subcommittee's activities.

Duties. TLV®-CS Subcommittee Chairs are members of the Steering Subcommittee. (Vice Chairs, as described above, should be included in Steering Subcommittee meetings, as well.) The TLV®-CS Subcommittees have the most important function within the TLV®-CS Committee. Thus, the Chair of a TLV®-CS Subcommittee carries the largest degree of responsibility for assuring that the Committee's products are of high quality and fulfill the goals of the Committee. It is very important that the TLV®-CS Subcommittee Chair communicates and consults regularly with the Chair, Steering Subcommittee, Staff, and with members of their Subcommittee.

TLV®-CS Subcommittee Chairs are responsible for the *Documentation* preparation activities of their Subcommittee. In this capacity, TLV®-CS Subcommittee Chairs:
- Assign substances to individual members, following the definitions offered as guidance in the Conflict of Interest section of this manual
- Assure that each member meets the expectations for *Documentation* preparation
- Assist members, when necessary, with aspects of *Documentation* development
- Assign a mentor to all new members and Member Candidates
- Keep members informed of relevant decisions of the Steering Subcommittee
- Track the progress of *Documentation* preparation and keep members informed of this progress

- Provide feedback to members about their activities with respect to membership expectations.

TLV®-CS Subcommittee Chairs are responsible for their Subcommittee's productivity, both in quality and quantity of *Documentation*. In this capacity, they will arrange regular Subcommittee meetings throughout the year, establish meeting agendas in consultation with members, and run well-organized and productive meetings. They will also ensure formal minutes are taken for all meetings and will provide copies of these minutes to all Subcommittee members and the Committee Chair. Minutes may consist of decisions and a simple "to do" list, rather than a formal description of the discussion.

Generally, no voting takes place in the TLV®-CS Subcommittees. Decisions are made by consensus, if possible. However, the TLV®-CS 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 TLV®-CS Subcommittee Chair must seek Subcommittee consensus for all substances currently on the NIC and on the Under Study list. In a case where the Subcommittee could not reach consensus or majority vote, the TLV®-CS Subcommittee Chair may not bring a TLV® to all members of the Committee without receiving approval from the Committee Chair and Vice Chair.

TLV®-CS Subcommittee Chairs are responsible for ensuring that full communication takes place within the Committee, particularly among the Steering Subcommittee members and with the Staff. As such they should:

- Review communications received from external parties and ensure that members of their Subcommittee have an opportunity to review and discuss comments.
- Respond to questions from the Staff in a timely manner.
- Direct all questions and comments (written and oral) received from external parties directly to the Staff. TLV®-CS Subcommittee Chairs are not to contact external parties. TLV®-CS Subcommittee Chairs are expected to respond to all external parties by directing them to the Staff.
- Work with the relevant Administrative Subcommittees on activities not directly related to the preparation of TLV® *Documentation*. For example, internal education events should be planned in consultation with the TLV®-CS Education Development Coordinator; external education events should follow the guidelines of the ACGIH® Events Development Planner worksheet; and changes to the TLV® notations, appendices, etc. should be discussed and coordinated with the Notations Subcommittee.

Terms. There is no established term for a TLV®-CS Subcommittee Chair.

Reporting. The TLV®-CS Subcommittee Chairs report to the TLV®-CS Committee Chair.

TLV®-CS Subcommittee Vice Chairs

Method of Selection and Appointment. Each TLV®-CS Subcommittee Chair shall select a Vice Chair, in consultation with the Committee Chair.

The TLV®-CS Subcommittee Vice Chair will work closely with the TLV®-CS Subcommittee Chair to assist in leadership and decision-making responsibilities. The Subcommittee Vice Chair may take on the duties of the Subcommittee Chair, in case of the latter's absence. The Subcommittee Vice Chair participates fully in all Committee leadership activities (Steering Subcommittee, etc.).

Reporting. The TLV®-CS Subcommittee Vice Chair reports directly to the TLV®-CS Subcommittee Chair.

Term. There is no established term for a TLV®-CS Subcommittee Vice Chair.

Administrative Subcommittee Chairs

Method of Selection. The Administrative Subcommittee members are responsible for identifying a Chair.

Reporting. The Administrative Subcommittee Chair is responsible for ensuring that the duties of the Subcommittee are adequately fulfilled, as described in the Operations Manual. The Administrative Subcommittee Chair is responsible for reporting the Subcommittee's activities to the Chair, Vice Chair and Steering Subcommittee. The Chair of the Membership Subcommittee is expected to work most closely with the Vice Chair, who holds primary responsibility for their activities. The Chair of the Notations Subcommittee will work most closely with the Chair, who holds primary responsibility for their activities.

Description of Administrative Subcommittees

Steering Subcommittee

Method of Selection and Appointment. The Steering Subcommittee consists of the TLV®-CS Committee Chair and Vice Chair, as well as the TLV®-CS Subcommittee Chairs and Vice Chairs (HOC, D&I, MISCO). 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 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.
- Assures 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 and Administrative Subcommittees.

Membership Subcommittee

Method of Selection. The Membership Subcommittee will consist of at least one member from each of the TLV®-CS Subcommittees. Membership Subcommittee members are appointed annually by the TLV®-CS Committee Vice Chair. The Subcommittee members, in consultation with the TLV®-CS Committee Vice Chair, will identify the Subcommittee Chair.

Duties.

New Members. The Membership Subcommittee is responsible for recruiting, reviewing, and recommending Member Candidates or new members for consideration by the Committee Chair and Vice Chair, and for monitoring the probationary progress of Member Candidates. Recruitment may be accomplished by various methods, including advertisements and personal communications.

Any person indicating interest in participating on the TLV®-CS Committee will be sent an application form by Staff. Applicants will be asked to submit a completed membership application and their resumé/curriculum vitae. Applicants will be informed of the expectations and responsibilities of members of the TLV®-CS Committee, and will be asked to review and accept these responsibilities as part of their application. Staff will review the completeness of applications received and issue a letter confirming receipt of the application. Completed applications with resumés/curriculum vitae will be sent to the members of the Membership Subcommittee and the TLV®-CS Committee Chair and Vice Chair. The Membership Subcommittee will meet and consider all new applications at least once per year, or more frequently if necessary.

The Membership Subcommittee Chair will advise the TLV®-CS Committee Chair and Vice Chair of the applicants and of their backgrounds. The TLV®-CS Committee Chair and Vice Chair may consult with other members of the TLV®-CS Committee as to their opinions about the prospective member(s).

Once this process is completed, the TLV®-CS Committee Chair will assess each application and forward to the ACGIH® Board of Directors the name(s) of those whom he/she recommends for approval to appoint as a Member Candidate of the TLV®-CS Committee. A copy of the applicant's resumé/curriculum vitae will be provided to the Board, as part of the Chair's recommendation. After Board approval, the Committee Chair can extend an invitation to the Member Candidate to attend and participate in a Full Committee meeting. The Member Candidate will be given the opportunity during a Committee meeting to attend a portion of each of the three TLV®-CS Subcommittee meetings and the Full TLV®-CS Committee meeting, as well as a meeting of the Notations Subcommittee, if possible.

The TLV®-CS Committee Chair will assign the applicant to a TLV®-CS Subcommittee for a probationary period. Applicants will be referred to as "Member Candidates" during this period. As such, they will be expected to attend all meetings of their TLV®-CS Subcommittee and of the Full TLV®-CS Committee. The respective TLV®-CS Subcommittee Chair and Vice Chair will identify and assign responsibilities to the

Member Candidate during the probationary period. These responsibilities will include assignment of a *Documentation* to be developed as a draft to the TLV®-CS Subcommittee during the probationary period, administrative activities, and other duties. The Member Candidate may not vote in Full Committee meetings, but will be expected otherwise to participate fully in TLV®-CS Subcommittee and Committee discussions.

During the probationary period, the TLV®-CS Subcommittee Chair will make a recommendation to the Membership and Steering Subcommittees for full membership. The Membership Subcommittee will then submit the names of all applicants who have completed their probationary period satisfactorily to the TLV®-CS Committee Chair. If needed, the Chair will solicit input from all Committee members concerning membership for Member Candidates completing their probationary period. The TLV®-CS Committee Chair will evaluate each Member Candidate and make the final decision concerning a recommendation for membership. Names of recommended Member Candidates will then be forwarded by the TLV®-CS Committee Chair to the ACGIH® Board of Directors for a decision regarding approval and formal appointment as a TLV®-CS Committee member.

The ACGIH® Staff will handle all communication with applicants and candidates regarding the status of their application or membership.

Nominating the Committee Chair. The Membership Subcommittee will serve as the nominating group for the TLV®-CS Committee Chair. [See the section on Method of Selection and Appointment for the Committee Chair for more details on this process.]

Reporting. The Chair of the Membership Subcommittee will be asked to report the activities and progress of the Membership Subcommittee to the TLV®-CS Committee Chair, Vice Chair and the Steering Subcommittee on a regular basis.

Notations Subcommittee

Method of Selection. The Notations Subcommittee will consist of at least one member from each of the three TLV®-CS Subcommittees, designated by the Vice Chair. The Subcommittee will select its own Chair, in consultation with the Vice 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:

- Review current notations and recommend changes and modifications as necessary in their definitions.
- Develop criteria that guide authors in determining which notations are appropriate and how they should be applied.

- Identify experts (internal and external to the Committee) that can be consulted for specific notations.
- Recommend workshops, seminars, webinars or tutorials for the purpose of providing input to the Committee on emerging issues.
- Establish ad hoc groups, where necessary, to consider special issues.
- Develop "standard" language for the *Documentation* Guidelines that can be used in *Documentation* development and in the TLVs® and BEIs® book to describe notations and special issues.
- Provide attention to the consistent application of notations across the three TLV®-CS Subcommittees.
- Create and revise 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:

- Carcinogen
- Skin
- BEI®
- Sensitizer (SEN)
- TLV® Basis
- Mixtures
- Atypical work schedules
- STEL
- TWA
- Ceiling

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 will report activities and progress to the Chair and Steering Subcommittee on a regular basis.

Other

TLV®-CS Education Development Coordinator. This individual is responsible for coordinating and overseeing educational event development internal and external to the Committee.

COMMUNICATIONS

External to the Committee

The Committee recognizes that there are many different groups with an interest in the TLV® process and its outcomes. The Committee's goal is to assure that all such parties are given timely and complete information about its process and decisions. At the same time, it is important that these external parties not compromise the Committee's decision process, which is based primarily on peer-reviewed scientific information. Thus, the Committee has established a written process that allows input from external groups to the Committee concerning substances currently under review. Also, comments are welcome for any other substances as well. The TLV®/BEI® Development Process is available on the ACGIH® website at www.acgih.org. There are several important points to consider throughout this process:

- The appropriate method for an interested party to contribute to the TLV® and BEI® process is through the submission of literature that is peer-reviewed and public. ACGIH® strongly encourages interested parties to publish their studies, and not to rely on unpublished studies as their input to the TLV® and BEI® process. Also, the best time to submit comments to ACGIH® is in the early stages of the TLV® and BEI® development process, preferably while the substance or agent is on the Under Study list.

- An additional venue for presentation of new data is an ACGIH®-sponsored symposium or workshop that provides a platform for public discussion and scientific interpretation. ACGIH® encourages input from external parties for suggestions on symposium topics, including suggestions about sponsors, speakers and format. See the Symposium section within this Operations Manual for further information.

- ACGIH® periodically receives requests from external parties to make a presentation to a committee about specific substances or issues. It is *by exception* that such requests are granted. While there are various reasons for this position, the underlying fact is that the Committee focuses on data that have been peer-reviewed and published and not on data presented in a private forum. A committee may grant a request when the data are significantly new, has received peer review, are the best vehicle for receipt of the information, and are essential to the Committee's deliberations. The presentation is not a forum to voice opinions about existing data. In order for a committee to evaluate such a request, the external party must submit a request in writing that, at a minimum, addresses the following elements: (a) a detailed description of the presentation; (b) a clear demonstration of why the information is important to the Committee's deliberations; and (c) a clear demonstration of why a meeting is the necessary method of delivery. This request must be sent to the ACGIH® Science Group (science@acgih.org).

The TLV®-CS Committee may invite subject experts to present/speak at Committee education sessions.

Confidentiality

The TLV®-CS Committee communicates with its users and interested parties by publishing its decisions as *Documentation*, following a clearly delineated process. Authorship of *Documentation* is a confidential matter. Such authorship may not be discussed with any person external to the Committee. Methods for seeking information from external parties while ensuring anonymity should be discussed with the Subcommittee Chair or Committee Chair and performed through ACGIH® Staff. Information, materials, *Documentation*, etc. may not be shared with anyone external to the Committee. Draft Chemical Substance *Documentation* can be shared with other TLV®/BEI® Committees once approved by the applicable Subcommittee or approved by the Subcommittee Chair/Vice Chair. Committee members are to follow the ACGIH® Public Affairs and Communication Policy and ACGIH® Information Release Policy.

Internal Communications

Communications Within the Committee

The TLV®-CS Committee relies on meeting minutes for documenting its activities and tracking its progress.

Formal minutes will be taken at Full Committee meetings, generally by ACGIH® Staff or Assistant to the Chair. These minutes are used to record the activities and formal votes of the Full Committee (typically without identification of individual names). Copies will be sent to members of the Committee and the Board Liaison.

Formal minutes are required at TLV®-CS and Notations Subcommittee meetings. At a minimum, Subcommittee notes should indicate the date, members present and absent, important points of discussion, major decisions taken and future activities planned. Copies of these minutes will be made available to the Committee Chair (or the Assistant to the Chair).

Communications Between the Committee and ACGIH® Staff and Board of Directors

The Committee assures timely and consistent communication with the ACGIH® organization through its Board Liaison and ACGIH® Staff. ACGIH® Staff attends Full Committee meetings and many of the TLV®-CS and Administrative Subcommittee meetings. The Staff communicates regularly with the Committee Chair about Committee activities. ACGIH® Staff works closely with the Committee Chair on issues, including budgeting and spending, meeting arrangements, publications, communications with external parties, etc.

The Board Liaison also attends Full Committee meetings, providing input to the Committee from the Board of Directors and relaying Committee concerns and thoughts to the Board. The Board Liaison also works with the Chair during budgeting, policy-making and other issues that bear directly on the organization.

SYMPOSIA AND WORKSHOPS

Procedure for Developing a Symposium or Workshop

The education of TLV® Committee members is an important aspect of the development of TLVs® and TLV® *Documentation*. Suggestions for educational symposium topics should be forwarded to the Science Department of ACGIH® or TLV®-CS Education Development Coordinator in writing. Symposium topics can come from Committee members, ACGIH® Staff, and external parties. The proposal should include a justification for the necessity of the symposium, the topic's relevance to the TLV®-CS Committee, a suggested list of participants, and if possible, a list of potential academic, governmental, or industrial sponsors.

The Events Development Planner (EDP) will serve as the formal planning document during symposium development. The ACGIH® Staff will work with the Committee through all aspects of planning and executing a workshop or symposium.

Several criteria will be used by the Committee to determine the appropriateness of the symposium as being of interest to the TLV®-CS Committee. A symposium must be the most efficient format in which to present TLV®-CS Committee members with new information that will assist in the scientific judgment used in the setting of TLVs® and in the writing of supporting *Documentation*.

Because of the timing of TLV® setting and *Documentation*, it is important that a symposium be suggested as early in the process as possible. Symposia require considerable time, commitment, and resources to develop and, thus, proposals should preferably be submitted while a substance is on the Under Study list. Symposium suggestions submitted while a substance is on the NIC will be considered, but usually this will be too late in the decision-setting process. A symposium will not be favorably reviewed if its purpose is solely to provide a forum for voicing opinions about existing data. Rather, there must be on-going research, scientific uncertainty about currently available data, or another scientific reason for the symposium.

Representatives of external organizations may have expressed a desire to meet with the TLV®-CS Committee because the Committee might benefit from discussions of the scientific data or because the many issues to be discussed on a given chemical are likely to be important and of interest to a wide range of interested parties. Yet symposia require commitment of substantial resources and presentations and discussions are often scheduled for a period as long as two days, far more time than the TLV®-CS Committee could commit to a single topic. Thus, it is important that care be taken in the review and selection of topics for symposia.

The Steering Subcommittee will review the original proposal. It may choose to seek further input from individual groups or members of the Committee in its review. The Steering Subcommittee will make a final recommendation to the Committee Board Liaison, indicating whether the TLV®-CS Committee has an interest in and wishes to participate in the development of a particular symposium. It will communicate its

recommendation to the individual(s) and/or Subcommittee that proposed the symposium topic, as well.

If a symposium proposal recommended by the TLV®-CS Committee is approved by the Board of Directors, the Steering Subcommittee will identify a small "task force" to work with ACGIH® Staff during the development phase. It is recommended that a member of the Steering Subcommittee serve as a member. In addition, a Board member will act as liaison to the task force. The task force will work closely with the Staff and, in addition to regular reporting to the Steering Subcommittee, will seek input and ideas from TLV®-CS Committee members about sponsors, speakers, format, etc. The task force will be responsible for ensuring that the TLV®-CS Committee's scientific decision-making needs are met and that all relevant external parties have an opportunity to give input to the planning of a symposium. To ensure that there is appropriate balance of scientific viewpoints and to maximize the available research to choose from, each symposium will utilize a call for papers to initiate and announce the planned symposium. The task force will be responsible for selecting speakers from responses as well as those identified from any other internal and external sources.

The symposium will typically be held immediately preceding or immediately following a scheduled meeting of the TLV®-CS Committee to facilitate the attendance of Committee members. Since the attendance of Committee members is in the interest of both the symposium and the TLV® development process, members will be encouraged to attend in their capacity as representatives of the TLV®-CS Committee.

If a symposium proposal is rejected, the Staff will be informed of the proposal and the Steering Subcommittee's review. The individual who submitted the proposal will also be notified. The organization may decide to proceed without the TLV®-CS Committee's formal sponsorship or involvement. In this latter case, potential symposium sponsors and attendees must be made aware that the TLV®-CS Committee has expressed no interest in formal sponsorship or participation. In addition, it must be made clear that TLV®-CS Committee members will not attend the meeting in their capacity as members or representatives of the TLV®-CS Committee, although they may, of course, attend as interested scientists.

APPENDICES

APPENDIX A

TLV® *Documentation* Guidelines

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 a new TLV® *Documentation*. It includes procedures and conventions for not only completing, gathering information, and reviewing the literature but also for incorporating a balance of information to support the TLV® recommendation. Among the many resources found in this guideline is a TLV® *Documentation* Template, which is designed to aid the author in drafting TLV® *Documentation*. It contains all required headings and some boilerplate language for assistance in writing *Documentation*. This guideline is updated periodically and should be considered a work in progress.

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. Although the *Documentation* is not intended to be a comprehensive review of the literature for a substance, it should describe the key literature studies that define the range of exposure information and animal and human health effects associated with 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 TLV® or any of its notations should be different from that selected, the reason for discounting this study should be provided.

Definitions

In order 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, Skin, SEN, etc.). The ACGIH® TLV®-CS Committee periodically reviews, clarifies, updates, and/or adds new definitions that must be considered in the development of the TLV® *Documentation*.

Responsibilities

Specific responsibilities for authors are described in the TLV®-CS Operations Manual.

Procedures

<u>Getting Started</u>

- A TLV® *Documentation* is assigned to an author by the specific TLV®-CS Committee (D&I, MISCO, HOC).
- Conduct a literature search yourself or with the assistance of ACGIH® Staff or the Assistant to the Chair. See Appendix B, the Literature Search Process Guidelines, of this document for recommended websites and procedures.

General Procedures

- 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, and evidence or reproducibility).
- The text of each section should present the studies regarded as most relevant and reliable to 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, etc.).
- Keep summaries of papers cited concise.
- If no studies are available for a major heading (e.g., Animal Studies, Human 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 discussed first, before any subheadings. Information in reviews relevant to subheading topics should be summarized there.
- Bibliographic references in the body of the *Documentation* should be presented as follows: …text. [Smith et al., 1999]. Do not use italics or bolding. Note, when the document is published, the references within the body of the document will be alphabetized by ACGIH® Staff.
- 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.

APPENDIX A

TLV® Documentation Outline

Section	Comments / 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.	Merck is a good reference for this. Also include common trade names.
Chemical Formula • Provide chemical equation. • Provide chemical structure on separate line, if appropriate.	Provided by ACGIH® Staff.
TLV®–TWA • List current TLV®–TWA expressed in appropriate units. • If particulate, describe appropriate form.	
TLV®–STEL • List value in appropriate units. • If no value assigned, do not list.	
TLV®–C • List value in appropriate units. • If no value assigned, do not list.	
Skin If no "Skin" notation assigned, do not list.	
Sensitizer (SEN) If no "Sensitizer" 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.	

APPENDIX A

Section	Comments / Common Boilerplate

TLV® Recommendation
• Focus only on study(s) 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 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. Adjustments 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).
  • SEN (see Annex D).
  • Skin (see Definition in the *TLVs® and BEIs®* book).
• Refer to BEI®, if available for substance.
	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 back up evidence supports the rationale.
	Some useful boilerplate language:
	• A TLV®–TWA of __ mg/m^3, measured as **inhalable particulate matter (or IFV, or 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 *acute irritation* associated with occupational exposure to _____.
	• Sufficient data were not available to recommend a **Skin** notation.
	• Sufficient data were not available to recommend a **SEN** notation.
	• Available data on sensitization from exposure to _____ warrants the addition of the **SEN** (sensitizer) notation.
	• _____ 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.	See TLV® Basis Table – Annex B. 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 there is no TLV® Basis, leave it blank. Do not use "other". • If a TLV® Basis is not on the current list of TLV® Basis, contact ACGIH® Staff. • Use Cancer as a TLV® Basis only if it drives the TLV® Basis. In this case, specify the type of cancer. Use "cancer" without a type in rare instances. • 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,	Log octanol/water partition coefficients (sometimes called log K o/w) should be included, if available. When there is more than one partition coefficient use

Section	Comments / Common Boilerplate

color, composition, contaminants, decomposition products, and known odor or taste 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: XXX.XX
  • Specific gravity: X.XXX at XX°C
  • Melting point: (Centigrade)
  • Boiling point: (Centigrade)
  • Vapor pressure: Use torr and specify temperature (Centigrade)
  • Saturated Vapor concentration: (especially for compounds which will have an IFV endnote)
  • Flash point: (Centigrade)
  • Flammable limits: lower and upper
  • Autoignition temperature: (Centigrade)
  • Solubility:
  • Conversion factors at 25°C and 760 torr: X ppm = XX.X mg/m^3, 1 mg/m^3 = X ppm
	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 o/w 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).
	
	List odor threshold, if available. Useful references include:
	
	AIHA: Odor Thresholds for Chemicals with Established Occupational Health Standards (1989).
	
	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.

APPENDIX A

Section	Comments / Common Boilerplate
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. • TSCA database – check for production volumes. • U.S. Geological Survey/Dept of Interior: http://minerals.usgs.gov/minerals/pubs/commodity/ List tonnage and year, e.g., date from Department of Commerce via internet.
Animal Studies This major heading and its subheadings describe the relevant *in vivo* and *in vitro* 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-Effect Levels (NOELs/NOAELs), Lowest-Observed-Effect Levels (LOELs/LO), and 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 LC_{50} value(s) or equivalent indicator(s) of toxicity. • Describe minimum lethal concentrations / doses (LC_{Lo}, LC_{50}) and any reported clinical signs. • If no lethality found, indicate full range of concentrations, clinical observations, and NOEL and effect-level concentrations. • If relevant, include particle size characterization or lack thereof. **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.);	For LD_{50} and LC_{50} studies, the results can usually be summarized in a single sentence such as: • The LC_{50} for substance XXX ranged from 588 to 1004 mg/m^3 in mice and rats with signs of wheezing and coughing.

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Section	Comments / Common Boilerplate
include assessment (classification) of toxic response (non-irritant, type of irritant — corrosive). • As available, incorporate minimum information noted above. • Describe LD_{50} value(s) or equivalent indicator(s) of toxicity. • Describe minimum lethal doses (LD_{Lo}, LC_{50}) and any reported clinical signs. • If no lethality found, indicate full range of doses, clinical observations, and NOEL and effect-level doses. **SENSITIZATION** Include species, doses, routes of administration, protocol used, ancillary information (adjuvant used, etc.), end results (dose-response; NOEL, ancillary skin irritation, skin and/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 RD_{50} studies (measures sensory irritation).	Schaper M (1993): Development of a database for sensory irritants and its use in establishing occupational exposure limits. Am Ind Hyg Assoc J 54(9):488–544.
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. • Give the strain and #s of animals if more than one similar study. • Report studies low to high dose. • Give LOEL/LOAEL, NOEL/NOAEL, if can. • Summarize by kind of study, species, route, dose, # applications, and results.
Animal Studies: **Chronic/Carcinogenicity (> 3 months ≤ animal lifetime)** • Same information as above, organized by route of exposure. • 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.).	The 2-year bioassay is considered the "gold standard."

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Animal Studies: **Genotoxicity** The results should be described briefly and may be useful in the selection of the carcinogenicity category. Therefore, the results of *in vitro* and *in vivo* studies should be described very briefly.	Example: Several genotoxicity studies have been reported but were generally negative. Positive findings were noted only in *in vitro* studies using the Ames test, forward mutation assays, and xx only with metabolic activation. Negative findings were found in other *in vitro* studies and *in vivo* studies using the micronuclei test in mice and chromosomal aberrations in rats.
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.	For most substances, this section does not drive the TLV® Basis, but may be used as a modifier of the TLV® Recommendation.

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Section	Comments / Common Boilerplate
Absorption, Distribution, Metabolism, and Excretion (Toxicokinetics) Describe the animal studies first followed by human studies within each section. • Absorption information may be available for oral, inhalation, and/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). • 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.	• 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., P_{450} (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. • Dose-response evaluations such as slope factors (for cancer) or model-based extrapolations of NOELs 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 epidemiological 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 is 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 of groups of people 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

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	analyses, air measurements, questionnaires, etc); 5. The analysis, if not obvious based on the description of results 6. 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 7. Other potential causes of the health effect 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®, those that indirectly contribute to our understanding of the critical effects. For non-key studies it is acceptable to 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.
TLV® Chronology • The purpose of this section is to describe only the historical and/or pending/actionable activities (dates) associated with the TLV® *Documentation*. It is not intended to describe the detailed history of actions completed on the *Documentation*. ACGIH® Staff completes this section. See example below: • Because the author knows exactly where inserts have been made, Staff would appreciate guidance in identifying the new section(s) and reference(s) when a *Documentation* is updated, but the TLV® remains the same. This precludes a word-for-word proofing of an updated *Documentation* against its original. The "Comments/Common Boilerplate" column at right provides examples. 19XX: *Proposed*: TLV®–TWA, XX ppm 19XX–present: TLV®–TWA, XX ppm 20XX: *Documentation* revised. Describes current *Documentation* revision efforts; use only when *Documentation* is revised but TLV® is not changed. 20XX: *Proposed:* TLV®–TWA, XX ppm, notation(s). If necessary, describe published (NIC) *Proposed*	Example statements to insert in historical section of TLV® *Documentation* when there are no changes to the TLV® or Notations: • _____ (cite year of change): TLV Basis update to *Documentation* _____ (cite year), retaining adopted TLV(s)® and notation(s)…see section (cite section), paragraph ____ (cite paragraph number)…cite additional sections/paragraphs as appropriate). ▪ Example: 2004: TLV® Basis update to *Documentation* 2001, retaining adopted TLV(s)® and notation(s) – see Summary; Animal Studies; and TLV® Recommendation. • _____ (cite year of change): Editorial clarification made to *Documentation* _____ (cite year), retaining adopted TLV(s)® and notations see section (cite section), paragraph ____ (cite paragraph number)…cite additional sections/paragraphs as appropriate). • _____ (cite year of change): New information and reference(s) added to *Documentation* _____ (cite year), retaining adopted TLV(s)® and notations; see section (cite section) and new reference # ____ (cite reference numbers). Cite additional

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Section	Comments / Common Boilerplate
TLV® values and associated notations that have not been adopted by ACGIH®.	sections/paragraphs/new references as appropriate). ▪ Example: 2004: New information and references added to *Documentation* 1996, retaining adopted TLV(s)® and notation(s) – see Animal Studies *Acute*, paragraphs two and four; Animal Studies Chronic/Carcinogenicity, paragraph one; Human Studies *Cancer*, paragraphs one, two, and six; new Human Studies *Reproduction* section; and new references 14,23, and 31. • _____ (cite year of change): New section(s) and reference(s) added to *Documentation* _____ (cite year), retaining adopted TLV(s)® and notations; see section (cite section) and new reference # ____ (cite reference numbers), cite additional sections/paragraphs/new references as appropriate. • _____ (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.

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References List in alphabetical order. Unlike the reference style of the past, use a modified MedLine style, e.g., all extraneous punctuation and capitalization are eliminated in journal citations (e.g., article titles are treated as a sentence).	**Journal Articles:** List all authors when there are four or less. If five or more, list the first three, followed by "et al." Davies CN: Dust sampling and lung disease. Br J Ind Med 9:120 (1952). Deskin R; Bursain SJ; Edens FW: The effect of chronic manganese administration on some neurochemical and physiological variables in neonatal rats. Gen Pharmacol 12:279–280 (1981). Wagner WD; Fraser DA; Wright PG; et al.: Experimental evaluation of the threshold limit of cristobalite — calcined diatomaceous earth. Am Ind Hyg Assoc J 29:211–221 (1968). **Online Citations:** U.S. National Library of Medicine: Substance name. In: Hazardous Substances Data Bank. Toxicology Data Network (TOXNET). Online at: http://toxnet.nlm.nih.gov/ Accessed: xx/xx/xx U.S. Environmental Protection Agency: Integrated Risk Information System (IRIS) Substance File: Substance name. U.S. EPA, Washington, DC (1996). Online at: http://www.epa.gov/iris/subst/0373.htm Accessed: xx/xx/xx U.S. National Toxicology Program: Substance name. In: Testing Information and Study Results, Results and Status. Online at: http://ntp-server.niehs.nih.gov/main_pages/NTP_ALL_STDY_PG.html Accessed: xx/xx/xx **Federal Agency Publications:** U.S. National Toxicology Program: Toxicology and Carcinogenesis Studies of Manganese (II) Sulfate Monohydrate (CAS No. 10034-96-5) in F344/N Rats and B6C3F1 Mice (Feed Studies) Technical Report No. 428. DHHS (NIH) Pub. No. 94-3159. NTP, Research Triangle Park, NC (1993). U.S. Agency for Toxic Substances and Disease Registry, Toxicological Profile for Manganese (Update). U.S. Department of Health and Human Services, ATSDR, Atlanta, GA (September 2000). *With Author(s)* Anderson HA; Dally KA; Hanrahan LP; et al.: The Epidemiology of Mobile Home Formaldehyde Vapor Concentration and Residents' Health Status. Pub. No. EPA-905/1-83-001. U.S. Environmental Protection Agency, Washington, DC (1983).

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Section	Comments / Common Boilerplate
	Books: *Sections/Chapters with Specific Author(s)* Beliles RP: The metals. In: Patty's Industrial Hygiene and Toxicology, 4th ed., Vol. 2C, Toxicology, pp. 2106–124. Clayton GD; Clayton FE (Eds.). John Wiley & Sons, New York (1994). Matanoski GM: Risk of cancer associated with occupational exposure in radiologists and other radiation workers. In: Cancer Achievements, Challenges, and Prospectives for the 1980s, Vol. 1, pp. 241–254. J.H. Burchenal JH (Ed.). Grune and Stratton, New York (1981). *With Editor(s) Only* Hathaway GJ; Proctor NH; Hughes JP (Eds.): Substance name. In: Proctor and Hughes' Chemical Hazards of the Workplace, 4th ed. Van Nostrand Reinhold, New York (1996). Lide DR; Frederikse HPR (Eds.): Substance name. In: Handbook of Chemistry and Physics, 77th ed. CRC Press, Boca Raton, FL (1996). **Proceedings:** Andersen I: Formaldehyde in the indoor environment — health implications and the setting of standards; and discussion. In: Indoor Climate: Effects on Human Comfort, Performance and Health in Residential, Commercial, and Light Industry Buildings, pp. 65–87. Fanger PO; Volbjorn O (Eds.). Proceedings of the First International Indoor Climate Symposium, Copenhagen, August 30–September 1, 1978. Danish Building Research Institute, Copenhagen (1979). Failing A; Knecht U; Woitowitz HJ: Biological monitoring of a standardized tetrahydrofuran exposure (in German). In: Proceedings of the 34th Meeting of the German Society of Occupational and Environmental Medicine in Wiesbaden, pp. 375-376. Kessel R (Ed.). Gentner Verlag, Stuttgart (1994). Boyle MJ: Tropic of Capricorn — assessing hot process conditions in northern Australia. In: Proceedings of 14th Annual Conference, pp. 54–57. Australian Institute of Occupational Hygienists, Adelaide (1995). Budd GM: Stress, strain and productivity in Australian wildfire suppression crews. In: Proceedings of the Society of American Foresters National Convention, San Francisco, pp. 119–123. SAF, Bethesda, MD

Section	Comments / Common Boilerplate
	(1991). Industrial Health Foundation: Proceedings of a Symposium on an Industry Approach to Chemical Risk Assessment: Caprolactam and Related Compounds as a Case Study. IHF, Arlington, VA (1984). **CD-ROMs:** U.S. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard: Occupational Exposure to Substance name. DHEW (NIOSH) Pub. No. Fill in the number from original reference; 19??. In: NIOSH Criteria Documents Plus CD-ROM. DHHS (NIOSH) Pub. No. 97-106; NTIS Pub. No. PB-502-082. National Technical Information Service, Springfield, VA (1997). Merck & Co., Inc.: Substance name. In: The Merck Index, 12th edition on CD-ROM, Version 12:1. S Budavari, M O'Neil, A Smith, et al., Eds. Chapman & Hall, New York (1996). Lewis Sr, RJ (Ed.): Hawley's Condensed Chemical Dictionary, 13th ed. In: Comprehensive Chemical Contaminants Series CD-ROM. Van Nostrand Reinhold, New York (1997).

Selecting an Appropriate TLV®

1. Decide critical health effects – those that occur at the lowest exposure levels and will drive the TLV® number.
2. Decide which type of TLV® (TWA, STEL, C) is warranted.
   a. Review definitions to select the appropriate form of a TLV®.
   b. 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. Although calculating the average concentration for a workweek, rather than a workday, may be appropriate in some instances, ACGIH® does not offer guidance regarding such exposures.
      - **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 of time 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 will not

necessarily protect against these effects if the daily TLV®–TWA is exceeded. The TLV®–STEL usually supplements the TLV®–TWA where there are recognized acute effects from a substance whose toxic effects are primarily of a chronic nature; 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 of time sufficient to detect exposures at or above the ceiling value.

c. Some substances may fit into more than one category.
d. In exceptional cases, other schemes may be chosen, if clearly described and supported in the *Documentation*.

3. Decide the value of the TLVs®
   a. 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.
   b. Describe the relationship of recommended TLV® to known human or animal toxicity responses.
   c. Describe how the TLV® reflects uncertainties in the available data. If the uncertainty in the available data is high, so state. Using professional judgment, adjust the TLV® to reflect an appropriate degree of conservatism.
   d. 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.
      - If route-to-route conversion factors are used, be explicit/transparent.
      - See Annex C for conversion guides.
4. Consider whether the substance may occur or be generated in the form of an aerosol.
   a. If so, it may be necessary to develop a TLV® for an aerosol form in addition to the vapor form.
      - It may be necessary to determine separate TLVs® for these two forms.
      - If the TLV® number is the same for both forms, then a designation of both vapor and aerosol must be made.
   b. If the TLV® may refer to an aerosol, one of the three 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

   c. Exposure data that include particle size distributions may be useful in helping identify the PSS.
5. Identify appropriate notations and explain reasoning for their selection

a. Carcinogenicity designation (see Appendix A in the *TLVs® and BEIs®* book)
b. SEN (see Definition in *TLVs® and BEIs®* book)
c. Skin (see Definition in *TLVs® and BEIs®* book)

6. Author should insert the boilerplate language if and when particular TLV® forms are not recommended or certain notations are not assigned. ACGIH® Staff will insert, if missing. See TLV® *Documentation* Outline above for recommended boilerplate.

APPENDIX A:

Annex A

TLV® Documentation Template

This *Documentation* is in DRAFT format, and its content is subject to change. We are providing it as such because we believe it is important to provide access as early as practical to the data and technical information cited herein which are the basis for the proposed TLV(s)®, BEI(s)®, and related notations.

(Note: Header should be on every page.)

CHEMICAL NAME

CAS number:

Synonyms:

Molecular formula:

Chemical structure:

TLV®–TWA,

TLV®–STEL,

TLV®–Ceiling,

Skin

Sensitizer (SEN)

Carcinogenicity Classification

TLV® Recommendation

A TLV®–TWA® of XX mg/m^3, measured as inhalable particulate matter (or IFV, or R, T), is recommended for occupational exposure to XXXX.

If there is a BEI® state: XXXX is a substance for which *Biological Exposure Indices* (BEIs®) have been recommended (see BEI® *Documentation* for XXXX).

If there are no other notations recommended state: Sufficient data were not available to recommend a TLV®–STEL. Sufficient data were not available to recommend a Skin or SEN notation.

TLV® Basis

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Chemical and Physical Properties

Molecular weight:
Specific gravity:
Melting point: °C
Boiling point: °C
Vapor pressure: °C
Saturated vapor concentration:
Flash point: °C
Flammable limits:
Autoignition temperature: °C
Solubility:
Octanol/water partition coefficients:
Conversion factors at 25°C and 760 torr:

Major Sources of Occupational Exposure

Animal Studies

Acute/Subacute

ORAL

DERMAL

INHALATION

SENSITIZATION

OTHER STUDIES

Subchronic

Chronic/Carcinogenicity

Genotoxicity

Reproductive/Developmental Toxicity

APPENDIX A:
Annex A

Absorption, Distribution, Metabolism, and Excretion

Human Studies

TLV® Chronology

References

APPENDIX A:

Annex B

TLV® Basis Table

Terms used as the TLV® Basis with abbreviations (last updated October, 2006).

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

APPENDIX A:

Annex B

Group	Effect Name	Abbreviation (if necessary)
	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
	Porphyrin effects	Porphyrin
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
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
	Dermatitis	Dermatitis
	Skin damage	Skin dam
	Skin irritation	Skin irr

APPENDIX A:

Annex B

Group	Effect Name	Abbreviation (if necessary)
	Skin photosensitization Skin sensitization	Skin photosen Skin sens
Teeth	Dental erosion Dental fluorosis	Dental erosion Dental fluorosis
Bones	Bone damage Fluorosis	Bone dam Fluorosis
Thyroid	Thyroid effect	Thyroid
Liver	Hepatic necrosis Liver damage	Hepatic necrosis Liver dam
Spleen	Spleen damage	Spleen dam
Kidney/Urinary tract	Bladder irritation Glomerular damage Kidney damage Kidney irritation Tubular damage	Bladder irr Glomerular dam Kidney dam Kidney irr Tubular dam
Embryo or fetus	Embryo/fetal damage Teratogenic effect	Embryo/fetal dam Teratogenic
Genetic effects	Mutagenic effect	Mutagenic

Alphabetical Listing

Alopecia
Anemia
Anosmia
Argyria
Asthma
Auditory nerve impairment
Autonomic nervous system impairment
Berylliosis
Beryllium sensitization
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

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Dental erosion
Dental fluorosis
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
Hematologic effects
Hemolysis
Hemosiderosis
Hepatic necrosis
Hypoxia/Cyanosis
Immune system impairment
Increased platelet count
Inflammation
Inhibition of heme synthesis
Kidney cancer
Kidney damage
Kidney irritation
Larynx cancer
Larynx metaplasia
Leucopenia
Leukemia
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

APPENDIX A:

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Peripheral neuropathy
Peripheral nervous system impairment
Pneumoconiosis
Pneumonitis
Porphyrin 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
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

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

ACGIH® TLV®-CS COMMITTEE: GUIDE #1
CONVERSION FROM ANIMAL DIETARY PPM TO ANIMAL MG/KG/DAY

Assuming that a *diet* contains 25 ppm of a particular chemical substance (CS): this is equivalent to 25 mg per 1 kg diet (or ingestion of 25 mg per 1 kg diet)

Mouse: body weight is approximately 30 g; mouse consumes -2.0 g diet per day

Rat: body weight is approximately 350 g; rat consumes -20 g diet per day

Dog: body weight is approximately 10 kg; dog consumes -300 g diet per day

Monkey: body weight is approximately 3.5 kg; monkey consumes -100 g diet per day

General Equation

$$\frac{\text{Concentration of chemical substance in diet} \times \text{Amount of diet consumed per day}}{\text{Body weight}}$$

Units

$$\frac{\text{mg/kg} \times \text{kg/day}}{\text{kg}} \quad \text{or} \quad \textbf{mg/kg/day}$$

Examples:

Mouse	$\frac{[25 \text{ mg CS} / 1 \text{ kg diet}] \times 0.002 \text{ kg diet/day}}{0.025 \text{ kg body weight}}$	2.0 mg/kg/day
Rat	$\frac{[25 \text{ mg CS} / 1 \text{ kg diet}] \times 0.02 \text{ kg diet/day}}{0.333 \text{ kg body weight}}$	1.5 mg/kg/day
Dog	$\frac{[25 \text{ mg CS} / 1 \text{ kg diet}] \times 0.3 \text{ kg diet/day}}{10 \text{ kg body weight}}$	0.75 mg/kg/day
Monkey	$\frac{[25 \text{ mg CS} / 1 \text{ kg diet}] \times 0.1 \text{ kg diet/day}}{3.5 \text{ body weight}}$	0.70 mg/kg/day

Some Convenient Rules of Thumb:

Mouse or Rat: use dietary concentration of CS in ppm and divide by 10.

Dog or Monkey: use dietary concentration of CS in ppm and divide by 40.

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ACGIH® TLV®-CS COMMITTEE: GUIDE #2 CONVERSION FROM ANIMAL DIETARY PPM TO ANIMAL INHALATION EXPOSURE

Assuming that a diet contains 5.0 ppm of a particular chemical substance (CS): this is equivalent to 5.0 mg per 1 kg diet (or ingestion of 5.0 mg per 1 kg diet)

SCALING FACTORS:

Species	**Size*** (gms)	**Respiratory Rate** (breaths/min)	**Tidal Volume** (mL/breath)	**Food Consumption**** (gms)
Human	70,000	12–17	750–1000	700
Dog	10,000	20	200	175
Monkey	3,000	40	21	75
Guinea Pig	500	90	2	20
Rat	350	160	1.4	15
Mouse	30	180	0.25	3

*Size: 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)

**Food Consumption (grams): $0.234 \times M^{0.72}$ where M in grams (Calder, 1996)

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

Concentration of chemical substance in diet × Amount of diet consumed per day

Units: mg/kg × kg/day = **mg/day**

Example: Rat [5.0 mg CS / 1 kg diet] × 0.015 kg diet/day = 0.075 mg/day

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

Respiratory Rate × Tidal Volume × Length of Exposure

Units: br/min × mL/br × min = **mL (or can convert to m^3)**

Example: (assume rat exposure for 6 hrs, = 360 min)
Rat 160 br/min × 1.4 mL/br × 360 min= 80,640 mL (~80 L) = 0.08 m^3 inhaled air

Step 3: What is the "equivalent" airborne concentration of this CS?

0.075 mg/0.08 m^3 = 0.94 mg/m^3

Thus, the rat that eats a diet with 5.0 ppm of a CS per day receives the same "dose" as the rat that inhales 0.94 mg/m^3 of the CS over a 6-hour exposure period.

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ACGIH® TLV®-CS COMMITTEE: GUIDE #3
CONVERSION FROM ANIMAL DIETARY PPM TO MAN INHALATION EXPOSURE

Assuming that a diet contains 5.0 ppm of a particular chemical substance (CS): this is equivalent to 5.0 mg per 1 kg diet (or ingestion of 5.0 mg per 1 kg diet)

SCALING FACTORS:

Species	**Size*** (gms)	**Respiratory Rate** (breaths/min)	**Tidal Volume** (mL/breath)	**Food Consumption**** (gms)
Human	70,000	12–17	750–1000	700
Dog	10,000	20	200	175
Monkey	3,000	40	21	75
Guinea Pig	500	90	2	20
Rat	350	160	1.4	15
Mouse	30	180	0.25	3

*Size: 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)

**Food Consumption (grams): $0.234 \times M^{0.72}$ where M in grams (Calder, 1996)

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

Concentration of chemical substance in diet × Amount of diet consumed per day

Units: mg/kg × kg/day = **mg (each day)**

Example: Rat [5.0 mg CS / 1 kg diet] × 0.015 kg diet/day = 0.075 mg (each day)

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

Mass of CS ingested by rat (from Step 1) – Body weight of rat

Units: mg ÷ kg = mg/kg (each day)

Example: Rat 0.075 mg ÷ 0.35 kg = 0.21 mg/kg (each day)

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

[Mass of CS per Mass of Rat (from Step 2)] × Mass of Man

Units: mg/kg × kg = **mg (each day)**

Example: Man 0.21 mg/kg × 70 kg = 15 mg (each day)

Step 4: What is the "equivalent" airborne concentration of this CS in man?

15 mg/10 m^3 = 1.5 mg/m^3

Thus, the man who inhales 1.5 mg/m^3 of the CS over an 8-hour workshift (inhales ~10 m^3) receives the same "dose" as the rat that eats a diet with 5.0 ppm of a CS each day.

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Sensitization

(Note: See the glossary starting on page 13 for terminology definitions.)

Introduction

This document is intended to provide guidance to authors on assigning "SEN" notations. Dermal and respiratory sensitization are complex toxicological endpoints and evaluation of the myriad of potential human and animal study designs and diversity of available data requires 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, “SEN”, in the “Notations” column in the *TLVs® and BEIs®* book refers to the potential for an agent to produce sensitization, as confirmed by human or animal data. The SEN notation does 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 SEN notation does not signify that the agent lacks the ability to produce sensitization but may reflect the paucity or inconclusiveness of scientific evidence.

Sensitization often occurs via an immunologic mechanism and should not to be confused with 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

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., FEV_1, 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 his/her 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, with respect to 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.

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Dermal Sensitization

Two areas of evidence are sufficient alone to support a designation of SEN notation. Human evidence, as described in the following section, is the primary and strongest criteria. Animal evidence alone can also support a designation of SEN 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 as supportive in nature, 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 ≥30% is considered positive. For a non-adjuvant test method, such as the Buehler test (Buehler, 1965), a response of ≥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.

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The following information may be considered as supportive in nature, 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 (Q)SAR 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.

Other Considerations

Due to the fact that some available studies do not conform to standard protocols and results are often equivocal, a significant amount of professional judgment is required to properly assign a SEN notation. In some cases, only a small number of subjects or test animals show positive evidence of a sensitization response. Generally, the SEN notation should not be applied if the number of responders does not lead to the classification of an agent as a sensitizer for labeling purposes. However, if a series of different animal tests show evidence of sensitization but not sufficient to label the agent as such, combined with some evidence of sensitization in humans, a collective assessment of the available data may still support use of a SEN notation.

Tests involving subjective measures of response (e.g., rating the level of redness) can be confounded by non-specific irritant response if the studies are not performed properly or do not use adequate controls. The overall weight-of-evidence and quality of the available dataset must be taken into account when deciding if a SEN notation is appropriate.

The SEN notation is reserved for agents that have clear evidence of the potential to cause respiratory or dermal sensitization. Respiratory hypersensitivity is an immediate Type I, IgE-mediated immune response involving B-lymphocytes. Dermal sensitization leading to allergic contact dermatitis is usually a cell-mediated Type IV sensitization response that involves T-lymphocytes. Dermatitis and other skin lesions that do not involve a

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Type IV cell-mediated immune mechanism are not sufficient, on their own, to merit a SEN notation. There are other forms of T-cell mediated sensitization reactions (e.g., beryllium sensitization). The SEN notation is not intended to include agents that cause non-specific (i.e., non-immune related) airway hyperreactivity as in reactive airway dysfunction syndrome (RADS). This medical condition can result following brief exposures to highly irritating or corrosive substances and does not involve a specific immune response.

The SEN notation is not used to indicate agents that produce systemic effects other than sensitization in a subset of the worker population that may be considered "sensitive" or "susceptible" individuals. This is addressed by considering inter-individual variability when setting the TLV®.

Grid

		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**

Standard terminology to use in the Documentation

A, B, F, G
A sensitizer notation is assigned based upon both the reported sensitization in humans and 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 CS should be "flagged" as sensitizers.

C, D, E
A sensitizer notation is assigned based upon the positive response in animals alone.
Rationale: For these CS, the animal studies were 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 sensitizers to protect workers.

K, P, U
A sensitizer notation is assigned based upon the reported sensitization in humans alone.
Rationale: For these CS, 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 CS should be "flagged" as sensitizers since the data directly pertain to human exposures and no extrapolation is needed.

H, I, L, Q

A sensitizer notation is not proposed at this time based upon weak or equivocal responses in human and/or animals.
Rationale: For these CS, there are questions surrounding the human reports and/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 CS as sensitizers.

M, N, R, S
A sensitizer notation is not proposed based upon the lack of sensitization 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 clearly inappropriate to "flag" such CS as sensitizers.

J, O, T, V, W, X, Y
A sensitizer notation is not proposed based upon inadequate data in humans and/or animals.
Rationale: For these CS, there are many questions surrounding the human reports and animal studies. Data are missing. In this instance, it is clearly inappropriate to "flag" such CS as sensitizers.

Examples of sensitizers

Respiratory*

An example of a chemical that should clearly have a SEN 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, FEV_1 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 a SEN 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

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An example of a chemical that should clearly have a SEN 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 10 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 SEN 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 cause "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.

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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.

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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 (EC_3) in the auricular lymph nodes, a measure of induction, compared to controls following topical application to mouse ears. See 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 vehicle alone is applied to the contralateral ear. Mice are considered positive responders if the challenged ear thickness is ≥120% that of the contralateral control ear thickness. Results can also be reported as group mean relative thickness of challenged ears. See 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.

APPENDIX B

Literature Search Process Guidelines

General Literature Searching Steps

Beginning a Literature Search

This section outlines how to begin a literature search for a substance, including information on search terms, core references, and useful databases.

- Refer to the Literature Searching Process Diagram in Section 2 for details concerning the literature searching process.
- The core reference list included in Annex A should be completed for each chemical substance assignment. The websites listed can all be accessed free of charge through the internet.
- The first step in the process is to pick the search terms. Picking out the right search terms can help eliminate irrelevant hits.
    - It is generally best to search by the substance's Chemical Abstract Service number (CAS #). Searching by CAS # tends to narrow the search more than searching on the name of the substance, which may be a component of many other substance names and therefore return more "hits". However, searching by CAS # is not always feasible, particularly with D&I substances.
    - Searching may result in hundreds, and in some cases thousands, of hits for some substances. In this circumstance it's useful to narrow the search parameters. For example, include a date range or add additional search terms such as "effect", "health effect", "toxic effect", "toxic", "adverse", "exposure", "health hazards", etc.
    - Use Boolean operators. Boolean operators are the words AND, OR, and NOT. They can be used to refine the search term to focus on applicable records.
        - AND: Using AND between search words returns only those records that contain the words on either side of the AND.
        - OR: Using OR between search words returns records that contain either or both of the words. It is used to broaden a search.
        - NOT: This operator narrows a search by excluding records containing the word that follows "NOT".
    - Most online database search engines will accept Boolean operators. It's a good practice to always capitalize the operators since some databases will only accept them in uppercase format. Boolean operators can be strung together to be more effective. However, use care when doing this to avoid eliminating relevant hits. For example, the search term "manganese AND toxicity" will leave out many epidemiology studies. A better term would be "manganese AND (toxicity OR epidemiology).
- It is also useful to check if the substance has been reviewed and published by other occupational exposure limit (OEL)-setting organizations, governmental (e.g., ATSDR) and non-governmental agencies/authors (e.g., academic reviews). Their reference lists could be useful for comparison purposes. Annex B contains a list of links to other occupational exposure limit (OEL)-setting websites.

- There are many sources not listed in the Core Reference list that may also be useful, depending on the substance under review. Annex C contains a list of several of these sources. Some are not available in electronic format.
- **PubMed/MEDLINE vs. TOXLINE (or Both)**
  - ***PubMed/MEDLINE***
    - MEDLINE is a product of the National Library of Medicine (NLM) and focuses on citations from biomedical journals. PubMed is also sponsored by the NLM, but is somewhat broader in scope, including pre-MEDLINE citations (citations dating back to the 1950s), as well as some biomedical journals not listed in MEDLINE. New citations are also more likely to show up in PubMed before MEDLINE because PubMed uses a different indexing system. It is therefore preferable to use PubMed rather than MEDLINE.
    - A potential drawback of using either PubMed or MEDLINE is they both contain only journal citations.
  - ***TOXNET/TOXLINE***
    - TOXNET is another National Library of Medicine (NLM) website. TOXNET is actually not one database, but a website that hosts a number of databases that focus on topics in toxicology and hazardous substances. TOXLINE is one of those databases and can be accessed through the TOXNET website. TOXLINE is available in 2 formats: TOXLINE Core and TOXLINE Special. TOXLINE Core is a component of PubMed narrowed down to toxicology subjects. TOXLINE Special contains TOXLINE Core but also includes information from sources not included in PubMed/MEDLINE (see the following paragraph).
    - TOXLINE is narrower in scope than PubMed/MEDLINE, focusing primarily on the biochemical, pharmacological, physiological, and toxicological effects of drugs and chemicals. Epidemiology studies may not be picked up in TOXLINE searches. However, TOXLINE Special does contain information from sources not included in PubMed/MEDLINE, such as Toxic Substances Control Act Submissions (TSCATS) (unpublished reports), NIOSH Health Hazard Evaluations (HHE), books, and others sources.
  - ***The decision whether to use PubMed/MEDLINE or Toxline depends therefore on the substance as well as the type of information the author is looking for. Often it is useful to search both databases (particularly if the number of hits returned is manageable).***
- **Finding Chemical and Physical Properties**
  - ACGIH® Staff has taken on the responsibility of finding the chemical and physical properties for the substances covered under the *Documentation.* However, there are many free online databases that provide a wealth of information in this area if the author chooses to look for this information. Chemfinder (produced by CambridgeSoft Corporation) is one of the most comprehensive. Annex D contains a table listing some of these sources.

Narrowing Down the Search Results

This section provides tips on how to narrow the search results down to those that are applicable to writing TLV® *Documentation*.

- Once the search terms have been selected and the search conducted using them, the next step is to review the article titles, eliminating those that are obviously not applicable.
- Review abstracts from the remaining list and select those citations that are useful for establishing a TLV®. This can be the most difficult part and is the responsibility of the author(s), relying heavily on experience and professional judgment.

Acquiring References

Once the initial literature search has been completed, the next step is to obtain copies of the references.

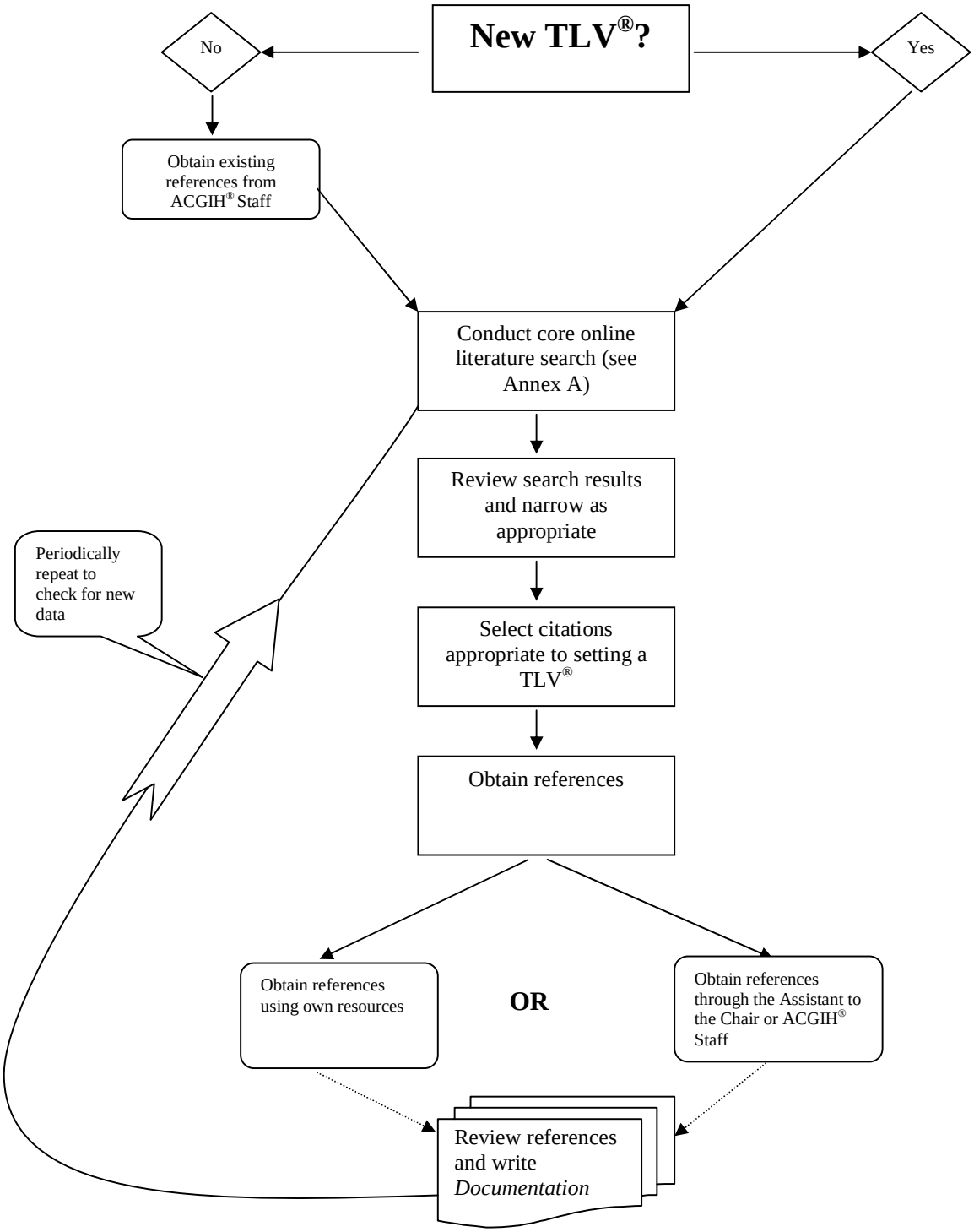
- Many journals are available online in electronic format. First check to see if they are available for free. Many online journals also offer access to their current issue for free, even if other issues have a cost. Most online journals charge for access to their articles. Additionally, many online journals don't have older volumes available in electronic format.
- If an article is not available for free, it can be acquired through the library systems of most major universities, or through the TLV®-CS Assistant to the Chair. To obtain copies of citations through the Assistant to the Chair, submit a request along with the complete citation.
- Toxic Substances Control Act Test Submissions (TSCATS) unpublished studies can be obtained on microfiche for ~$25.00 or on CD-Rom for ~$150.00 through the National Technical Information Service (NTIS). If purchased, the Assistant to the Chair can print microfiche documents from a fiche viewer and scan them into PDF format for the author. Sometimes these studies can be obtained for free through other sources. The author should provide the Assistant to the Chair or ACGIH® Staff the reference information. This information should include the name of the company that completed the study (e.g., Bayer, DuPont, Kodak). Refer to the Literature Search section in this Operations Manual for guidance on using unpublished studies.

Reviewing References – Ongoing Process

- It is often useful to keep track of the review status of articles. A spreadsheet can provide a useful summary format for the key points of each article. Some have also found it helpful to create a word processing file for each abstract and to annotate comments regarding the article in the document.
- It is also useful to review the reference lists within the articles. Article reference lists often contain additional citations that for one reason or another don't show up on the database searches.
- Literature search requests conducted by the TLV®-CS Assistant to the Chair are saved to an account, which receives weekly updates on any new studies.
- Finally, the literature process should be recurrent throughout the course of writing *Documentation*, particularly if the discussion process takes a long time. The author should periodically conduct a search for additional relevant data. The Assistant to the Chair will conduct a literature search for draft NIC *Documentation* every July.

APPENDIX B

Literature Searching Process Diagram



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Annex A

Core References

The websites outlined in the following table should be searched during every literature search.

Core Online Search Sites		
Online Site & URL	**Description of Site**	**Checked**
PubMed/MEDLINE http://www.ncbi.nlm.nih.gov/entrez/query.fcgi	➢ Sponsored by the National Library of Medicine (NLM). ➢ Contains MEDLINE (articles from 1966 to present), as well as out-of-scope citations, journal citations pre-dating Medline indexing, and additional full text life science journals. ➢ Contains many full text links; most require a subscription. ➢ Can access OLDMEDLINE (pre-1966) citations by selecting "limits", and then "OLDMEDLINE pre-1966) subset. Limitations of OLDMEDLINE: Does not work well with CAS #'s, no abstracts, missing data.	
OR		
TOXLINE Special http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE	➢ TOXLINE (Toxicology Literature Online) Special: Broad range of literature citations pertaining to biochemical, pharmacological, physiological and toxicological effects of drugs and other substances. Also contains information from other sources, including citations for unpublished TSCATS submissions.	
TOXNET (Other than TOXLINE) http://toxnet.nlm.nih.gov	➢ Sponsored by the National Library of Medicine (NLM). ➢ Contains databases related to toxicology & environmental health.	
• ChemIDplus	• ChemIDplus: Dictionary of over 370,000 chemicals (names, synonyms, and structures). o Includes links to NLM and other databases and resources, such as EINECS, Haz-Map, PubMed, EPA TRIs, ATSDR, NTP, as well as NIOSH and OSHA. This site also contains SRC CHEMFATE which has links to TSCATS info. o The Superlist Locator found within this site contains info such as IARC, HPV, S302's, CAA1 and much more. o These links are only available if it applies to the chemical.	
• HSDB	• HSDB (Hazardous Substance Data Bank): Access through TOXNET. Information on human and animal toxicity of numerous substances. Peer-reviewed by a scientific review panel. Also contains NTP Repository information.	
• IRIS	• IRIS (Integrated Risk Information System):	

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	Data from the EPA. Focuses on hazard identification & connection between dose & response.	
• CCRIS	• CCRIS (Chemical Carcinogenesis Research): Access through TOXNET. Developed and maintained by the National Cancer Institute (NCI). Contains information on carcinogenicity, mutagenicity, tumor promotion, and tumor inhibition. Test results reviewed by experts in carcinogenesis and mutagenesis.	
• GENE-TOX	• GENE-TOX (Genetic Toxicology): Access through TOXNET. Created by U.S. EPA. Contains mutagenicity test data. Peer-reviewed.	
• DART/ETIC	• DART/ETIC (Developmental and Reproductive Toxicology and Environmental Teratology Information Center): Contains information on developmental and reproductive toxicology.	
IARC Monographs http://monographs.iarc.fr/	➢ International Agency for Research on Cancer. ➢ Part of the World Health Organization (WHO). Contain assessments of carcinogenic risks.	
NTP Testing Information 1. NTP Testing Information and Study Results http://ntp.niehs.nih.gov/index.cfm?objectid=72016715-BDB7-CEBA-F4CF107673CF0C15 2. 10th Report on Carcinogens http://ehp.niehs.nih.gov/roc/ 3. NTP Study Reports http://ehp.niehs.nih.gov/ntp/docs/ntp.html	➢ National Toxicology Program • NTP study results. • Prepared by the NTP with intent of identifying substances that cause/may cause cancer and to which a significant population is exposed. • Study reports online or referenced where they can be obtained.	
ATSDR Toxicological Profiles http://www.atsdr.cdc.gov/toxpro2.html	➢ Toxicological profiles for hazardous substances found at NPL sites.	

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Global OEL Links

The following references may be useful in a literature search:

Global OEL Links	
Online Site & URL	**Description**
OSHA PELs • http://www.osha.gov/SLTC/pel/ • http://www.osha.gov/html/a-z-index.html	➢ U. S. Occupational Safety and Health Administration Permissible Exposure Limits ➢ Statutory limits for the United States
ESIS • http://ecb.jrc.it/esis	➢ European chemical Substance Information System ➢ Sponsored by the European Chemicals Bureau of the European Union ➢ Contains information regarding the following: • EINECS (European Inventory of Existing Commercial Substances) • HPVs (High Production Volume Chemicals) • LPVs (Low Production Volume Chemicals) • Classification and Labeling (Risk and safety phrases) • IUCLID Chemical Data Sheets
European Agency for Safety and Health at Work • http://osha.europa.eu/en	➢ General information on the derivation/use of OELs in the European Union, as well as links to member country websites. NOTE: Not all links are in English.
European Union OELs • http://europa.eu.int/comm/employment_social/health_safety/docs_en.htm#pub4 • http://europa.eu.int/comm/employment_social/health_safety/docs/oels_en.pdf	➢ Contains a list of legally binding OELs in place within the EU.
SCOEL Criteria Documents • http://europa.eu.int/comm/employment_social/health_safety/docs_en.htm#pub4	➢ Scientific Committee for Occupational Exposure Limits ➢ This committee is part of the OEL process for the EU. It prepares criteria documents that recommend an OEL based upon the available science for the substance. SCOEL recommendations are not legally binding – the recommendations are forwarded to other agencies to determine feasibility and adoption. ➢ SCOEL criteria documents can be accessed through the European Union OEL website.
DECOS • http://www.gr.nl/adviezen.php	➢ Dutch Expert Committee on Occupational Standards ➢ DECOS determines health-based occupational exposure limits. These limits are not legally binding (Government determines feasibility, etc.)
National Occupational Health and Safety Commission (Australia) • http://www.nohsc.gov.au/OHSInformation/Databases/ExposureStandards/expsearch.asp	➢ Contains the Australian National Exposure Standards Database.
AIHA WEEL Guides http://www.aiha.org/content/insideaiha/volunteer+groups/weelcomm.htm	➢ American Industrial Hygiene Association Workplace Environmental Exposure Levels

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Global OEL Links	
Online Site & URL	**Description**
Nordic Expert Group (NEG) http://www.nordicexpertgroup.org/	➢ Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. ➢ Consists of scientists from Denmark, Finland, Iceland, Norway and Sweden, representing the disciplines of toxicology, occupational hygiene, and occupational medicine. ➢ Mission is to produce criteria documents to be used as the scientific basis for setting chemical exposure standards for the 5 countries. ➢ Documents are available for a fee from the group's website. Many can also be found for free as .pdf files by using a search engine and searching on the substance name, as well as NEG.

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Annex C

Other Reference Sources

The following references may be useful in a literature search:

Other References Sources	
Online Site & URL	**Description**
Kirk-Othmer Encyclopedia of Chemical Technology (John Wiley and Sons)	• Broad scope of topics related to chemical science, including analytical methods, chemistry, health effects, toxicology data, and uses. • Online and print formats available. Online versions require subscription access. • Subscription access available through the University of Minnesota Library system
NLM Gateway – Old Medline (pre-1970s) http://gateway.nlm.nih.gov/gw/Cmd	• Can be used to search Old Medline (pre-1970s citations) • Can be used to search BOTH PubMed and Toxline Special simultaneously, but is less user friendly than the PubMed and Toxline Special sites themselves. • Limitations: No abstracts, missing data, does not work well with CAS numbers.
IARC Cancer Databases http://www.iarc.fr/ENG/Databases/index.php	• In addition to the IARC monographs noted in the Core Reference table, the IARC website hosts the following databases: • IARC Cancer Epidemiology Database • IARC TP53 Database • EPIC – European Prospective Investigation into Cancer and Nutrition • Genetic Epidemiology Database
High Production Volume (HPV) Chemicals and Screening Information Data Set (SIDS) Testing 1. HPV (U.S.) Lists: • http://cfpub.epa.gov/hpv-s/ 2. SIDS (International): • http://cs3-hq.oecd.org/scripts/hpv/ OR • http://www.inchem.org/pages/sids.html	• Dossiers and robust summaries and dossiers are available for many high production volume chemicals
NIOSH 1. NIOSH Criteria Documents • http://www.cdc.gov/niosh/critdoc2.html	• National Institute for Occupational Safety and Health • Developed to provide basis for development of comprehensive occupational health standards.
2. NIOSH Health Hazard Evaluations • http://www.cdc.gov/niosh/hhe/	• Reports of investigations of potential workplace health hazards conducted by NIOSH.
ILO 1. International Hazard Datasheets on Occupations • http://www.ilo.org/public/english/protection/safework/cis/products/hdo/htmold/idhindex.htm	• International Labour Organization • Produced by ILO • Contains information on the hazards and risks of a number of occupations

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2. Encyclopedia of Occupational Health and Safety, 4th Edition (1998) • http://www.ilocis.org/en/default.html	• Produced by ILO • Provides an overview of multiple health and safety issues and topics.

IPCS Inchem
• http://www.inchem.org/
	• Chemical Safety Information from Intergovernmental Organizations
	• Produced by International Program on Chemical Safety (IPCS) and the Canadian Centre for Occupational Health and Safety (CCOHS)
	• Contains:
	  • Concise International Chemical Assessment Documents (CICADs)
	  • Environmental Health Criteria (EHC) Monographs
	  • Health and Safety Guides (HSGs)
	  • IARC Summaries and Evaluations
	  • International Chemical Safety Cards (ICSCs)
	  • Screening Information Data Sets (SIDS) for High Production Volume Chemicals

BOOKS ***(Some available online or by other electronic formats)***
CRC Handbook of Chemistry and Physics, CRC Press, Boca Raton, FL.
Clinical Toxicology of Commercial Products, Williams and Wilkins.
Ethel Browning's Toxicity and Metabolism of Industrial Solvents, Elsevier Health Sciences.
Grant's Toxicology of the Eye, Charles C Thomas Pub Ltd.
Hazardous Chemicals Desk Reference, Van Nostrand Reinhold Company.
Hawley's Condensed Chemical Dictionary, John Wiley and Sons.
Kirk-Othmer Encyclopedia of Chemical Technology, John Wiley and Sons
The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, CRC Press.
Patty's Industrial Hygiene *and* Patty's Toxicology, John Wiley and Sons
Sax's Dangerous Properties of Industrial Materials, Wiley-Interscience.
Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens, Noyes Publications.
Ullmann's Encyclopedia of Industrial Chemistry, John Wiley and Sons.

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Annex D

Finding Chemical and Physical Properties

Chemical and physical property links:

Website	Link
ATSDR Toxicological Profiles	***http://www.atsdr.cdc.gov/toxpro2.html***
MERCK Index Online	***http://library.dialog.com/bluesheets/html/bl0304.html***
ChemFinder	***http://chemfinder.cambridgesoft.com/***
Hazardous Substances Data Bank (HSDB)	***http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB***
International Chemical Safety Cards (ICSC)	***http://www.inchem.org/pages/icsc.html***
KOW Online Log P(octanol/water partition coefficient) database	***http://www.syrres.com/esc/est_kowdemo.htm***
New Jersey Hazardous Substances Fact Sheets	***http://web.doh.state.nj.us/rtkhsfs/indexfs.aspx?lan=english***
NIOSH Pocket Guide to Chemical Hazards	***http://www.cdc.gov/niosh/npg/npg.html***
NIST Chemistry WebBook	***http://webbook.nist.gov/***
SRC PHYSPROP Physical Properties Database	***http://www.syrres.com/esc/physdemo.htm***

APPENDIX C

Committee Organization Chart