



ACGIH®

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Defining the Science of Occupational and Environmental Health®

OPERATIONS MANUAL

**THRESHOLD LIMIT VALUES (TLV®) FOR CHEMICAL SUBSTANCES
COMMITTEE**

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OPERATIONS MANUAL

THRESHOLD LIMIT VALUES (TLV®) FOR CHEMICAL SUBSTANCES COMMITTEE

Committee Mission

The Threshold Limit Value for 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 with support from *in vitro* 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
- Well-supported (i.e., TLVs® are based on ACGIH®'s review of peer-reviewed scientific literature and robust data summaries)
- Scientifically valid
- Reliable
- Understandable and clear
- Produced with a balanced, unbiased and clearly-defined process, free of conflicts of interest

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

The Committee will consist of individuals representing the disciplines necessary for establishing TLVs® (e.g., industrial hygiene, occupational medicine, occupational epidemiology, and toxicology). A range of professional affiliations is necessary to ensure a balance of disciplines; however, the Committee will consist of a simple majority of members professionally affiliated with academia or government. Committee members serve in their individual capacity and do not serve as representatives of their organization or employer. Each member of the Committee will have full voting rights for the purposes of the business of the Committee. Committee leadership (Committee Chair and Vice-Chair) must be Voting Members of ACGIH. A Voting Member of ACGIH shall be a professional who currently spends greater than 50% of his or her employment in the field of Occupational and Environmental Health and Safety, a professional who has retired from employment that involved greater than 50% of his or her time in the field of Occupational and Environmental Health and Safety, or a full-time student officially matriculated in an undergraduate or graduate program in environmental health, occupational health and safety or related discipline.

Member Selection

Individuals interested in joining the TLV®-CS Committee will be asked to complete an application and provide a current resumé or curriculum vitae. The Membership Subcommittee will review the application and determine whether the applicant is eligible and has qualifications that fit the current 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:

- Relevant training and education
- Professional background
- Past relevant experience
- Personal attributes necessary to meet committee goals

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 assigned to a TLV®-CS subcommittee (Dusts and Inorganic Compounds; Hydrogen, Oxygen and Carbon Compounds; Miscellaneous Compounds). TLV®-CS Committee members are expected to prepare and review *Documentation* for TLV®-CS chemical 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 committee's priorities. In addition to chemical substance subcommittee activities, each member of the Committee is encouraged to participate on at least one administrative subcommittee (e.g., Notations, Membership). Individual members will coordinate 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 annually attending face-to-face meetings, preparing and reviewing TLV® *Documentation*, and participating in administrative subcommittee activities. More senior members are expected to provide guidance and mentorship to new members.

Members are expected to comply with all Policies and Procedures of ACGIH®. At all times, members are expected to interact 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 within the Committee, which may include preparing additional *Documentation*, chairing a chemical substance 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*.

Membership Terms

Members are annually appointed by the Board of Directors and begin their term on January 1. The TLV®-CS Committee Chair will consult with the appropriate TLV®-CS Subcommittee Chairs/Vice Chairs and other members of the Committee prior to recommending re-appointment. Expectations for continuing membership include, at a minimum:

- Attendance at and constructive contributions to meetings;
- Participating in scheduled conference calls;
- Satisfactory progress in completing assignments, including but not limited to preparing and reviewing *Documentation*. It is expected that each member will complete at least one new and one revised document each year.

Member Candidates

The TLV®-CS Committee may choose to invite potential members to participate in committee activities, including authoring one or more TLV *Documentation* (e.g., completing Doc update(s)), as “member candidates” before recommending them for formal appointment. 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 appoint individuals before they become member candidates. Member candidates do not have voting privileges for purposes of committee business but are expected to participate. The default expectation is that member candidates are to complete at least one new and one revised document during their probation period, attend all meetings of the Committee, and participate fully in committee discussions. Member candidates must follow all ACGIH® policies and procedures.

Consultants

Periodically the TLV®-CS Committee may need specific technical expertise and may utilize the help of volunteer consultants to fill that void. Consultants are identified and vetted in a similar fashion as member candidates and nominated by the TLV-CS Committee Chair for review and appointment by the ACGIH Board of Directors. Consultants should only be utilized when the technical expertise is needed temporarily. Consultants do not have voting privileges and attend meetings only at the invitation of the Chair and are expected to 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. 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 do not have voting privileges, attend meetings only at the invitation of the Chair and must follow all ACGIH® policies and procedures.

Awards

MEMBERSHIP SERVICE 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 OELs.

The contributions of the TLV®-CS Committee members will be recognized by membership service awards based on years of service. 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 managed through ACGIH.

WILLIAM D. WAGNER AWARD

The William D. Wagner Award was established in 2003 and is presented annually to honor any person in the field of national and international worker health and safety who has been an outstanding example of commitment and dedication to the creation and dissemination of occupational exposure values (OEVs). The award recipient will be chosen by the TLV®-CS Committee, on a rotating basis, with the other three

standing ACGIH OEV Committees (Bioaerosols Committee, Biological Exposure Indices Committee, Threshold Limit Values for Physical Agents).

Every fourth year, the TLV®-CS Committee will submit a recommendation to the Board of Directors regarding appointment of the award recipient. The award will be presented at one of the meetings of the TLV®-CS Committee and the awardee will be invited to speak to the Committee on some aspect of national and international health and safety. Funds to support the travel for the recipient will be determined by the Board of Directors and managed through ACGIH.

Committee Structure

Organization Chart

The Committee organization chart is shown in Appendix 3.

Position Descriptions

TLV®-CS COMMITTEE CHAIR

Method of Selection and Appointment: The Chair is nominated through an internal committee selection and vote process, the results of which are sent to the Board of Directors for final approval. Potential candidates may be the Vice-Chair, current committee members or qualified individuals from outside the Committee. Candidates must meet membership criteria of the Committee and be a Voting Member, in good standing, of ACGIH. The membership subcommittee will seek nominations from the Committee for candidates. The membership subcommittee will screen nominees and present names to the Committee, accompanied by background information and a statement from each nominee. All voting members will be asked to vote for one of the nominees. The membership subcommittee will tally the 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 approval. In order to learn the duties of the position, the Chair-elect may be asked to serve as the Vice-Chair during the last year of the Chair's term.

The Chair of the TLV-CS Committee will hold the appointment for three years. This appointment may be renewed for more than one term, following the nomination and selection process described above. The Chair will hold the position, contingent upon annual re-appointment by the Board of Directors.

Succession: If the Chair position becomes vacant before the end of the term, the Vice-Chair shall assume the role of the Chair and shall serve the remainder of his/her predecessor's term. At the end of the term, a Chair will be selected following the selection and appointment process described above.

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:

- Oversees and assists TLV®-CS Committee and 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.
- Assures regular, clear communications with staff and Board of Directors by interacting with the Board liaison, staff, or Board members, as necessary.
- Assures regular, clear communications with external parties by reviewing all comments received and providing input to replies prepared by staff.
- Assures communication between all members of the Committee by consulting regularly with the steering subcommittee.
- 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 the 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.

TLV-CS® COMMITTEE 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. The Vice-Chair will hold the appointment for a three-year term. The Vice-Chair must be a Voting Member, in good standing, of ACGIH and will hold the position contingent upon appointment by the Board of Directors.

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. 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:

- Assists the Chair as necessary.
- Serves to fulfill the responsibilities of the chair when s/he is unable or unavailable to do so.
- Assures the internal functioning of the Committee. As such, the Vice-Chair will assist in overseeing the administrative subcommittees.
- Work with the Chair to ensure an appropriate mix of members (by TLV®-CS Subcommittee affiliation, professional background, skills, etc.) on the administrative subcommittees.
- 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.

Reporting: The Vice-Chair will report to the Chair of the Committee and provide periodic updates on his/her individual activities and the activities and make-up of the membership subcommittee.

Description of Chemical Substance Subcommittees

Generally, no voting takes place in the TLV®-CS chemical substance subcommittees. Decisions are made by consensus, if possible. However, the 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 Subcommittee Chair may bring the discussion of the particular substance to all members of the full Committee with approval from the Committee Chair.

The Committee consists of three chemical substance subcommittees:

- Dusts and Inorganic Compounds (D&I),
- Hydrogen, Oxygen and Carbon Compounds (HOC), and
- Miscellaneous Compounds (MISCO).

TLV®-CS SUBCOMMITTEE CHAIRS

Method of Selection and Appointment: Each of these subcommittees is headed by a Chair, who is appointed by the TLV®-CS Chair in consultation with the Vice-Chair. There is no established term for a subcommittee Chair. The TLV®-CS Committee Chair will review the activities of each 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 the subcommittee 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 the 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 and Vice-Chairs are members of the steering subcommittee. 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 and Vice Chair communicate and consult regularly with the TLV-CS Committee Chair, steering subcommittee, staff, and with members of their subcommittee.

Subcommittee Chairs and Vice-Chairs are responsible for the *Documentation* preparation activities of their subcommittee. In this capacity, the TLV®-CS Chemical Substance Subcommittee Chair and Vice Chair:

- 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.

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 should briefly summarize salient points of a discussion and the outcome of the discussion.

The chemical substance 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 Chemical Substance Subcommittee Chairs are not to contact external parties. Chemical Substance 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 chemical substance 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 Committee Chair, with the assistance of the administrative subcommittee members, is responsible for identifying an administrative subcommittee 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 Notations and Membership Subcommittees will work closely with the Committee Chair in the deliberation of the subcommittee 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, the TLV®-CS Subcommittee Chairs and Vice-Chairs (HOC, D&I, MISCO), and the Administrative Subcommittee Chairs. The Committee Chair also chairs the Steering Subcommittee.

Duties: The Steering Subcommittee:

- Advises the Committee Chair on issues.
- Reviews Committee productivity, progress toward goals and mission, and spending and budget.
- Recommends specific annual goals and an annual committee work plan to the Committee Chair to be submitted to the Board of Directors for approval.
- Reviews, changes, and updates committee policies, for full Committee approval.
- Assures the Committee resources are reviewed and properly allocated.
- Identifies and uses external resources, as necessary.
- Reviews special projects and requests from subcommittees, as necessary.
- Reviews the progress of the TLV®-CS Subcommittees and Administrative Subcommittees.
- Assists the Chair and Vice-Chair in organizing an annual education session.

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 by the TLV®-CS Committee Chair. The membership subcommittee members, in consultation with the TLV®-CS Committee Chair, will identify the Subcommittee Chair.

Duties: 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 resumé/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 each meeting.

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 will 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, in consultation with the Vice-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 for consideration by the TLV®-CS subcommittee during the probationary period. 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.

At the end of the probationary period, the TLV®-CS Subcommittee Chair and Vice-Chair will make a recommendation to the membership subcommittee 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 communication with applicants and candidates regarding the status of their application or membership.

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 TLV-CS 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. Members will be designated by the TLV-CS Committee Chair. The subcommittee will select its own Chair, in consultation with the TLV-CS Committee Chair. Other ACGIH® Committees or task groups (e.g., BEI®, Physical Agents, Air Sampling Instruments) may also be identified and asked to participate in the subcommittee’s activities, as the need arises.

Duties: The Notations Subcommittee has as its mission to:

- Determine the appropriate types of notations for TLVs®.
- Facilitate consistent use of all notations.
- Respond to emerging issues as they arise.

Specific responsibilities of the subcommittee include:

- Reviewing current notations and recommending changes and modifications as necessary in their definitions.
- Developing criteria that guide authors in determining which notations are appropriate and how they should be applied.
- Identifying experts (internal and external to the Committee) that can be consulted for specific notations.
- Recommending workshops, seminars, webinars or tutorials for the purpose of providing input to the Committee on emerging issues.
- Establishing *ad hoc* groups, where necessary, to consider special issues.
- Developing “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.

- Providing attention to the consistent application of notations across the three TLV®-CS subcommittees.
- Creating and revising appendices and other related documents.

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

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

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

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

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

CHEMICAL SELECTION SUBCOMMITTEE

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

Duties: The Chemical Selection Subcommittee has as its mission to:

- Determine the chemicals for which the Committee will establish new or revised TLVs®.
- Optimize the deliberations of the Committee by providing recommendations on the most important chemicals with respect to occupational exposure, i.e., to ensure that efforts will have the greatest positive impact on worker health.
- Respond to emerging issues related to specific chemicals as they arise.

Specific responsibilities of the subcommittee include:

- Monitoring key information sources and organizations that prioritize their own activities based on the greatest risk to human health due to their inherent hazards and/or exposure potential. Examples include the Agency for Toxic Substances Disease Registry (ATSDR), Environment

Protection Agency (EPA), European Chemicals Agency (ECHA), International Agency for Research on Cancer (IARC), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA).

- Developing criteria that guide the chemical selection subcommittee members in determining which chemicals are appropriate to consider and how they should be identified.
- Preparing an annual report with specific recommendations on chemical substances for consideration by the Chairs and Vice-Chairs of each Chemical Substances Subcommittee (D&I, HOC, MISCO). Each annual report will provide background on why the recommendation was made and provide links to useful data summaries.

Reporting: The Chair of the Chemical Selection Subcommittee reports to the TLV-CS Committee Chair and provides updates on the activities and progress on a regular basis.

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 or subcommittee must orally disclose the conflict of interest to the full TLV®-CS Committee and that “member’s” respective subcommittee. In addition, an annual written COI declaration must be completed. It is essential that “members” identify potential, real, or perceived conflicts of interest and recognize 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 also complete an annual oral 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 publication history and identify any technical biases. This declaration is not only required annually, but also when material changes in a “member’s” status occur. The degree of potential, real or perceived conflict of interest can range from low to high.

- 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 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 themselves 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 conflicts of interest is key to this process. The degree of potential, real or perceived conflict of interest can range from low to high. The classification of conflict and the selection of the corresponding 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 TLV®-CS Committee Chair and ACGIH science staff should be informed of all 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.

High Degree of Conflict

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” 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.
- E. A “member” that performs consultation services for an associated trade organization, law firm, or a producer of a chemical substance under review by the TLV®-CS Committee and plays a direct role in the development or review of exposure levels.

Where a high degree of conflict exists, “members” are not permitted to author or co-author *Documentation* and must recuse themselves from discussions about the recommended TLV® value and notations. 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” that performs consultation services for an associated trade organization, law firm, or a producer of a chemical substance under review by the TLV®-CS Committee but who plays a minor role in the development or review 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. For some substances, these discussions may determine that it is appropriate for a member to author a *Documentation* with a co-author or reviewer, while for other substances, as in a high degree of conflict situation, it may not be appropriate to author or co-author a *Documentation* or vote.

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” 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®.

- B. 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.
- C. A “member” working for a regulatory agency that regulates the substance but whose role is non-regulatory.
- D. A “member” working for a company that is a minor producer and has no role in the development of internal occupational exposure levels.
- E. A “member” that performs consultation services for an associated trade organization, law firm, or a producer of a chemical substance under review by the TLV®-CS Committee but who has no role in the development or review of occupational exposure levels.

When a low 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 reviewer for the *Documentation*.

In many cases, simply informing the subcommittee and committee members about low-level conflicts is appropriate.

“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, however, “members” must recuse themselves from any discussions of values or notations, 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.

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.

Substances are initially assigned to the [Under Study list](#) by a consensus of the respective subcommittee, and can be added to or removed throughout the year as needed, by the TLV®-CS Subcommittee Chair(s). 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 a Notice of Intended Changes (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 Under Study 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 during this stage of the development process and is not released until it is at the NIC stage.)

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

The Subcommittee Chair, Vice Chair or subcommittee member summarizes the draft *Documentation* and proposes a motion to place it on the NIC. If the motion is seconded, the full Committee will discuss and then vote on the proposed action. Voting requires a quorum (greater than 50% of the voting committee membership) be present. All present committee members have an obligation to vote. The Chair only votes to make or break a tie; member candidates, consultants, and emeritus members do not have voting privileges for the purposes of committee business. Recommendations to place draft *Documentation* on the NIC may be made at any meeting or teleconference if a quorum is present.

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 on February 1.

DRAFT DOCUMENTATION ON THE NOTICE OF INTENDED CHANGE (NIC)

A substance is held on the NIC for at least one year before adoption. The period for public review and comments 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, co-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 a subcommittee member will summarize the draft *Documentation* and propose a motion for one of the following actions:

- A. Retain the TLV® value(s)/notations and draft *Documentation* on the NIC for an additional year.
- B. Change the TLV® value(s)/notations and draft *Documentation* and retain on the NIC for an additional year.
- C. Adopt the NIC TLV® value(s)/notations and draft *Documentation*.
- D. 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. All present committee members have an obligation to vote. The Chair only votes to make or break a tie; member candidates, consultants, and emeritus members do not have voting privileges for the purposes of committee business. Recommendations to adopt, withdraw, or retain NIC *Documentation* may be made at any meeting or teleconference if a quorum is present.

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 as adopted.

Voting Procedures

The Committee follows the ACGIH Committee Voting Procedure.

TLV® Documentation Guidelines

An outline of a TLV® *Documentation*, with suggested language, is included in Appendix 1.

The purpose of the TLV® *Documentation* is to clearly describe, present, and interpret the appropriate scientific information supporting the derivation of the TLV® and its associated notations for a given chemical substance. In general, the entire *Documentation* should be no longer than 10 pages in length excluding references; however, exceptions will be made where circumstances warrant it. *Documentation* should be formatted as designated by the *Documentation* Template (also included in Appendix 1). It should be kept in mind that TLV® *Documentation* is not a complete review of all the

literature available on a particular substance. It has as its purpose the derivation of a number from references and the identification of notations, to protect employees in occupational settings. The primary user of the TLV® *Documentation* is intended to be the industrial hygiene professional.

Literature Searches

For new TLVs®, the author of the *Documentation* or staff shall conduct a full literature search using the appropriate online databases. ACGIH® staff 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 2).

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 2.

If the information is contained in a “government” or “industry” document, it should not be assumed that it has undergone peer review.

Secondary sources such as books and reviews may be used for an overview of the data. However, whenever possible, primary sources should be relied upon for discussion of specific studies that serve as the primary basis for the TLV. In addition, 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. Copies of any translations should be sent to the ACGIH Staff.

The Use of Non-Peer Reviewed Literature

The TLV® *Documentation* is to rely primarily 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. Other sources may be unpublished, not peer reviewed, and/or unavailable. With regard to the latter, in some cases the owners of information do not want it widely distributed, while in the other cases the costs of obtaining such information are so high as to make it practically unavailable to the public.

If unpublished data are used, a signed copy of permission to use and cite must be filed with ACGIH® staff before they can be used or referenced in an NIC or final *Documentation*. The Committee may use unpublished information that is practically unavailable to the public. If release to a third party upon request is not allowed by the data owner, it may still be used by the committee under certain circumstances.

1. The information should undergo some form of peer review. The importance of the information to the *Documentation* determines the degree of peer review necessary. It will be up to the subcommittee to determine the nature of peer review that is appropriate. When conducting an internal peer review, the Subcommittee and/or Committee should ensure that accepted scientific methods were used to obtain and analyze the data.
 - a. 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.
 - b. 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.
2. If unpublished data are 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. For use of available robust summaries of unpublished and unavailable data, a statement must be provided indicating that the Committee had access to the data supporting the robust summary.
4. Robust summaries with unavailable data may be used as supporting information in the *Documentation*. For the development or basis of a TLV®, robust summaries alone may also be used with the following limitations:
 - a. Robust summaries may be used to support primary, peer-reviewed source reference(s).
 - b. Robust summaries may be used alone as the basis for a TLV® or notation if they provide 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 (1a and 1b above) and will be accompanied by appropriate justification that addresses the reliability of the summary.

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 <https://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations/tlv-bei-development-process>. There are several important points to consider throughout this process:

- One appropriate method for an interested party to contribute to the TLV® 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® process. Also, the best time to submit comments to ACGIH® is in the early stages of the TLV® 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® accepts 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 primarily 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, have 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 the 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 for the purposes of sharing experience and expertise. Committee meetings are closed to the public and outside presenters/speakers are not permitted to participate in Committee deliberations. The meeting minutes will reflect when guests were present and detail the extent of their participation.

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 ACGIH Committees once approved by the applicable Subcommittee or approved by the appropriate committee leadership. 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 the 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, chemical substance subcommittee and administrative subcommittee meetings. At a minimum, subcommittee minutes 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.

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 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 and Education Department of ACGIH® in writing at science@acgih.org. 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 ACGIH Educational Event Planning Worksheet 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.

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, a planned symposium will utilize a call for papers to initiate and announce the symposium. The taskforce 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.

APPENDIX 1, Annex 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. The *Documentation* is not intended to be a comprehensive review of the literature for a substance, but it should describe the key studies that define the range of exposure information and animal and human health effects associated with exposure to a substance. To facilitate an organized description of this literature, the TLV® Documentation Guidelines are divided into appropriate sections for description and analysis of the relevant studies. The review of the literature should not be just a recitation of the findings and conclusions of individual reports, but also must provide appropriate integrated analyses as to which study(s) are most appropriate for consideration in derivations of the TLV®. When a study seems to suggest the recommended TLV® or any of its notations should be different from that selected, the study should be included and discussed.

In developing a written *Documentation*, the Committee gives precedence to human studies, including case reports and epidemiologic evaluations. Animal studies with endpoints and routes of exposure and in relevant species are also considered. Genotoxicity and metabolic data are also considered and may inform the choice of TLV. The threshold concept guides the Committee's decision-making. The ACGIH process for establishing occupational exposure guidelines relies on risk assessment whose basic elements are: 1) a priority of human over animal data; 2) the use of a threshold approach; and 3) reliance on good science and expert judgment. In arriving at a TLV, the Committee may consider various uncertainty factors (also known and adjustment or safety factors) to address sources of variability and uncertainty. However, there are no rigid rules for their application and professional judgement is used to determine the overall margin of safety reflected in the TLV recommendation. choice. Also, the Committee does not develop values associated with specific levels of risk; however, modeling approaches (e.g., benchmark dose calculations) may be used to inform the TLV value. Rather, the scientific data are examined to identify the critical effect ("worst case" health endpoints), no-observed- or lowest-observed-adverse-effect levels, before selecting a TLV associated with the key health endpoint(s).

Definitions

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, TLV®-SL, Skin, RSEN/DSEN, OTO, 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

Getting Started

- 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. See Appendix 2, 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, comprehensiveness of robust summaries, 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, lack of consistency with other studies, 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 cited first for reference, without providing details. The key studies will be discussed within the section. Bibliographic references in the body of the *Documentation* should be presented as follows: ...text. (Smith et al., 1999). Do not use italics or bolding. The references within the body of the document should be alphabetized.
- Use of unpublished information requires that the entire study or communication be on file at ACGIH® headquarters and be available for public release if requested.
- Robust studies and registration dossiers, which provide comprehensive data summaries, can be used with appropriate peer-review by the subcommittee, and the full committee, as appropriate.

TLV® Documentation Outline

Section	Comments / Common Boilerplate
Title Provide formal chemical name in all capitals.	Subcommittee may decide on most common name for document title
CAS Number(s) Provide CAS number(s) describing the substance.	
Synonyms Provide listing of other chemical synonym(s) for this substance.	PubChem is a good reference for this. Also include common trade names.
Chemical Formula - Provide chemical equation. - Provide chemical structure on separate line, if appropriate.	Provided by ACGIH® Staff if one cannot be found
TLV®–TWA - List current TLV®–TWA expressed in appropriate units. - If particulate matter, describe appropriate size fraction.	For aerosols, use mg/m ³ For gases and vapors, use ppm
TLV®–STEL - List value in appropriate units. - If no value assigned, do not list.	For aerosols, use mg/m ³ For gases and vapors, use ppm
TLV®–C - List value in appropriate units. - If no value assigned, do not list.	For aerosols, use mg/m ³ For gases and vapors, use ppm
TLV®–SL List value in appropriate units. If no value assigned, do not list.	For solids and liquids, use mg/100 cm ²
Inhalable Fraction and Vapor (IFV) Listed when Saturated Vapor Concentration (SVC)/TLV® (in mg/m ³) ratio is between 0.1 and 10.	SVC $= \frac{\left(\left(\frac{Vapor\ Pressure}{760} \right) \times Molecular\ Weight \times \right)}{\left(\left(\frac{0.08206}{1000} \right) \times 298 \right)}$
Skin If no “Skin” notation assigned, do not list.	
Respiratory Sensitizer (RSEN) If no “RSEN” notation assigned do not list.	
Dermal Sensitizer (DSEN) If no “DSEN” notation assigned do not list.	
Ototoxicant (OTO) If no “OTO” notation assigned do not list.	
Carcinogenicity List notation as A1, A2, A3, A4, or A5, with summary definition. If no information, do not list cancer designation.	

Section	Comments / Common Boilerplate
TLV® Recommendation • Focus only on studies providing the rationale for deriving the TLV® recommendation, including notations. For example: • human study(s). • animal study(s) expressing most relevant route of exposure, doses, and appropriate responses. • Include the relevant bibliographic references (e.g., Smith, 1999). The results of these studies should not be repeated in detail; provide only the key details (doses/concentrations) and conclusion(s) as they support the rationale for the TLV® recommendation. • This section should have a clear explanation about each of the following items: a description of the key health effects, a discussion of why particle size fraction was selected for the TLV® (for aerosols), and the reasoning for the selection of a value. Various sources uncertainty and variability do not need to be quantified, but rather explained. Notations and other relevant information should also be described and explained. • Identify appropriate notations and explain reasoning for their selection. • Carcinogenicity designation (see Appendix A in the TLVs® and BEIs® book). • RSEN/DSEN (see Annex D). • Skin (see Definition in the TLVs® and BEIs® book). • OTO (see Definition in the TLVs® and BEIs® book). • Refer to BEI®, if available for substance.	Look at the critical study for the basis. Has enough been said about it? Is it clear to the reader? Look for contradictions. • How do you select the appropriate TLV®? – see the description below this outline. • Do not restate definition of a notation used. • When assigning a cancer designation, revisit the definition in the TLVs® and BEIs® book and make sure that the evidence supports the rationale. Some useful boilerplate language: • A TLV®-TWA of ___ mg/m³, measured as inhalable particulate matter (or IFV, 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 <i>acute irritation</i> associated with occupational exposure to _____. • A TLV®-SL of ___ mg/100 cm² ___ is recommended to minimize the potential for <i>dermal sensitization</i> associated with occupational exposure to _____. • Sufficient data were not available to recommend a Skin notation. • Sufficient data were not available to recommend a RSEN/DSEN notation. • Available data on sensitization from exposure to _____ warrants the addition of the RSEN/DSEN (sensitizer) notation (include refs). • Sufficient data were not available to recommend an OTO notation. • Available data on ototoxicity from exposure to _____ warrants the addition of the ototoxicant (OTO) notation (include refs). • _____ is a substance for which Biological Exposure Indices (BEIs®) have been recommended (see BEI® <i>Documentation</i> for _____).

Section	Comments / Common Boilerplate
TLV[®] Basis This section should briefly list the critical health effects <u>that support derivation of the TLV[®]</u>. This description will be used to complete the “TLV[®] Basis – Critical Effect(s)” column in the TLVs[®] and BEIs[®] book. In general, the listed Basis (Bases) should only be those at or near the TLV[®] (e.g., within a factor of 10). It is acceptable to introduce a new critical effect as it will be added to the TLV[®] Basis table for future use upon adoption of the <i>Documentation</i>.	See TLV[®] Basis Table – Annex B. Each TLV[®]-CS Subcommittee will ensure that the TLV[®] Basis is appropriate for each new or revised TLV[®] <i>Documentation</i>. Consider the following rules of thumb in selecting the appropriate TLV[®] Basis: • If a TLV[®] Basis is not on the current list of TLV[®] Basis, discuss new Basis with Committee and ACGIH[®] Staff for addition to the Basis list. • Use Cancer as a TLV[®] Basis only if it drives the TLV[®]. In this case, the organ or type of cancer is usually specified. • The first TLV[®] Basis listing should be the primary effect. • If there is already a Skin or SEN notation, use care in using as a TLV[®] basis, unless its the primary basis.

Section	Comments / Common Boilerplate
Chemical and Physical Properties - Refer to Appendix 2, Finding Chemical and Physical Properties, for links. - Provide a brief text description of the chemical and physical forms of the substance (e.g., solid, liquid, color, composition, contaminants, decomposition products, and known odor properties). - The text section is followed by a specific listing of properties, some examples of which are provided below. If some of the specific data are not available, do not list the subheading. - Molecular weight: XXX.XX - Specific gravity: X.XXX at XX°C - Melting point: °C (°F) - Boiling point: °C (°F) - Vapor pressure: Use torr and specify temperature (Centigrade) - Saturated Vapor concentration in ppm (mg/m³) - Flash point: °C (°F) - Flammable limits: lower and upper, method - Autoignition temperature: °C (°F) - Solubility: - Conversion factors at 25°C and 760 torr: X ppm = XX.X mg/m³, 1 mg/m³ = X ppm	Log octanol/water partition coefficients (sometimes called log K_{ow}) should be included, if available. When there is more than one partition coefficient use the middle of the range. The best reference is: Leo A; Hansch C; Elkins D: Partition Coefficients and Their Uses. Chem Rev 71(6):525-616 (1971). A combination of the Log K_{ow} and molecular weight of the chemical can be used to (very roughly) estimate skin permeability from an AQUEOUS solution. The best reference is: Potts RO; Guy RH: Predicting Skin Permeability. Pharm Res 9(5):663-669 (1992). Saturated Vapor Concentration (SVC) should be listed especially for those compounds which will have an IFV endnote. SVC can be calculated using the following equation: $\text{SVC (mg/m}^3\text{)} = 53.81 \times \text{MM} \times \text{VP}$ 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.
Major Sources of Exposure Describe in text format where available- - How the substance is produced (e.g., methods of manufacture, by-product of...). - Uses. - Production volumes and estimated numbers of workers exposed. - Major routes of exposure associated with manufacture and use (what forms are encountered during use, e.g., vapor, dusts, aerosol, liquid, etc.). - Particle size issues and characterizations, if relevant.	Resources - Use EPA Section Interagency Testing Committee for estimated number of employees exposed. Include the date. - Trade Association websites - TSCA database – check for production volumes. - U.S. Geological Survey/Dept of Interior: http://minerals.usgs.gov/minerals/pubs/commodity/ List tonnage and year, e.g. date from Department of Commerce via internet.

Section	Comments / Common Boilerplate
Animal Studies This major heading and its subheadings describe the relevant <i>in vivo</i> animal studies supporting assessment and derivation of the TLV®-TWA.	Detailed descriptions of animal toxicology studies are generally not required. However, if known, the minimum information for each study should include: • Species, sex, route and mode of administration (inhalation, oral gavage, oral diet, dermal, etc.), duration of dosing, specific doses tested, relevant toxic effects, No-observed-adverse-effect levels (NOAELs), Lowest-observed-adverse-effect levels (LOAELs), and frank toxic responses at higher dose levels. • Mechanistic studies (e.g., animal model and pharmacokinetic relevance) that provide perspective for appropriate extrapolation of animal findings to humans. • Published expert reviews (IARC, WHO, U.S. EPA, U.S. NIOSH, etc.) that offer analysis of human relevance of animal studies.

Section	Comments / Common Boilerplate
Animal Studies: Acute (less than 2 weeks duration) INHALATION • As available, incorporate minimum information noted above in the animal studies comments column. • Describe LC₅₀ value(s) or equivalent indicator(s) of toxicity. • Describe minimum lethal concentrations/doses (LC_{Lo}, LC₅₀) and any reported clinical signs. • If no lethality found, indicate full range of concentrations, clinical observations, and effect-level concentrations. • Include particle size characterization to assess the human relevance of particle deposition in the test animal. DERMAL Same as inhalation above. Include description of nature of applied substance (neat, concentration of solutions and vehicles, formulations, etc.) • Describe systemic toxicity resulting from skin absorption. • Describe specific toxicity to skin (irritation, burns, etc.); include assessment (classification) of toxic response (non-irritant, type of irritant — corrosive). • As available, incorporate minimum information noted above. • Describe LD₅₀ value(s) or equivalent indicator(s) of toxicity. • Describe minimum lethal doses (LD_{Lo}) and any reported clinical signs. • If no lethality found, indicate full range of doses, clinical observations, and effect-level doses. SENSITIZATION Include species, doses, routes of administration, protocol used (e.g., GPMT, LLNA), ancillary information (adjuvant used, etc.), end results (dose-response (e.g., number of responders at each challenge dose); severity of response, NOAEL, EC3 value, ancillary skin irritation, skin 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 RD₅₀ studies (measures sensory irritation).	For LD₅₀ and LC₅₀ studies, the results can usually be summarized in a single sentence such as: • The LC₅₀ for substance XXX ranged from 588 to 1004 mg/m³ in mice and rats with signs of wheezing and coughing. Schaper M: Development of a database for sensory irritants and its use in establishing occupational exposure limits. Am Ind Hyg Assoc J 54(9):488–544 (1993).

Section	Comments / Common Boilerplate
Animal Studies: Subchronic (>2 weeks ≤ 3 months) • Same information as acute studies. • Organized by route of exposure.	• Subchronic studies are often the driver of the TLV® Basis, therefore more details may be needed than for acute studies. • Give the strain and #s of animals if more than one similar study. • Report studies low to high dose. • Give LOAEL, NOAEL, if you can. NOELs/LOELs for non-adverse effects can be included if considered relevant. • Summarize by kind of study, species, route, dose, # applications, and results.
Animal Studies: Chronic/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.).	Historically, the 2-year bioassay has been considered the “gold standard.” However, new tests including the 1-month Pig-A assay and the 6-month transgenic rat and mouse assays, are becoming more prevalent. Non-neoplastic effects (e.g., target organ toxicity) should also be discussed since these could be the effects that actually drive the TLV.
Animal Studies: Genotoxicity The results should be described briefly and are becoming more useful in the selection of the carcinogenicity category. Therefore, the results of <i>in vitro</i> and <i>in vivo</i> studies should be described briefly.	Example: Several genotoxicity studies have been reported but were generally negative. Positive findings were noted only in <i>in vitro</i> studies using the Ames test, forward mutation assays, and only with metabolic activation. Negative findings were found in other <i>in vitro</i> studies and <i>in vivo</i> studies using the micronuclei test in mice and chromosomal aberrations in rats. The weight-of-evidence indicates that this substance does not represent a significant genotoxic risk.
Animal Studies: Reproductive/Developmental Toxicity This section should briefly describe adverse changes, presenting reproductive studies first, followed by developmental toxicity studies. The studies should also be organized by route of exposure with relevant routes of exposure, such as inhalation and skin, described first.	Reproductive/developmental toxicity is important to consider and sometimes serves as the basis of the TLV.

Section	Comments / Common Boilerplate
Absorption, Distribution, Metabolism, and Excretion (including toxicokinetics and toxicodynamics) 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). • Discuss ADME for a related substance if it is a known metabolite of the compound under consideration. • If a PB-PK or classical compartmental model is available for the chemical it should be referenced. • Dose-response evaluations with relevance to the TLV[®] should be included. • Include information on the mechanism of action for the critical effect(s) and interpretation of the ADME data provided from a toxicokinetic and toxicodynamic perspective.	• Studies may address the amount of chemical absorbed when the chemical is given orally and an absorption fraction for inhalation. For dermal absorption studies, the order of preference for absorption information is 1) permeability coefficient (kp), 2) flux, and 3) percentage of applied dose absorbed. • Distribution of the chemical should be described if known, the octanol/water partition is important information that helps understand distribution. Any tissues that act as a “sink” for the chemical (such as fat) could be identified. • It may be important to identify types of metabolism the chemical undergoes, i.e., P₄₅₀ (with specific isozyme if known) or glutathione conjugation. If metabolism is significant, a diagram could be useful. Relative toxicities of the parent and metabolite may be important. • Primary route of elimination should be identified, e.g., exhalation, urine, or feces. Relative amounts eliminated through each route may be important, if known. Elimination half-lives may be useful. • References to published compartmental or physiologically based pharmacokinetic models (PB-PK) should be cited if known. Details are not necessary but number of compartments for classical and general type of model for PB-PK (stochastic, flow or diffusion limited) could be described). The exposure route(s) that the models have been validated for should also be described. • Dose-response evaluations such as slope factors (for cancer) or model-based extrapolations of NOAELs may be available.

Section	Comments / Common Boilerplate
Human Studies Studies among occupationally exposed populations should be given priority for detailed description. • The organization of the human studies and the order in which they are presented will vary greatly between substances based on the critical effects and the amount of human data available. • If there are relatively few human studies, it may be appropriate to describe all in detail. However, if there are many studies only the key studies for deciding the TLV® or the notations should be described in detail. • Where there are many epi studies, use the boilerplate which states that many studies exist, but only discuss those used in the derivation of the TLV®. • Cite available process-related occupational exposure findings, even if dose-response data/results are not available.	• Key studies are generally those which: 1. Evaluate health effects in relation to level of exposure (i.e., assess dose-response) 2. In the absence of #1, provide some information on the level of exposure 3. Cohort and case-control studies that contribute to assigning the cancer notation 4. Studies that evaluated respiratory and skin sensitization 5. Studies that demonstrate systemic toxicity following dermal exposure • For key studies, include the following information: 1. Type of study (e.g., cross sectional, case control, cohort, experimental, or other); 2. Study population (include location of study, number of participants, and pertinent demographic information); 3. Measurements of disease or death (e.g., death certificates, physical examination, laboratory analyses, questionnaires, etc.); 4. Measurements of exposure (e.g., laboratory analyses, air measurements, questionnaires, etc.); 5. The results relevant to setting the TLV® or assigning notations. Include the measure of health effect (i.e., odds ratio, relative risk, standardized mortality/morbidity ratio [SMR], cross-shift change in physiologic measurement, etc.) and the confidence intervals or p-values. Present the results for critical health effects regardless of the statistical significance 6. Other potential causes of the health effect or confounders considered (e.g., age, sex, smoking, and other exposures present) and whether the results were adjusted for these factors. • Non-key studies are those that describe health effects without any indication of level of exposure, those that describe health effects that occur at levels well above the proposed TLV®, and those that indirectly contribute to our understanding of the critical effects. For non-key studies, it is acceptable to briefly summarize the results of studies and to cite reviews from the peer-reviewed literature or those conducted by public agencies that are widely available (i.e., ATSDR, IARC). • If there are many human studies with similar designs, make tables of the data where possible to summarize the key information listed above.
TLV® Chronology The purpose of this section is to describe only the historical and/or pending/actionable activities (dates) associated with the TLV® <i>Documentation</i>. It is not intended to describe the detailed history of actions completed on the	Example statements to insert in historical section of TLV® <i>Documentation</i> when there are no changes to the TLV® or Notations: • _____ (cite year of change): TLV® Basis update to <i>Documentation</i> _____ (cite year), retaining adopted TLV(s)® and notation(s)...see section (cite

Section	Comments / Common Boilerplate
<i>Documentation</i>. ACGIH® Staff completes this section. See example below: For updated documents, authors should upload or submit documents with <i>track changes</i> so staff can see the new edits. 19XX: <i>Proposed</i>: TLV®–TWA, XX ppm 19XX–present: TLV®–TWA, XX ppm 20XX: Documentation revised. Describes current <i>Documentation</i> revision efforts; use only when Documentation is revised but TLV® is not changed 20XX: <i>Proposed</i>: TLV®–TWA, XX ppm, notation(s). If necessary, describe published (NIC) <i>Proposed</i> TLV® values and associated notations that have not been adopted by ACGIH®.	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 <i>Documentation</i> ____ (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 <i>Documentation</i> ____ (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). ▪ Example: 2004: New information and references added to Documentation 1996, retaining adopted TLV(s)® and notation(s) – see Animal Studies <i>Acute</i>, paragraphs two and four; Animal Studies Chronic/Carcinogenicity, paragraph one; Human Studies <i>Cancer</i>, paragraphs one, two, and six; new Human Studies <i>Reproduction</i> section; and new references 14,23, and 31. • ____ (cite year of change): New section(s) and reference(s) added to <i>Documentation</i> ____ (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 <i>Documentation</i> ____ (cite year), retaining adopted TLV(s)® and notations or • The TLV® <i>Documentation</i> has been updated and revised to reflect new scientific data, but the TLV® recommendation has not been changed.

References

List in alphabetical order.

Additional examples of different citations can be found at the National Library of Medicine website:

https://www.nlm.nih.gov/bsd/uniform_requirements.html

Journal Articles:

List all authors when there are three or less. If more than three, list the first three, followed by "et al."

Halpern SD; Ubel PA; Caplan AL: Solid-organ transplantation in HIV-infected patients. *N Engl J Med.* 347(4):284-7 (2002).

Rose ME; Huerbin MB; Melick J; et al.: Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. *Brain Res.*;935(1-2):40-6 (2002).

Forooghian F; Yeh S; Faia LJ; et al.: Uveitic foveal atrophy: clinical features and associations. *Arch Ophthalmol.*127(2):179-86 (2009). PubMed PMID: 19204236; PubMed Central PMCID: PMC2653214.

Online Citations:

Aboud S: Quality improvement initiative in nursing homes: the ANA acts in an advisory role. *Am J Nurs* [Internet]. Jun [cited 2002 Aug 12];102(6):[about 1 p.] (2002). Available from: https://journals.lww.com/ajnonline/Fulltext/2002/06000/Quality_Improvement_Initiative_in_Nursing_Homes.31.aspx Subscription required.

Who's Certified [Internet]. Evanston (IL): The American Board of Medical Specialists. c2000 - [cited 2001 Mar 8]. Available from: <https://www.abms.org/verify-certification/>

MeSH Browser [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2002 - . Meta-analysis; [cited 2017 Dec 1]; [about 1 p.]. Available from: <https://meshb.nlm.nih.gov/record/ui?ui=D017418> MeSH Unique ID: D017418.

Federal Agency Publications:

American Occupational Therapy Association, Ad Hoc Committee on Occupational Therapy Manpower. Occupational therapy manpower: a plan for progress. Rockville (MD): The Association; 1985 Apr. 84 p.

With Author(s)

Vallancien G; Emberton M; Harving N; et al.: Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *J Urol.*169(6):2257-61 (2003).

Robust Summaries:

As above for Federal Agency Publications, preceded by "As cited in" before the publication name.

Books:

Sections/Chapters with Specific Author(s)

Section	Comments / Common Boilerplate
	Murray PR; Rosenthal KS; Kobayashi GS; Pfaller MA: Medical microbiology. 4th ed. St. Louis: Mosby; 2002. Breedlove GK; Schorfheide AM: Adolescent pregnancy. 2nd ed. Wiecezorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001. <i>With Editor(s) Only</i> Gilstrap LC 3rd; Cunningham FG; VanDorsten JP; editors: Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

Selecting an Appropriate TLV[®]

1. Decide what the critical health effect(s) is(are), i.e., those adverse effects that occur at the lowest exposure levels and will drive the TLV[®] value.
2. Decide which type of TLV[®] (TWA, STEL, C, SL) 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.
 - **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 may not protect against these effects if the 8-hour TLV[®]–TWA is exceeded. The TLV[®]–STEL usually supplements the TLV[®]–TWA where there are recognized acute effects; however, the TLV[®]–STEL may be a separate, independent exposure guideline.
 - **Threshold Limit Value–Ceiling (TLV[®]–C)**: The concentration that should not be exceeded during any part of the working exposure. If instantaneous measurements are not available, sampling should be conducted for the minimum period of time sufficient to detect exposures at or above the ceiling value.
 - **Threshold Limit Value–Surface Limit (TLV[®]–SL)**: The concentration on workplace equipment and facility surfaces that is not likely to result in adverse effects following dermal exposure or incidental ingestion. The TLV[®]–SL is intended to supplement airborne TLVs and especially those with Skin, DSEN and RSEN notations, to provide quantitative criteria for establishing acceptable surface concentrations, expressed as mg/100 cm².
3. Decide the value of the TLVs[®]
 - a. If sufficient studies are available, develop a summary table of key studies and findings as they relate to the TLV[®]. From this information, select a point at which it appears no adverse health effects are likely to occur in nearly all workers.
 - 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, state so. 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 (extremely rare).
 - If route-to-route conversion factors are used, be explicit/transparent.
 - See Annex C for conversion guides.
4. Consider whether a volatile 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[®] value is the same for both forms, then a designation of both vapor and aerosol must be made.
 - b. If the TLV[®] refers to an aerosol, one of the three Particle Size Selective (PSS)-TLV[®] designations must be selected. In general, the following relationship will determine which one:

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

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

Selecting Appropriate Notations

1. Identify appropriate notations and explain reasoning for their selection
 - a. Carcinogenicity designation (see Appendix A in the TLVs® and BEIs® book)
 - b. RSEN (see Definition in TLVs® and BEIs® book and Appendix 1)
 - c. DSEN (see Definition in TLVs® and BEIs® book and Appendix 1)
 - d. Skin (see Definition in TLVs® and BEIs® book and Appendix 1)
 - e. OTO (see Definition in TLVs® and BEIs® book and Appendix 1)

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.

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.

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DRAFT — DO NOT CITE OR QUOTE

Chemical name – page 1

(Note: Header should be on every page.)

CHEMICAL NAME (DRAFT date:)

CAS number:

Synonyms:

Molecular formula:

Chemical structure:

TLV®–TWA,

TLV®–STEL,

TLV®–Ceiling,

TLV®–SL,

Skin

Respiratory Sensitizer (RSEN)

Dermal Sensitizer (DSEN)

OTO (Ototoxicant)

Carcinogenicity Classification

TLV® Recommendation

A TLV®–TWA® of XX mg/m³, 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 RSEN/DSEN notation.

TLV® Basis

Chemical and Physical Properties

Molecular weight:

Specific gravity:

Melting point: °C (°F)

Boiling point: °C (°F)

Vapor pressure: °C @ 25 °C

Saturated vapor concentration: ppm @ 25 °C

Flash point: °C (°F) method

Flammable limits: uel %; lel %

Autoignition temperature: °C (°F)

Solubility: mg/mL

Octanol/water partition coefficients: @ 25 °C

Conversion factors at 25 °C and 760 torr: ppm = mg/m³; mg/m³ = ppm

Major Sources of Occupational Exposure

Animal Studies

Acute/Subacute

ORAL

DERMAL

INHALATION

SENSITIZATION

OTHER STUDIES

Subchronic

Chronic/Carcinogenicity

Genotoxicity

Reproductive/Developmental Toxicity

Absorption, Distribution, Metabolism, and Excretion

Human Studies

TLV[®] Chronology

References

APPENDIX 1, ANNEX B

TLV® Basis Table

Terms used as the TLV® Basis with abbreviations (last updated 26-Sep-2020).

Group	Effect Name	Abbreviation (if necessary)
Cancer	Bladder cancer Cancer Kidney cancer Laryngeal 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

Group	Effect Name	Abbreviation (if necessary)
	Central nervous system convulsion Central nervous system impairment Cochlear impairment Cognitive decrements Dizziness Headache Neurotoxicity Ocular nerve damage Vestibular impairment Visual impairment	CNS convul CNS impair Cochlear impair Cognitive decrement Dizziness Headache Neurotoxicity Ocular nerve dam Vestibular impair Visual impair
Peripheral Nervous System	Peripheral nervous system impairment Peripheral neuropathy	PNS impair Periph neuropathy
Gastrointestinal System	Gastrointestinal damage Gastrointestinal irritation	GI dam GI irr
Cardiac System	Cardiac sensitization Cardiac system impairment Myocardial effect	Card sens Card impair Myocard
Vascular System	Vascular system impairment Vasoconstriction Vasodilation	Vasc sys impair Vasoconstriction Vasodilation
Hematopoietic System	Anemia Carboxyhemoglobinemia Coagulation problems Hematologic effects Hemolysis Hemosiderosis Hypoxia/Cyanosis Increased platelet count Inhibition of heme synthesis Leucopenia Methemoglobinemia Nitrosylhemoglobin formation Porphyrin effects	Anemia COHb-emia Coagulation Hematologic Hemolysis Hemosiderosis Hypoxia/Cyanosis Incr platelets Inhib heme synth Leucopenia MeHb-emia Nitrosyl-Hb form Porphyrin
Immune System	Immune system impairment	Immun impair
Reproductive System	Female reproductive system damage (excluding teratogenic effects and embryonic and fetal damage Male reproductive system damage Pregnancy loss Reproductive effects Testicular damage	Female repro Male repro Pregnancy loss Repro Testicular dam
Eye	Cataract Corneal necrosis Eye damage Eye irritation Eye photosensitization	Cataract Corneal necrosis Eye dam Eye irr Eye photosen
Skin	Alopecia Argyria Chloracne Dermatitis Skin damage Skin irritation Skin photosensitization Skin sensitization	Alopecia Argyria Chloracne Dermatitis Skin dam Skin irr Skin photosen Skin sens
Teeth	Dental erosion	Dental erosion

Group	Effect Name	Abbreviation (if necessary)
	Dental fluorosis	Dental fluorosis
Bones	Bone damage Fluorosis	Bone dam Fluorosis
Thyroid	Thyroid effect	Thyroid
Liver	Hepatic necrosis Liver damage Liver Effects	Hepatic necrosis Liver dam Liver
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
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
Hearing impairment
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
Liver cancer
Liver damage
Lower respiratory tract irritation
Lung cancer
Lung damage
Malaise
Male reproductive system damage
Mesothelioma
Metabolic acidosis
Metal fume fever
Methemoglobinemia
Muscular stimulation
Mutagenic effect
Myocardial effect
Nasal cancer
Nausea
Neurotoxicity
Nitrosylhemoglobin formation
Ocular nerve damage
Peripheral neuropathy
Peripheral nervous system impairment
Pneumoconiosis
Pneumonitis
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

APPENDIX 1, ANNEX C

GUIDE #1: CONVERSION FROM ANIMAL DIETARY PPM TO ANIMAL MG/KG/DAY

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

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

Some useful normative values*:

Mouse: body weight (BW) is approximately 30 g; mouse consumes ~4 g diet per day

Hamster: BW is approximately 100 g; hamster consumes ~10 g diet per day

Rat: BW is approximately 350 g; rat consumes ~20 g diet per day

Dog: BW is approximately 10 kg; dog consumes ~300 g diet per day

General Equation (mg CS/kg BW/day)

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

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

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

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

GUIDE #2: CONVERSION FROM ANIMAL DIETARY PPM TO ANIMAL INHALATION EXPOSURE

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

SCALING FACTORS (assuming normative values):

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

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

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

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

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

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

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

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

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

Respiratory Rate x Tidal Volume x Duration of Exposure

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

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

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

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

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

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

GUIDE #3: CONVERSION FROM ANIMAL DIETARY PPM TO HUMAN INHALATION EXPOSURE

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

SCALING FACTORS (assuming normative values):

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

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

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

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

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

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

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

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

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

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

Units: mg/day ÷ kg BW = **mg/kg/day**

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

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

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

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

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

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

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

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

References, Appendix 1, Annex C

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APPENDIX 1, ANNEX D, PART 1

Carcinogenicity

Introduction

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

Background

General

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

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

Cross-Sectional Study

A cross-sectional study examines the relationship between disease (or other health related state) and other variables of interest as they exist in a defined population at a single point in time or over a short period of time (e.g. calendar year). Cross-sectional studies can be thought of as providing a snapshot of the frequency of a disease or other health related characteristics (e.g. exposure variables) in a population at a given point in time. Cross-sectional studies are used to assess the burden of disease or health needs of a population and are particularly useful in informing the planning and allocation of health resources

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

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

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

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

Animal bioassays can be reasonable, but not infallible, predictors of the qualitative response in humans exposed under certain conditions. Species concordance between tumor type(s) is not necessarily anticipated or expected. It is not at all clear, however, whether the doses used in animal studies are predictors of the quantitative potency of such chemicals in their carcinogenic potential in humans. Maximum tolerated doses (MTDs), often defined for purposes of animal studies on the basis of elevated mortality, increased body weight loss or other toxicological effects not related to carcinogenicity, are justified based on the low statistical sensitivity associated with animal studies. It is recognized, however, that extraordinarily large doses greatly exceeding those typical of human exposures are also associated with marked physiological and often bizarre pharmacokinetic consequences. For chemicals of relatively low carcinogenic potency, but high local or systemic toxicity, it may be difficult to detect a carcinogenic response using currently available animal bioassay protocols and it is possible that such agents could be overlooked. Nevertheless, human exposures to such highly toxic chemicals would probably be controlled by TLVs that are based on their acute and chronic toxicities, with an expected concomitant reduction in their carcinogenic potential.

It is the opinion of ACGIH that an ideally planned experimental carcinogenicity study should have at least three dose groups in addition to a concurrent vehicle control group and a concurrent untreated control group: a high dose (typically a MTD) which will produce an effect, a suitably selected no-effect dose, and an intermediate dose. The high dose effect need not necessarily induce death or elicit other marked acute toxicity, but it may include the agent's known pharmacologic or toxicologic manifestations. The most acceptable evidence of carcinogenicity is a dose-response gradient for the various experimental groups which correlates with the exposure levels. In this manner, using properly selected models, one may be able to estimate the lowest dose (exposure) associated with a neoplastic response and subsequently assess the risk associated with airborne exposure levels and excursions. Where the evidence indicates

skin penetration as a significant route of exposure, this will be indicated by the TLV Skin notation. Replication of results in multiple species or confirmatory experiments enhance the overall "weight-of-evidence" given to study results. The importance of time-to-tumor and incidence of distant and multiple tumor sites is recognized, since differences between the exposed and control groups can be an important factor in the estimation of carcinogenic potential.

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

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

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

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

- Two species of test animals (usually rats and mice) tested at three dose levels; one a high level (typically the MTD) and the others some fraction of the high level (usually one-half the MTD) based on the results of a 90-day subchronic toxicity study wherein the chemical under study is administered preferably by a route relevant to worker exposure.
- Dosing and observation for the animal's lifetime (in the case of rodents, usually 2 years).
- At least 50 animals per sex per dose group with adequate concurrent controls.
- Adequate historical controls.
- Detailed, quality controlled, histopathological examination of tissues.
- Appropriate statistical evaluation of the results.
- Study carried out under Good Laboratory Practice conditions.
- Evidence for classification of an agent as an experimental (animal) carcinogen includes:
- Statistically significant dose-related increase in malignant tumors.
- An increase in the occurrence of very rare malignant tumors (example, - increases in tumors having a near zero incidence rate among the historical control data).
- The occurrence of neoplasms at sites distant from the initial chemical contact.
- Earlier onset of cancers among the treated animals.

Malignant tumors are of greatest concern, but the presence of benign tumors can be considered as supportive evidence for other findings of carcinogenicity; the presence of benign tumors is not taken as

evidence for the carcinogenicity classification in and of itself. For example, other histologic alterations, such as the development of squamous metaplasia of the respiratory epithelium, may be a precursor of malignancy. Such changes by themselves, however, should not be taken as evidence for the classification as a carcinogen in experimental animals.

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

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

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

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

Key Characteristics of Carcinogens	
Characteristic	Example of Relevant Evidence
Electrophile	Parent or metabolite with an electrophilic structure (e.g. epoxide), formation of DNA and protein adducts
Genotoxic	DNA damage (DNA strand breaks, DNA-protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g. chromosome aberrations, micronuclei formation)
Alters DNA repair or induces genomic instability	Alteration of DNA replication or repair (e.g. topoisomerase II, base-excision or double-strand break repair)
Epigenetic alterations	DNA methylation, histone modification, microRNA expression
Oxidative Stress	Oxygen radical and damage to macromolecules

Chronic Inflammation	Increased WBC, myeloperoxidase activity, altered cytokine and/or chemokine production
Immunosuppression	Decreased immunosurveillance, immune system dysfunction
Modulated receptor-mediated effects	Receptor (in)activation (e.g. Estrogen, AhR) or modulation of endogenous ligands
Induces Immortalization	Inhibition of senescence, cell transformation
Alters cell proliferation, cell death, or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Recommendation

Classification with notations A1-A5 is limited to substances for which evidence exists (either positive or negative) regarding carcinogenicity, e.g., carcinogenicity bioassay data, epidemiologic studies, supporting mechanistic data. ACGIH modified the descriptions of IARC categories 2A and 2B to eliminate the words "probable" and "possible" in defining our new categories A2 and A3. It is believed that such a modification is more easily understood by practicing occupational hygienists and will avoid misinterpretation of the intent of ACGIH. ACGIH is most interested in the predictive relevance to human risk due occupational exposures.

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

Strength of Evidence Descriptors			
Strength	Human Evidence	Experimental Animal Evidence	Mechanistic Evidence
Sufficient	A positive association has been observed in epidemiological studies in which bias, confounders, and coincidence are ruled out. A plausible mechanism of action can be attributed to the association.	A positive association has been observed in a well-designed and conducted studies. A plausible mechanism of action can be attributed to the association.	Data from multiple experimental studies support a mechanism of carcinogenicity that is consistent with the findings in human and/or experimental animal studies
Limited	A positive correlation between an exposed population and exposure to an agent is demonstrated; however, bias, confounders, and coincidence provide low confidence that the observation of carcinogenicity can be attribute to exposure.	Tumors, neoplasms, and/or lesions are observed but the data are limited or confounded such that a definitive carcinogenic diagnosis is possible. For example, evidence of carcinogenicity is only observed in one of many studies, the study demonstrates benign lesions, or the agent decreases tumor latency but does not increase tumor incidence	The evidence from experimental studies suggest interactions with DNA, nuclear receptor binding, etc., but there are inconsistencies in study design such as limited number of doses, cytotoxicity is present in the experiment, or there are unexplained inconsistencies between experimental systems.
Inadequate	No human data are available, or the available data lack statistical power, are of insufficient quality, or lack precision to make an association between exposure and carcinogenicity	There are limited or insufficient data with subchronic, chronic or lifetime exposures or studies with too short of an exposure period to allow for toxicity and preneoplastic lesion determination.	The studies that are available are in cell lines or species not relevant or validated for assessing an agent's ability to interact with DNA and subsequently induce a preneoplastic or neoplastic event at the cellular or nuclear level.

The following table provides guidance on the overall assessment of available data to determine the carcinogenicity category:

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

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

The recommended definitions are as follows:

Categories for Occupational Carcinogenicity

A1 — Confirmed Human Carcinogen

The agent is carcinogenic to humans based on the weight of evidence from epidemiologic studies.

A2 — Suspected Human Carcinogen

Human data are accepted as adequate in quality but are conflicting or insufficient to classify the agent as a confirmed human carcinogen; or, the agent is carcinogenic in experimental animals at dose(s), by route(s) of exposure, at site(s), of histologic types(s), or by mechanism(s) considered relevant to worker exposure. The A2 is used primarily when there is limited evidence of carcinogenicity in humans and

sufficient evidence of carcinogenicity in experimental animals is supported by mechanistic evidence of key characteristics of carcinogens that are relevant to humans.

A3 — Confirmed Animal Carcinogen with Unknown Relevance to Humans

The agent is carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), of histologic types(s), or by mechanism(s) that may not be relevant to worker exposure. Available epidemiologic studies do not confirm an increased risk of cancer in exposed humans. Available experimental animal evidence suggests mechanisms and/or dosimetry that the agent is unlikely to cause cancer in humans except under improbable routes or levels of exposure.

A4 — Not Classifiable as a Human Carcinogen

Agents which cause concern that they could be carcinogenic for humans, but which cannot be assessed conclusively because of a lack of human data. *In vitro* or animal studies do not provide mechanistic evidence of key characteristics of carcinogenicity which are sufficient to classify the agent into one of the other categories.

A5 — Not Suspected as a Human Carcinogen

The agent is not suspected to be a human carcinogen on the basis of properly conducted epidemiologic studies in humans. These studies have sufficiently long follow-up, reliable exposure histories, sufficiently high dose, and adequate statistical power to conclude that exposure to the agent does not convey a significant risk of cancer to humans; or, the evidence suggesting a lack of carcinogenicity in experimental animals is supported by mechanistic data demonstrating a lack of the key characteristics of carcinogenicity.

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

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

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APPENDIX 1, ANNEX D, PART 2

Sensitization (DSEN/RSEN)

(Note: See the glossary below for terminology definitions.)

Introduction

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

Definition

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

In the workplace, respiratory, dermal, or conjunctival exposures to sensitizing agents may occur. Similarly, sensitizers may evoke respiratory, dermal, or conjunctival reactions. The notation does not distinguish between sensitization involving any of these tissues. The absence of a DSEN or RSEN notation does not signify that the agent 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 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 (RSEN)

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

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

Dermal Sensitization (DSEN)

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

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

The following information may be considered 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 $\geq 30\%$ is considered positive. For a non-adjuvant test method, such as the Buehler test (Buehler, 1965), a response of $\geq 15\%$ is considered positive. Positive results (i.e., a stimulation index ≥ 3) in the murine local lymph node assay (LLNA) may also be used as evidence of a dermal sensitization hazard (Kimber *et al.*, 1989, 1991; Geberick *et al.*, 1999).

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

The following information may be considered 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.

Examples of sensitizers

Respiratory*

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

Tetryl is a compound for which possible respiratory sensitization was reported in 1950 and 1952. However, the evidence was insufficient to assign a RSEN notation. Some workers experienced

itchy eyes, sore throats, nose bleeds, and coughing bouts, some of which were “troublesome at night”. This chemical substance is also highly irritating, causing yellow discoloration of the skin and hair. The descriptions are more consistent with irritation of the respiratory tract, rather than respiratory sensitization. No animal sensitization data were available.

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

Dermal

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

Picric acid is a compound that has some evidence of skin sensitization in workers but the evidence was insufficient to assign a DSEN notation. One study published in 1944 reported that skin contact with the dry powder of picric acid and ammonium picrate powder during the manufacture of explosives 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.

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 $\geq 120\%$ 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 1, ANNEX D, PART 3

Inhalable Fraction and Vapor (IFV)

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

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

Other considerations:

1) Liquids with TLV reported in ppm with SVC/TLV ratios > 10

Liquids present in a closed environment will establish an equilibrium as determined by the temperature of liquid, generate a vapor phase. This vapor component is reported as the vapor pressure of that liquid. Compounds that have high ratios have a high tendency to exist in the vapor phase at the operating temperature. When work is done with the atmosphere at the TLV, this atmosphere is unsaturated, with much liquid aerosol that would continue to evaporate. This strongly favors the presence of vapor over aerosol. Typically, these liquids are generally considered to be low boiling liquids, often this means the boiling temperature is below 150 °C. It is appropriate to report the TLV for these compounds in ppm, indicating the industrial hygienist to pay particular attention to the vapor phase, the principal phase for worker exposure. Any aerosol generated is likely to quickly evaporate.

2) Liquids with TLV reported in ppm with SVC/TLV ratios < 10

Liquids where the vapor pressure of the liquid is lower such that the ratio is now below 10, indicates that work at the TLV is very close to, within an order of magnitude of, the saturation level for that substance. Where there is ventilation in the workplace that would reduce the total airborne concentration, this is scenario would generally require having aerosol present as well as vapor phase material. In this situation, the inclusion of the IFV endnote serves as a reminder to examine both phases to determine total airborne concentration.

3) Solids with TLV reported in mg/m³ with SVC/TLV ratios > 10

Solids will also generate an equilibrium vapor component and should have vapor pressures at room temperature reported if they are known. As a compound in the solid requires significantly more energy to enter the vapor phase than does the liquid, this generally results in a greater time needed to establish this vapor equilibrium phase, or saturated vapor concentration. It is difficult to estimate whether this SVC value can be reached in a workplace environment where there is both some degree of ventilation and perhaps variable temperatures of reagents.

A simple method to classify whether the solid may lead to the formation of the vapor phase to a significant degree during manipulation or use, is to examine the melting temperature. The melting temperature provides as rough indication of the relative energy needed to promote the sublimation of a compound to create the vapor phase material. Melting temperatures that are high, often higher than 150°C, generally have corresponding sampling methodologies that relies principally on the filtration of airborne aerosol onto a filter without any attempt to capture any generated vapor using an adsorbent tube. Such tested sampling methods suggest that this solid is then not likely to have a significant loss of sample due to failure to capture the vapor phase due to phase transfer of material from aerosol. And so, if the vapor phase contribution is likely negligible, then this material would not qualify for the inclusion of the IFV notation, even though upon first glance, the SVC/TLV is very high. The formation

of that saturated vapor phase is simply much too slow, not impacting the worker within the time frame they are exposed to the solid aerosol.

Solids with lower melting points, say just above room temperature, are much more likely to have material from the solid sublime to enter the vapor phase. This increases the importance of the vapor phase to the overall total airborne concentration. For these solids, the inclusion of the IFV notation would be seen as appropriate. This can be verified against a verified sampling methodology, where now the filtering of the solid is generally accompanied by an adsorbent tube that is used to capture any loss of this solid that has transferred to the vapor phase.

There are also solids that have fairly high melting points, however typical uses are not as pure compounds as they are typically dissolved in highly volatile solvents for use in spraying operations. The potential exposure to the worker could be solid aerosol when dealing with the pure substance, or to aerosolized droplets of solution where there is worker potential for worker exposure

4) Temperature and composition variables

The industrial hygienist should also consider both particle and vapor phases to assess exposures from spraying operations, from processes involving temperature changes that may affect the physical state of matter, when significant fraction of the vapor is dissolved into or adsorbed onto particles of another substance, such as water-soluble compounds in high humidity environments. It is important to remember that the above discussions of ratios from SVC/TLV stem from the analysis of how a compound behaves in the pure state, using that to predict what would be present in different phases at room temperature. Changing solvent or temperature directly affects how compounds partition between different phases, and as such the hygienist needs to evaluate these situations independently.

APPENDIX 1, ANNEX D, PART 4

Skin

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

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

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

Substances having a Skin notation and a low TLV may present special problems for operations involving high airborne concentrations of the material, particularly under conditions where significant areas of the skin are exposed for a long period. Under these conditions, special precautions to significantly reduce or preclude skin contact may be required.

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

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

Examples illustrating the use of the skin notation

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

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

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APPENDIX 1, ANNEX D, PART 5

OTOTOXICANT “OTO” Notation

Introduction

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

Statement in Introduction to TLV® Book

The designation “OTO” for ototoxicity in the “Notations” column highlights the potential for a chemical to cause hearing impairment alone or in combination with noise, even below 85 dB. The “OTO” notation is reserved for chemicals that have been shown, through animal studies or human experience, to adversely affect auditory capacity, usually manifested as a permanent threshold shift at specific frequencies. Certain solvents, predominantly aromatic hydrocarbons, but also some halogenated solvents and chemicals that cause anoxia, have been shown to cause hearing loss. Some solvents appear to act synergistically with noise. The “OTO” notation is intended to focus attention, not only on engineering controls, administrative controls and PPE needed to reduce airborne concentrations, but also on other means of preventing excessive combined exposures with noise to prevent hearing loss. Specifically, affected employees may need to be enrolled in hearing conservation and medical surveillance programs to more closely monitor auditory capacity.

Relationship to TLV® and TLV® Basis

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

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

Assessment of Human and Animal Studies

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

Evidence in humans that the agent can cause hearing impairment in a substantial number of people in occupational settings is the primary criteria in assigning an OTO notation. Results of the following common tests could be considered either alone or in combination to base a conclusion that an agent may produce ototoxicity in the workplace: pure tone audiometric testing, high-frequency audiometry, emittance audiometry, reflex modification audiometry (RMA), transient evoked otoacoustic emissions (TEOAE) testing, TEOAE suppression, acoustic reflex measurements, and distortion product otoacoustic emissions (DPOAE) testing. Other central auditory processing tests include electrocochleography, auditory brainstem response (ABR), cortical response audiometry, middle latency evoked function testing, and late latency evoked function testing. Other behavioural tests include behavioural audiometry (BA), conditioned avoidance response (CAR), psychoacoustic modulation transfer function, Random gap detection test

(RGDT), interrupted speech, speech recognition in noise, Northwestern “University auditory test No. 6, and dichotic digits test.

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

Other Considerations

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

Examples of Ototoxicants and Non-Ototoxicants

Styrene (“OTO” Notation Assigned)

TLV[®]-TWA, 10 ppm; TLV[®]-STEL, 20 ppm

High frequency hearing loss has been reported in workers exposed to styrene, with or without concurrent excessive noise exposure (Morata et al. 2002; Sliwiska-Kowalska et al., 2003; Johnson et al., 2006; Mascagni et al., 2007; Morata et al., 2011). Since hearing loss can be irreversible, it is unclear whether prior or current exposures contributed to the ototoxicity reported by these investigators. More recent studies by Triebig et al. (2009) and Sisto et al. (2013) suggest the threshold for styrene-induced hearing loss is likely to be between 20 and 40 ppm, expressed as mean exposure concentrations, assuming peak exposures are properly managed. Ototoxicity was only reported at concentrations ≥ 300 ppm in animals, especially in active compared to sedentary animals (Pryor et al., 1987; Albee et al., 1992; Lataye et al., 2005). The animal data demonstrate synergistic effects with styrene and noise exposure and the importance of concurrent continuous vs. impulse noise exposures in causing ototoxicity (Makitie et al., 2003; Chen and Henderson 2009; Campo et al. 2014). Collectively, the increased response with combined noise and styrene exposures in these studies rarely exceeded 2-fold. Based on the evidence for high frequency hearing impairment in animals and humans discussed above, an Ototoxicant (OTO) notation is recommended.

Xylene (“OTO” Notation Assigned only to p-xylene and not the other isomers)

TLV[®]-TWA, 20 ppm

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

participants with high cumulative dose of xylene exposure had poorer test results than participants with less xylene exposure (Fuente et al. 2013).

Weight-of-Evidence Assessment Grid

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

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

Boilerplate language to use in the Documentation

A, B, F, G

An OTO notation is assigned based upon both the reported ototoxicity in humans and a positive response in animals.

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

C, D, E

An OTO notation is assigned based upon the positive response in animals alone.

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

K, P, U

An OTO notation is assigned based upon the reported ototoxicity 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 ototoxicants since the data directly pertain to human exposures and no extrapolation is needed.

H, I, L, Q

An OTO notation is not proposed at this time based upon weak or equivocal responses in 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” to such CS as ototoxicants.

M, N, R, S

An OTO notation is not proposed based upon the lack of ototoxicity in humans and negative responses in animals.

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

J, O, T, V, W, X, Y

An OTO 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 ototoxicants.

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Glossary (From Johnson and Morata 2010)

- Action level** - A guideline used by many international occupational health bodies to express the level of a harmful or toxic substance/activity which requires medical surveillance, increased industrial hygiene monitoring or biological monitoring. For chemicals, it is usually 50 % of the occupational exposure limit. For noise, it indicates the sound level which, when reached or exceeded, necessitates implementation of activities to reduce the risk of noise-induced hearing loss. The new European noise directive has two exposure action levels (See Section 2.3).
- Continuous noise** - Noise of a constant level as measured over at least one second using the “slow” setting on a sound level meter. Note that a noise which is intermittent, e.g. on for over a second and then off for a period, would be both variable and continuous.
- Decibel (dB)** - A dimensionless unit expressing the relative loudness (intensity) of sound on a logarithmic scale. The decibel was named after Alexander Graham Bell. A-weighted decibels, dBA or dB(A). A-weighting is the most commonly used of a family of curves defined in various standards relating to the measurement of perceived loudness, as opposed to actual sound intensity. The others are B, C and D-weighting (for dBB, dBC and dBD). The A-weighting is the most used in noise measurements since its corrections are aimed to replicate the sensitivity of the average human ear to sound at different frequencies.
- Equivalent sound pressure level (Leq)** - The steady sound level that, over a specified period of time, would produce the same energy equivalence as the fluctuating sound level actually occurring. Occupational exposure limits for a hazard expressed as an 8-hour time-weighted average value includes the total exposure during a shift exposure. For noise, a single number gives the value in decibels that represents the equivalent average level of the actual changing noise levels. When the exchange rate (see below) of 3 dB is used in this calculation, the average noise level is called the Leq.
- Exchange rate** - The amount of decrease (or increase) in noise level which would allow doubling (or require halving) of the exposure time in order to have the same risk. The 3-dB exchange rate is also known as the “equal-energy” exchange rate because the equivalent acoustic energy is preserved when the sound level changes by 3 dB and the exposure duration changes by a corresponding factor of 2. Most countries use a 3dB exchange rate, thus, if the intensity of an exposure increases by 3 dB, the dose doubles or the allowable time is halved.

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

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

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

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

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

Noise - Any unwanted sound.

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

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

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

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

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

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

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

APPENDIX 1, ANNEX D, PART 6

TLV[®]-SL (Surface Limit)

Introduction

This annex is intended to provide guidance to authors when considering establishment of a surface limit. The TLV[®]-SL should be considered for all chemical substances that have a Skin notation or a DSEN notation. Those chemical substances that have an RSEN notation will also have a Skin notation if dermal exposure is known or suspected to cause induction of respiratory hypersensitivity. The TLV[®]-SL was introduced in 2019 and first applied to a skin and respiratory sensitizer (o-phthalaldehyde) based on an extrapolation from the EC3 value from the murine local lymph node assay (LLNA). An example calculation of a TLV[®]-SL using the LLNA EC3 is provided below. The methodology for basing the TLV[®]-SL on systemic effects is still under development; however, basic considerations will be discussed and illustrated with a short example.

Statement in Introduction to TLV[®] Book

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

Deriving a TLV-SL for Skin Sensitizers

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

Example Calculation - Derivation of the TLV[®]-SL for o-Phthalaldehyde:

The following example illustrates how a surface (wipe) limit can be derived using the LLNA EC3 value of 0.051% determined by Anderson et al.⁽²⁸⁾ for o-phthalaldehyde in which 25 µl was applied to 1 cm² surface area on both ears of the mouse.

Convert EC3 from volume percent to surface area concentration.

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

Calculate Wipe Limit

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

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

Deriving a TLV®-SL for a Systemic Toxicant

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

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

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

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

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

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

where:

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

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

AF_c = composite adjustment factor reflecting various sources of uncertainty and variability such as inter-individual variability, interspecies extrapolation, pharmacokinetic variability, extrapolation from a LOAEL

to a NOAEL, severity of adverse effects, consideration of sensitive subpopulations, and robustness (completeness) of the data set.

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

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

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

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

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

where:

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

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

In practice the following equation could be used:

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

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

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

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

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

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

References

Kimmel, TA, Sussman, RG, Ku RH, Ader, AW: Developing Acceptable Surface Limits for Occupational Exposure to Pharmaceutical Substances. J. ASTM Intl., published online August (2011).

Naumann, BD and Arnold, SF: Setting surface wipe limits for skin sensitizers. Toxiol. Indust. Hlth. Published on-line 23-Sep-2019. SF (2019). <https://doi.org/10.1177/0748233719875365>.

APPENDIX 2

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)".
 - You may not need much of the above two paragraphs. Most search engines are now very user friendly.
- 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 1950's), 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.
 - **PubChem**

PubChem is a Database from the NLM that provides a comprehensive overview of a compounds names and identifiers, chemical and physical properties, safety and hazards, toxicity, and mutagenicity studies. PubChem is a good starting point for literature searches because it will provide synonyms and other identifiers such as EPA chemical registration numbers. PubChem will also provide relevant literature in the "Toxicity" section that may be relevant to TLV development. The references on the literature provided may also be useful in development of a TLV.
 - **ChemIDplus**

ChemIDplus is a free, web search system that provides access to the structure and nomenclature authority files used for the identification of chemical substances cited in the NLM databases. ChemIDplus also has structure searching and direct links to resources at NLM, federal agencies, US states, and scientific sites. ChemIDplus is a good first step when starting a literature search. It will give you direct links to different organizations and groups that have performed research on the substance.
 - **Other Useful Resources**
 - **EPA National Service Center for Environmental Publications** – The EPA NSCEP can be used to find literature submitted to register the compound with the EPA
 - **EPA Aggregated Computational Toxicology Online Resource (ACToR)** – Aggregates data from thousands of public sources on over 500,000 chemicals and allows you to follow links to relevant data. Actor will also have information on IARC monographs for a compound
 - **Comparative Toxicogenomics Database** – Provides publicly available data that aims to advance understanding about how environmental exposures affect human health. This includes chemical-gene/protein interactions, chemical-disease and gene-disease relationships
 -
- **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.

- Some direct sources for these properties include: NLM, HSDB, Merck Index, CRC Handbook of Chemistry and Physics.

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

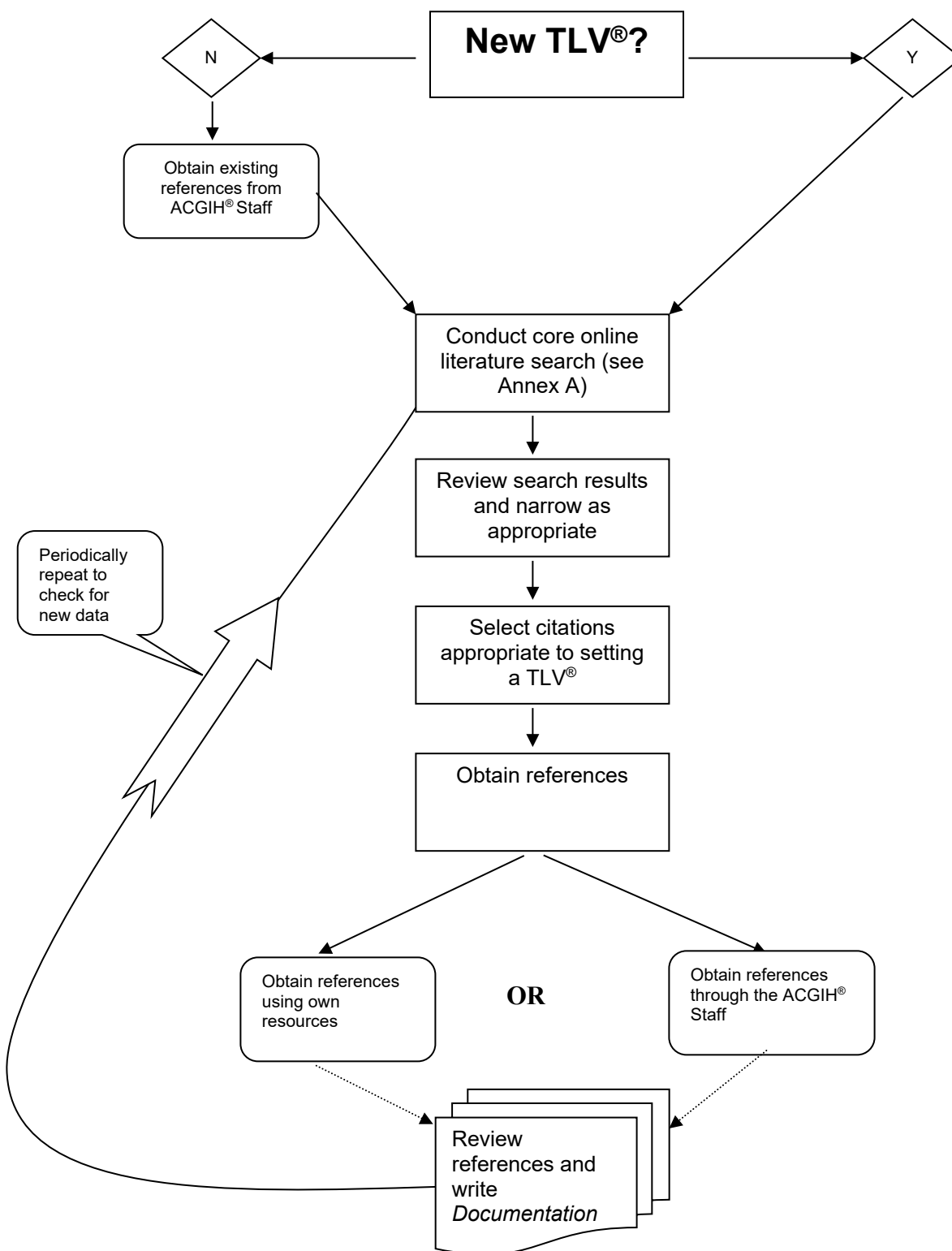
Once the initial literature search has been completed, the next step is to obtain copies of the references.

- 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, online library services such as Wiley for a cost, or by requesting the article directly from the author via Researchgate.

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. All searches performed are uploaded to the appropriate folder in Sharefile.
- 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* prior to the distribution of the fall meeting materials. Every Summer all NIC substances are automatically searched to include any new and relevant material. Any other substances that need to be researched must be made by request, to the Assistant to the Chair.

Literature Searching Process Diagram



APPENDIX 2

Annex A

Core References

The websites outlined in the following table should be looked at 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 older MEDLINE articles as well as out-of-scope citations, journal citations pre-dating Medline indexing, and additional full text life science journals. - Contains many free full text links; but some require a subscription. <i>Pubmed quick start guide is a comprehensive overview on how to successfully use the database.</i> Access to older publications are made by using the custom range publication dates.	
OR		
IRIS	☐ IRIS (Integrated Risk Information System): 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.	
Regulations.gov	Regulations.gov provides studies that are submitted to the EPA during chemical registration.	

APPENDIX 2

Annex A

ECHA https://echa.europa.eu/home	European Chemical Agency Chemical infocards and registration dossiers	
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Online Site & URL	Description of Site	Checked
NTP Testing Information 1. NTP Testing Information and Study Results and reports . http://ntp.niehs.nih.gov/index.cfm?objectid=72016715-BDB7-CEBA-F4CF107673CF0C15 2. 14 th 10 th Report on Carcinogens https://ntp.niehs.nih.gov/pubhealth/roc/index.html	- National Toxicology Program ☐ NTP study results and reports. ☐ Prepared by the NTP with intent of identifying substances that cause/may cause cancer and to which a significant population is exposed.	
ATSDR Toxicological Profiles http://www.atsdr.cdc.gov/toxpro2.html	Toxicological profiles for hazardous substances found at NPL sites.	

APPENDIX 2

Annex B

Global OEL Links

The following references may be useful in a literature search:

Global OEL Links	
Online Site & URL	Description
OSHA PEL's • 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) • HPV's (High Production Volume Chemicals) • LPV's (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 OEL's in the European Union, as well as links to member country websites. NOTE: Not all links are in English.
European Union OEL's https://www.dguv.de/ifa/fachinfos/occupational-exposure-limit-values/foreign-and-eu-limit-values/index.jsp •	□ The European Commission establishes two kinds of occupational exposure limit values or OELs (indicative OELs and binding OELs) which are published in various directives.
SCOEL Criteria Documents https://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684	□ 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.
ECETOC http://www.ecetoc.org/tags/dutch-expert-committee-on-occupational-standards/	□ European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) □ The Technical Reports address specific aspects of the science used in evaluating the hazards and risks of chemicals to human health and the environment.
The NOHSC was abolished in 2005	➤ Safe Work Australia and Hazardous Chemical Information System (HCIS)

APPENDIX 2

Annex B

Global OEL Links	
Online Site & URL	Description
http://hcis.safeworkaustralia.gov.au/	➤ SWA is an Australian government statutory body established in 2008 to develop national policy relating to <i>WHS</i> and workers' compensation.
AIHA WEEL Guides https://www.aiha.org/get-involved/AIHAGuidelineFoundation/WEELs/Pages/default.aspx	➤ American Industrial Hygiene Association Workplace Environmental Exposure Levels
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.
OEHHA Cal EPA https://oehha.ca.gov/	➤ The Office of Environmental Health Hazard Assessment (OEHHA) California EPA ➤ Proposition 65 protects the state's drinking water sources from being contaminated with chemicals known to cause cancer, birth defects or other reproductive harm, and requires businesses to inform Californians about exposures to such chemicals. ➤ This Proposition provides a published list of chemicals known to cause cancer or reproductive toxicity

APPENDIX 2

Annex B

Global OEL Links	
Online Site & URL	Description
MAK & BAT values https://onlinelibrary.wiley.com/doi/book/10.1002/3527600418	➤ The German Research Foundation ➤ Publications by the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Commission) provide essential information on hazardous compounds at the workplace. Threshold values and classifications for more than 1,000 substances are given, along with toxicological evaluations and recommended monitoring methods ➤ The Commission is internationally acknowledged for its neutrality, transparency and scientific criteria.

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
IARC Cancer Database https://monographs.iarc.fr/	IARC Cancer Epidemiology Database
High Production Volume Information System (HPVIS) Chemicals and Screening Information Data Set (SIDS) Testing 1. HPV (U.S.) Lists: https://iaspub.epa.gov/opthpv/public_search.html_page 2. SIDS (International): 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 https://www.cdc.gov/niosh/pubs/criteria_date_desc_nopubnumbers.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 the ILO - Contains information on the hazards and risks of a number of occupations
2. Encyclopedia of Occupational Health and Safety, 4 th Edition (1998) http://www.ilocis.org/en/default.html	- Produced by the 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
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BOOKS
<i>(Some available online or by other electronic formats)</i>
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.

Finding Chemical and Physical Properties

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/rthksfs/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 3

Committee Organization Chart

