2.2.2.3.4 Effect Level for a Response

1. State the species, effect, concentration, and exposure time to cause the effect.
2. Describe the toxicologic endpoint of concern.

When data are insufficient to estimate the highest exposure that does not cause lethality, exposure levels that cause severe toxicity in the absence of lethality are used in the selection of exposure levels to set AEGL-3 values. The endpoints of concern include decreased hematocrit, methemoglobin formation (70-80%), cardiac pathology, and severe respiratory pathology.

2.3 GUIDELINES AND CRITERIA FOR THE SEARCH STRATEGY, EVALUATION, SELECTION, AND DOCUMENTATION OF KEY DATA AND SUPPORTING DATA USED FOR THE DERIVATION OF AEGL VALUES

2.3.1 Search Strategy

The literature search strategy focuses on three general sources of information: (1) electronic databases, primarily peer-reviewed journals, and government databases; (2) published books and documents from the public and private sectors of the United States and foreign countries, including references on toxicology, regulatory initiatives, and general chemical information; (3) data from private industry or other private organizations. The search strategy also includes the use of search terms to enhance the relevance of the electronic databases identified and retrieved.

(*1) Electronic Database Coverage*

The following databases are searched:

TOXLINE database (1981-current) from the U.S. National Library of Medicine's TOXNET

TOXLINE covers the toxicologic effects of chemicals, drugs, and physical agents on living systems. Among the areas covered are adverse drug reactions, carcinogenesis, mutagenesis, developmental and reproductive toxicology, environmental pollution, and food contamination.

TOXLINE 65 database (1965-1980)

Subject coverage is identical to TOXLINE for time periods that precede that of TOXLINE.

HAZARDOUS SUBSTANCES DATA BANK (HSDB) (Current) from TOXNET

HSDB is a comprehensive factual and numeric chemical profile. Each chemical profile is peer reviewed for completeness and accuracy to reflect what is known about the chemical.

PUBLIC MEDLINE (PUBMED)

PUBMED includes MEDLINE and PREMEDLINE. MEDLINE, the U.S. National Library of Medicine's premier bibliographic database, covers medicine, nursing, dentistry, veterinary medicine, health-care systems, and the preclinical sciences. The above-mentioned TOXLINE searches include MEDLINE citations. PREMEDLINE, also produced by NLM, provides citation and abstract information before full records are added to MEDLINE. For a short period of time, this information is only available in PUBMED.

REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

RTECS, compiled by NIOSH (U.S. National Institute for Occupational Safety and Health), is a comprehensive database of basic toxicity information and toxic-effects data on more than 100,000 chemicals.

U.S. NATIONAL TECHNICAL INFORMATION SERVICE (NTIS)

The NTIS database provides access to the results of U.S. government-sponsored research, development and engineering, plus analyses prepared by federal agencies, their contractors, or grantees. It is a means through which unclassified, publicly available, unlimited distribution reports are made available from such U.S. agencies as National Aeronautics and Space Administration (NASA), Department of Energy (DOE), Department of Housing and Urban Development (HUD), Department of Transportation (DOT), and some 600 other agencies. In addition, some state and local government agencies contribute their reports to the database. NTIS also provides access to the results of government-sponsored research and development from other countries.

U.S. INTEGRATED RISK INFORMATION SYSTEM (IRIS)

IRIS contains data from EPA in support of human health risk assessment, focusing on hazard identification and dose-response assessment for specific chemicals.

U.S. FEDERAL RESEARCH IN PROGRESS (FEDRIP)

FEDRIP provides access to information about ongoing U.S. government-funded research projects in the fields of physical sciences, engineering, and life sciences.

U.S. DEFENSE TECHNICAL INFORMATION CENTER (DTIC)

DTIC is the central U.S. Department of Defense facility for access to scientific and technical information. The DTIC database includes technical reports, independent research and development summaries, technology transfer information, and research and development descriptive summaries. The scope of the DTIC collection includes areas normally associated with defense research, such as military sciences, aeronautics, missile technology, and nuclear science. The collection also includes information on biology, chemistry, environmental sciences, and engineering.

ORNL (U.S. Oak Ridge National Laboratory) IN-HOUSE DATABASES

CHEMICAL UNIT RECORD ESTIMATES (CURE)

The CURE database contains selected information from the EPA Office of Health and Environmental Assessment documents and Carcinogen Risk Assessment Verification Effort (CRAVE) and Reference Dose (RfD) work groups. Although the groups are not currently active, this database is a valuable compilation of historic information.

TOXICOLOGY AND RISK ANALYSIS (TARA) DOCUMENT LIST

This database lists all types of documents written by TARA staff over the past 15 years. These range from toxicity summaries to journal articles. This list provides good references for chemicals that overlap the AEGL priority list.

(2) Published Books and Documents from the Public and Private Sectors

GENERAL REFERENCES FOR TOXICOLOGY AND CHEMICAL INFORMATION

ATSDR (U.S. Agency for Toxic Substances and Disease Registry) Toxicological Profiles.
Chemfinder, Chemical Searching and Information Integration by CambridgeSoft Corporation
Current Contents, Life Sciences edition
HEAST (Health Effects Assessment Summary Tables)
Kirk-Othmer Encyclopedia of Chemical Technology
IARC (International Agency for Research on Cancer) Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans
Low-Dose Extrapolation of Cancer Risks, S. Olin et al. (editors)
Merck Index
NTP (U.S. National Toxicology Program) Division of Toxicology Research and Testing, published reports.
Patty's Industrial Hygiene and Toxicology
Respiratory System, Monographs on the Pathology of Laboratory Animals, T.C. Jones et al. (editors)
Synthetic Organic Chemicals, U.S. International Trade Commission
Toxicology of the Nasal Passages, C.S. Barrow (editor)
U.S. Air Force Installation Restoration Program Toxicology Guide

GENERAL REFERENCES FOR REGULATORY INFORMATION AND STANDARDS

AIHA (American Industrial Hygiene Association) Emergency Response Planning Guidelines (ERPGs) and Workplace Exposure Level Guides (WEELs)
ACGIH (American Conference of Government and Industrial Hygienists) Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices
ACGIH Documentation of Threshold Limit Values
NAAQS (U.S. National Ambient Air Quality Standards)
NIOSH (U.S. National Institute for Occupational Safety and Health) Documentation of IDLH's (immediately dangerous to life and health)
NIOSH Pocket Guide to Chemical Hazards
NIOSH Recommendations for Occupational Safety and Health, Compendium of Policy Documents and Statements
OSHA (U.S. Occupational Safety and Health Administration) Limits for Air Contaminants
SMACs (Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants), Committee on Toxicology, sponsored by the National Research Council
EPA Health Effects Documents

(3) Unpublished Data from Private Industry and Other Private Sector Organizations of All Nations

These data consist of reports and data that are not published in peer-reviewed scientific journals but are relevant to the development of AEGLs. Most often, the data represent acute toxicity data from controlled inhalation exposure studies available from private industry or other organizations in the private sector of all nations that may or may not be published in a peer-reviewed journal.

Search Terms

The U.S. Chemical Abstract Services (CAS) Registry number of the chemical is used as the first choice. Chemical nomenclature or common chemical names and synonyms are used if the CAS Registry number is unknown.

The CAS Registry number alone is used as the first step. If there are approximately 300 citations, then all are retrieved for review. If less than approximately 300 references are found, searches are conducted using chemical nomenclature and common chemical names in addition to the CAS number. Searches by chemical name or names also should be made if few data of high quality are found, irrespective of the number of citations found.

If more than 300 citations are found using any form of chemical identification, the references may be enriched in relevance and quality by adding any number of the following characterizations of the desired data to the search strategy:

short-term
threshold limit
permissible exposure limit
acute toxicity
ocular terms
inhalation terms
dermal terms

If the number or quality of single-exposure toxicity studies found is not deemed to be adequate, multiple exposure studies may be considered but may not achieve a consensus of the NAC/AEGL Committee. If a consensus or two-third majority of the committee cannot agree on the adequacy of the data, the chemical may be placed on the list for future acute toxicity testing.

2.3.2 Evaluation, Selection, and Documentation of Key and Supporting Data

As a detailed interpretation and supplementation of the NRC (1993a) guidelines, the NAC/AEGL Committee has developed guidelines for evaluating the quality of studies to be used in the calculation of proposed AEGL values. The proposed evaluation and documentation procedure created by the NAC/AEGL Committee is intended to provide technical-support-document writers, reviewers, committee members, interested parties, and the public with a clear and consistent list of elements that must be considered in their evaluations. The proposed evaluation and documentation system will add technical validity and administrative credibility to the process by providing a transparent, logical, and consistent methodology for selecting key studies used to calculate an AEGL value. Additionally, the system will allow the proper selection of uncertainty factors and modifying factors in a consistent and logical manner. The process is designed to allow maximum flexibility in professional judgment while promoting scientific uniformity and consistency and providing a sound administrative foundation on which committee members can function.

Many toxicology studies used in the development of an AEGL were not designed to meet current regulatory guidelines and are not necessarily consistent in protocol or scientific methodology. As a result, these valuable investigations cannot be judged solely on the basis of currently accepted experimental design criteria for such studies. Current guidelines from EPA (1998) and the Organization for Economic Cooperation and Development (OECD 1993) are used as the basis for conducting future studies on behalf of the NAC/AEGL Committee, but lack of consistency of older studies requires evaluation and qualification of each data set for scientific validity within the context of AEGL documentation. A study can be valuable in the derivation of AEGLs without conforming completely to a standard of detailed methodology, data analysis, and the results reported. The aim of the subject procedure is to provide specific criteria in the selection and use of specific data sets for development of defensible values, yet retain the ability to use logical scientific thinking and competent professional judgment in the data-selection process. If a study or some portion of a study uses scientifically valid methods, contains adequate and reliable data, and presents defensible conclusions relevant to the AEGL process, it may be included in the technical support document (TSD) and used to support the AEGLs.

It is important to emphasize that only toxicity data obtained directly from a primary reference source are used as the basis for "key" toxicity studies from which the AEGL values are derived. Additionally, all supporting data and

information important to the derivation of an AEGL value are obtained solely from the primary references. These data include those used to provide a "weight-of-evidence" rationale in support of the AEGL value derived. Secondary references may be used to provide data and information on commercial uses, production volumes, chemical and physical properties, and other nontoxicologic or epidemiologic information on a chemical. Secondary references also may be used to present background information on the toxicity of a chemical. Any other information not important or directly relevant to the actual derivation of the AEGL values may be used to provide supporting rationale for the AEGL values. Data and information from secondary references should not be included in data summary tables presented in the TSDs

The credibility of evaluation guidelines is enhanced when they are drawn from a widely accepted prescription for study protocol design. The guidelines for a study evaluation should be based on the scientific methodologies but not be so restrictive that it precludes competent professional judgment. Current Good Laboratory Practice (GLP) guidelines provide a basis for selection of a robust list of study elements that, in concert with the professional experience and judgment of the AEGL Development Team and NAC/AEGL Committee members in general, are used to qualify the data which support the AEGLs. Consequently the NAC/AEGL Committee has used the NRC guidelines (1993a), the OECD Guidelines for the Testing of Chemicals (OECD 1993), and the EPA Health Effects Test Guidelines (EPA 1998) as a basis for selection.

The NRC (1993a) guidance provides general insight on the use of toxicologic data for AEGL derivation from routes of exposure other than inhalation. The NRC (1993a) guidance states that the bioavailability and differences in the pharmacokinetics from different exposure routes of the chemical in question must be considered. Because of these complex biologic phenomena and the paucity of data to enable credible evaluation and consideration, the NAC/AEGL Committee to date has selected and used only inhalation toxicity data to derive AEGL values. Further, toxicity data on other exposure routes will not be included in discussions in the TSDs unless those data are considered important for the support of relevant pharmacokinetic or metabolism data or mechanisms of toxicity. In the absence of inhalation data to derive an AEGL value, the NAC/AEGL Committee may use toxicity data from other exposure routes if there are adequate data to perform scientifically credible route-to-route extrapolations. In the absence of acceptable data, the committee will refer the chemical for toxicity testing.

Each key and supporting study is evaluated using all listed "elements for evaluation" as guidance. A "key study" is defined as the human and/or animal study from which a toxicologic value is obtained for use in AEGL calcula-

tions. "Supporting studies" include those human and/or animal studies used to support the toxicologic findings and values obtained from the key study, and their use is consistent with the weight-of-evidence approach to scientific credibility. While all elements for evaluation listed below are considered when evaluating a study, only elements for evaluation from key and supporting studies that are relevant to the derivation of the AEGL values will be discussed in the TSD as they impact the derivation. In evaluating a study, a variety of endpoints are preferred. However, a study measuring, for example, only one endpoint may be selected for development of an AEGL if other studies have shown that other known inhalation toxicology endpoints are less sensitive, provided the data are considered reliable. The list of elements for evaluation is used for initial review of all studies evaluated for possible inclusion in the TSD in instances in which they are germane to the selection of studies.

The NAC/AEGL Committee is dependent upon existing clinical, epidemiologic, and case report studies published in the literature for data on humans. Many of these studies do not necessarily follow current guidelines on ethical standards that require effective, documented, informed consent from participating humans subjects. Further, recent studies that followed such guidelines may not include that fact in the publication. Although human data may be important in deriving AEGL values that protect the general public, utmost care must be exercised to ensure first of all that such data have been developed in accordance with ethical standards. No data on humans known to be obtained through force, coercion, misrepresentation, or any other such means will be used in the development of AEGLs. The NAC/AEGL Committee will use its best judgment to determine whether the human studies were ethically conducted and whether the human subjects were likely to have provided their informed consent. Additionally, human data from epidemiologic studies and chemical accidents may be used. However, in all instances described here, only human data, documents, and records will be used from sources that are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or indirectly. These restrictions on the use of human data are consistent with the "Common Rule" published in the *Code of Federal Regulations* (Protection of Human Subjects, 40 CFR 26, 2000).

In addition to the discussion of the elements for evaluation in the individual studies section of the TSD, a section entitled "Data Adequacy and Research Needs" is included in the text of the TSD. A summary of the data-adequacy discussion is also included in the derivation summary tables in the appendix of the TSD and in the summary section of the TSD. The text of the TSD relates the studies used to derive or support the derivation of the AEGL

values to the discussion of the adequacy of the available data. Brief summaries of this discussion are included in the summary and derivation summary tables. The data-adequacy section also presents and integrates the weight of evidence by considering all information as a whole for each AEGL developed. In addition to considering the elements for evaluation as relevant in the discussion, a number of other factors must be considered. They include repeatability of experiments between laboratories, consistency of data between experiments and laboratories, types and number of species tested, variability of results between species, and comparison of AEGL values with the valid human and animal data. Every data set is a unique, chemical-specific source of information that reflects the investigations conducted on the chemical and the properties of the chemical. This section reflects a "best professional judgment" approach in the evaluation of the data adequacy and future research needs.

Figure 2-1 contains a diagram of the decision process for the selection of key studies and supporting studies. A summary of the elements or criteria used to select key studies and supporting studies and to evaluate their adequacy in deriving AEGL values follows.

Elements for the Evaluation of Key and Supporting Data and Studies

1. Only toxicity data and information obtained directly from a primary reference source may be used as the basis for "key" toxicologic studies. All other studies important to the derivation of an AEGL value or that serve as a weight-of-evidence rationale are obtained from a primary source.
2. Secondary references may be used for nontoxicologic data, such as physical and chemical properties, production locations, quantities, and background information on the toxicity of a chemical, provided the information is not directly used in the derivation of the AEGL values.
3. Only human data from studies that meet the ethical standards discussed in the "Evaluation, Selection, and Documentation of Key and Supporting Data" section of this SOP manual will be used in the derivation of AEGL values.
4. The inhalation route of exposure is preferred. When the endpoint of concern is systemic toxicity and the hepatic first-pass effect is not significant, oral exposure may be considered. In the absence of scientifically sound inhalation data and with high confidence in a valid route-to-route extrapolation, routes of exposure other than inhalation will not be used for AEGL derivation.

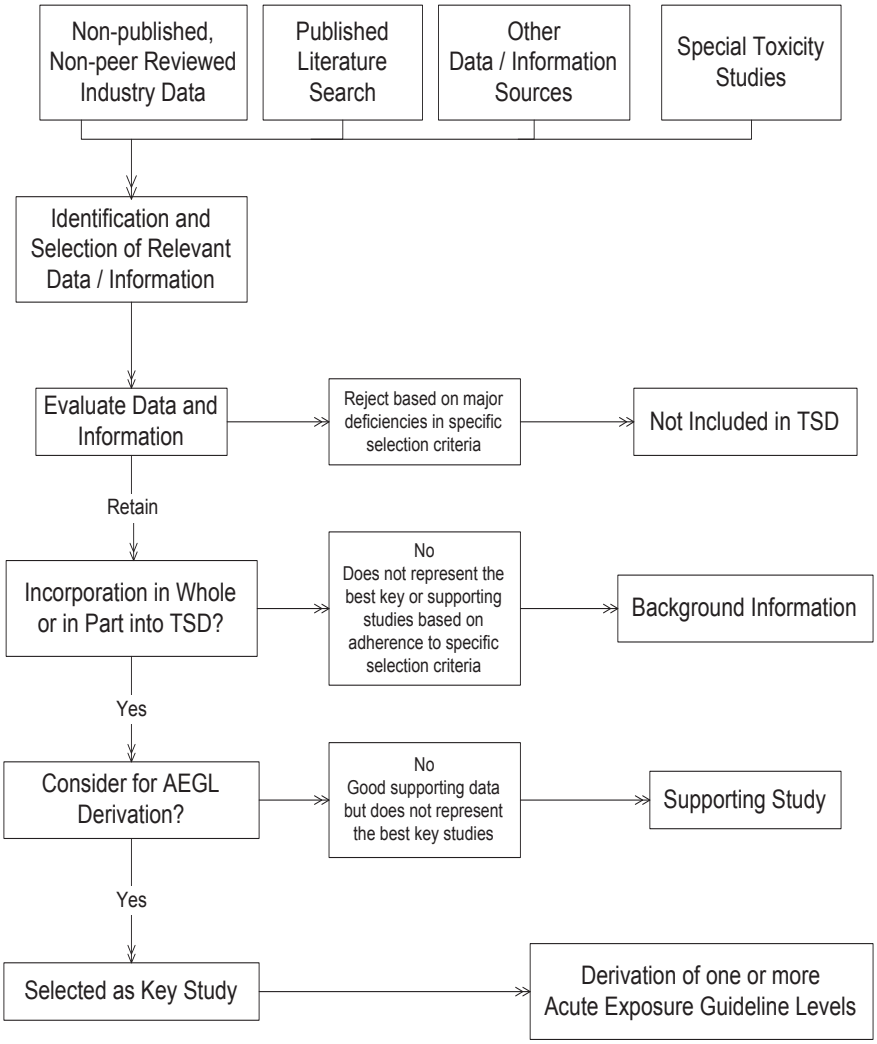

FIGURE 2-1 Decision tree for the selection of key and supporting studies.

5. Scientifically credible exposure concentration and exposure duration for the study are provided.
6. Analytical procedures are used to determine chamber concentration for inhalation exposure in controlled studies, and detailed, scientifically

credible methods, procedures, and data are used to measure chemical concentration in epidemiologic or anecdotal cases (accidental chemical releases). For oral exposure, dose may be determined from the amount of test chemical placed into the subject.

7. The number of subjects is not rigid; e.g., a general rule uses 5-10 rodents/sex/group as a valid measure, but as few as 2-3 primates or dogs/sex/group may be used. The acceptable number of subjects per group is influenced by the relationship between the within-group variability and the degree of change that is considered to be detrimental. Smaller numbers per group may be acceptable by increasing the number of treatment groups.
8. Humans are the most relevant species studied. Rats, mice, rabbits, guinea pigs, ferrets, dogs, or monkeys are acceptable. Other species require evaluation on a case-by-case basis. It is important to use a species for which there are historical control data and relevance to humans.
9. A concurrent control group is composed of the same species as that in the treatment groups. The control subjects should be housed and cared for in the same manner as exposed animals.
10. Concentration or dose selection establishes a clear dose-response relationship.
11. The observation period is variable based on the time of onset of the toxic effect. If it is rapid (minutes to 2-3 h) and associated with quick recovery, an observation period of 3-4 days may be sufficient. For effects that are slow in onset (2-3 days) and delayed in time, a minimum observation period of 14 days is recommended.
12. Signs and symptoms of toxicity are noted during and after exposure and reported separately by sex and concentration or dose.
13. For animal studies, body weights should be recorded throughout the study.
14. For repeated concentration or dose studies, the highest estimated or experimental (empirical) level of no effect is established for the specific AEGL endpoint of concern.
15. Toxicity data from routes of exposure other than inhalation generally will not be used as key or supporting data. Data from alternate routes are considered in the absence of inhalation data if sufficient data are available to perform a credible route-to-route extrapolation.
16. Number of concentrations or doses used are given.
17. If a NOAEL is selected or derived as the endpoint for an AEGL severity level of concern, identifying both the highest dose at which the effect is not seen and the lowest dose at which it is seen for each AEGL severity level strengthens the confidence in the study.
18. Time of death is recorded if applicable.

19. For animal studies, necropsy is conducted with at least gross examination results noted.
20. As available, data (e.g. histopathologic changes, clinical chemistry, and hematology) may reduce uncertainty.
21. Recovery group included in the study and data generated are sufficient to determine the degree of reversibility.
22. There is statistical treatment of data generated from study.
23. An evaluation of all relevant data should be performed and summarized in the TSDs to present an integrated weight-of-evidence picture for all information considered as a whole.

2.3.3 Elements for Discussion on Data Adequacy and Research Needs

The adequacy of the key and supporting data selected for AEGL derivation should be discussed in Section 8.3 of the TSD ("Data Adequacy and Research Needs"). Because of the different toxic endpoints used for the three AEGL tiers and the use of different data or studies for each tier, the data adequacy should be addressed separately for AEGL-1, -2, and -3 values. In addition to any discussion regarding the elements for evaluating key and supporting studies listed in this section of the TSD, the discussion should consider in general terms: (1) repeatability of experiments between laboratories, (2) consistency of data between experiments and laboratories, (3) types and number of species tested, and, (4) comparisons of the AEGLs with valid human and animal data.

A summary of the discussion in the TSD section "Data Adequacy and Research Needs" also should be included in the summary of the AEGL document and the derivation summary tables. The summary statements should address the adequacy of the data by AEGL tier.

2.4 DOSIMETRY CORRECTIONS FROM ANIMAL TO HUMAN EXPOSURES

When extrapolating from observed responses in animals to predicted human responses, the relationship between nominal exposure concentration and delivered dose to the target tissue is of concern. For inhaled toxicants, the target tissue is either a component of the respiratory system and/or other tissue or organ (systemic). A number of methods have been proposed to adjust for differences in the dose to target tissue in the respiratory system (EPA 1994) and those tissues located systemically (NRC 1993a; EPA 1994). The concern has been the lack of validated methodologies that would provide scientifically