Standing Operating Procedures

of the

National Advisory Committee

on

Acute Exposure Guideline Levels for Hazardous Substances

Version 08-02
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PREFACE

The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) was established to develop scientifically credible short-term exposure limits for approximately 400 to 500 acutely toxic substances. These short-term exposure limits, referred to as Acute Exposure Guideline Levels, or AEGLs, are essential for emergency planning, response, and prevention of accidental releases of chemical substances. Further, it is important that the values developed be scientifically credible so that effective planning, response, and prevention can be accomplished.

To insure scientific credibility, five major elements have been integrated into the AEGL development process. These include adherence to the 1993a National Resource Council with changes or additions as set forth in the Standing Operating Procedures Manual (SOP Manual), U. S. National Academy of Sciences (NRC-NAS) guidelines for developing short-term exposure limits, a comprehensive search and review of relevant data and information from both published and unpublished sources, the extensive evaluation of the data and the development of AEGLs by a committee of scientific and technical experts from both the public and private sectors, a multi-tiered peer review process culminating with final review and concurrence by the U. S. National Academy of Sciences (NAS), and, the use of scientifically acceptable processes and methodologies to insure consistent and scientifically credible AEGL values.

With the recent participation of certain member-countries of the Organization for Economic and Cooperation Development (OECD), it is anticipated that the AEGL program will be expanded to include the international community. This should result in increased scientific and technical support, a broader scope of the review process, and an even greater assurance of scientifically credible AEGL values.

This Standing Operating Procedures Manual (SOP Manual) represents the documentation by the NAC/AEGL Committee's SOP Workgroup of those procedures, methodologies, criteria and other guidelines employed by the NAC/AEGL Committee in the development of the AEGL values. The information contained herein is based on the guidance provided by the NAS in its 1993 publication *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC, 1993a) This manual contains additions and further details and clarification of specific procedures, methodologies, criteria, and guidelines interpreted from the NAS guidelines that have been determined by the NAC/AEGL Committee to be a necessary supplement to the 1993a NAS guidelines Procedures and methodologies included in this manual have been reviewed by the NAC/AEGL Committee, numerous OECD member countries, and have received a review and concurrence by the U S. National Academy of Sciences. New or modified procedures and methodologies that are developed and adopted by the NAC/AEGL Committee are classified as "Proposed." Such procedures and methodologies will, from time to time, be submitted to the NAS for review and concurrence. Upon concurrence by the NAS, they will be considered final and will serve as a supplement to the 1993 NRC-NAS guidelines and to the 2000 SOP guidance manual

It is believed that adherence to a rigorous AEGL development process in general, and the use of scientifically sound procedures and methodologies in particular, will provide the most scientifically credible exposure levels that are reasonably possible to achieve. This document is considered a "living document" and the various procedures and methodologies, including those classified as "Final", are

subject to change as deemed necessary by the NAC/AEGL Committee and the U. S. National Academy of Sciences (NAS Subcommittee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council). As new data become available and new scientific procedures and methodologies become accepted by a majority of the relevant scientific community, the NAC/AEGL Committee and the National Academy of Sciences, they will be integrated into the AEGL development process and the SOP Manual. With this approach, both the scientific credibility of the AEGL values and the reduction in risk to the general population will be insured

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1. OVERVIEW OF CURRENT AEGL PROGRAM AND NAC/AEGL COMMITTEE

HISTORY

The concerns of EPA, other U.S. federal agencies, state and local agencies, private industry and other organizations in the private sector regarding short-term exposures due to chemical accidents became sharply focused following the accidental release of methyl isocyanate in Bhopal, India in December of 1984. In November 1985, as part of EPA's National Strategy for Toxic Air Pollutants, the agency developed the Chemical Emergency Preparedness Program. This voluntary program identified a list of over 400 acutely toxic chemicals and provided this information, together with interim technical guidance, for the development of emergency response plans at the local community level. At that time the agency adopted the NIOSH Immediately Dangerous to Life and Health (IDLH) exposure values, or an approximation of these values in instances where IDLH values were not published, to serve as the initial airborne concentrations of concern for each chemical.

During this same period, the U.S. Chemical Manufacturers Association (CMA) developed and implemented the Community Awareness and Emergency Response (CAER) program. This program encouraged chemical plant managers to assist community leaders in preparing for potential accidental releases of acutely toxic chemicals. The program was intended to provide local communities with information on existing chemicals and chemical processes, technical expertise to assist in emergency planning, notification and response, as well as the training of response personnel.

In October, 1986 as part of the reauthorization of Superfund, Congress wrote into law an emergency planning program under the Superfund Amendments and Reauthorization Act (SARA Title III). Under this act, states were required to have emergency response plans for chemical accidents developed at the local community level. The EPA subsequently adjusted the level of concern values to one-tenth of the IDLH value or its equivalent as an approach to improving the safety of the levels used for the general public. Since that time, the agency and other organizations, including private industry, have been interested in adopting more rigorous methodologies for determining values that would be deemed safe for the general public. During this period, the American Industrial Hygiene Association (AIHA) established a committee, the Emergency Response and Planning Guidelines (ERPG) Committee to develop ERPGs and pioneered the concept of developing three different airborne concentrations for each chemical that would reflect the thresholds for important health effect endpoints. The Committee was later renamed the Emergency Response Planning (ERP) Committee. Although constrained by limited resources, the ERP Committee has managed to develop one-hour exposure limits for more than

70 chemicals during the past 10 years.

At a workshop hosted by EPA in 1987, it was proposed by EPA that the ERP Committee and scientists from federal and state agencies, as well as scientists and clinicians from academia and public interest groups pool their technical and financial resources and form a single committee comprised of scientists from both the public sector and the private sector to develop Acute Exposure Guideline Levels (AEGL values). EPA conceived the idea to formulate general guidance for developing short-term exposure limits and together with ATSDR subsequently funded a subcommittee of the Committee of Toxicology of the National Research Council, U. S. National Academy of Sciences (NRC/NAS) to develop guidance on the use of procedures and methodologies to establish emergency exposure guideline levels for the general public.

Since the 1940's, the NRC/NAS Committee on Toxicology has developed emergency exposure guidelines for 41 chemicals of concern to the U. S. Department of Defense (DOD). These values are referred to as "Emergency Exposure Guideline Levels" (EEGLs). Although the EEGLs were developed for use with military personnel, the NAS also developed special exposure guidelines for the general public, termed "Short-term Public Exposure Guidance Levels" (SPEGLs). Based on this extensive experience and the high level scientific and technical expertise continually available to the NAS, this organization was considered the most qualified entity to develop guidance on the methodologies and procedures used in the establishment of short-term exposure limits for acutely toxic chemicals.

The NAS guidance document, entitled *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances,* was published in 1993. The Community Emergency Exposure Levels (CEELs) and the Acute Exposure Guideline Levels (AEGLs) represent the identical short-term emergency exposure levels. The NAS name (CEELs) has been replaced by a new name (AEGLs) only to convey the broad applications of these values for planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of superfund sites. A discussion of how AEGLs might be used for emergency planning, response, and prevention appears later in this chapter.

The efforts to mobilize the federal and state agencies and individuals and organizations in the private sector to form the committee began shortly thereafter. In October, 1995 the committee was formally chartered and the charter filed with the U.S. Congress under the Federal Advisory Committee Act (FACA) with approval by the Office of Management and Budgets (OMB) and concurrence by the General Services Administration (GSA). Due to EPA budgetary constraints, the first meeting of the NAC/AEGL Committee was not held until June, 1996. This meeting represented the culmination of the efforts to solicit stakeholders, identify committee members, form the committee, obtain the technical support of the Oak Ridge National Laboratories (ORNL), and begin the development of the AEGL values.

PURPOSE AND OBJECTIVES OF THE AEGL PROGRAM AND THE NAC/AEGL COMMITTEE

The primary purpose of the AEGL Program and the NAC/AEGL Committee is to develop guideline levels for once in a lifetime short-term exposures to airborne concentrations of acutely toxic, high priority chemicals. These Acute Exposure Guideline Levels (AEGLs) are needed for a wide range of planning, response, and prevention applications. These applications may include the EPA's SARA Title III Section 302-304 emergency planning program, the U. S. Clean Air Act Amendments (CAAA) Section 112(r) accident prevention program, and the remediation of Superfund sites program; the DOE environmental restoration, waste management, waste transport, and fixed facility programs; the DOT emergency waste response program; the DOD environmental restoration, waste management, and fixed facility programs; ATSDR health consultation and risk assessment programs; NIOSH/OSHA regulations and guidelines for workplace exposure; State CAA Section 112(b) programs and other state programs; and private sector programs such as the AIHA-ERPG and the CMA Chemtrec programs.

A principal objective of the NAC/AEGL Committee is to develop scientifically credible, acute (short-term) once in a lifetime exposure guideline levels within the constraints of data availability, resources and time. This includes highly effective and efficient efforts in data gathering, data evaluation and data summarization, fostering the participation of a large cross-section of the relevant scientific community, and the adoption of procedures and methods that facilitate consensus-building for AEGL values within the Committee.

Another principal objective of the committee is to develop these AEGL values for approximately 400 to 500 acutely hazardous substances within the next ten (10) years. Therefore, the near-term objective is to increase the level of production of AEGL development to approximately forty (40) to fifty (50) chemicals per year without exceeding budgetary limitations or compromising the scientific credibility of the values developed.

Further, in addition to determining AEGL values for three different health effect end-points, it is intended to derive exposure values for the general public that are applicable to emergency (accidental) once in a lifetime exposure periods ranging from 10 minutes to 8 hours duration. Therefore, exposure limits will be developed for a minimum of 5 exposure periods (10 minutes, 30 minutes, 1 hour, 4 hours, 8 hours). Each AEGL tier is distinguished by varying degrees of severity of toxic effects, as initially conceived by the AIHA ERP Committee and further defined in the NAS' National Research Council report, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances*, published by the National Academy of Sciences in 1993 (NAS Guidance), and further defined by the NAC/AEGL Committee. These AEGL-1, AEGL-2, and AEGL-3 definitions are presented elsewhere in this SOP manual.

As stated in the NAS guidelines and described in the AEGL definitions, these exposure

limits are intended to protect most individuals in the general population, including those that may be particularly sensitive or susceptible to the deleterious effects of the chemicals. However, as stated in the guidelines and the definitions, it is recognized that certain individuals, subject to unique and idiosyncratic responses, could experience effects at concentrations below the corresponding AEGL.

An important objective of the NAC/AEGL Committee is the establishment and maintenance of a comprehensive "Standing Operating Procedures" manual (SOP Manual) that adheres to the 1993a NRC/NAS guidelines and supplements, clarifies, interprets or defines these guidelines with regard to the specific use of certain procedures and methods such as the selection of NOAELs, LOELs, etc., use of uncertainty factors, modifying factors, interspecies/intraspecies extrapolation methodologies, time scaling, carcinogenic risk assessment, and other methods and procedures relevant to the development of AEGL values.

COMMITTEE MEMBERSHIP AND ORGANIZATIONAL STRUCTURE

The NAC/AEGL Committee is comprised of representatives of federal, state and local agencies, and organizations in the private sector that derive programmatic or operational benefits from the AEGL values. This includes federal representatives from the U.S. Environmental Protection Agency (EPA), the Department of Energy (DOE), the Agency for Toxic Substances and Disease Registry (ATSDR), the National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA), the Department of Transportation (DOT), the Department of Defense (DOD), the Center for Disease Control (CDC), the Food and Drug Administration (FDA), and the Federal Emergency Management Agency (FEMA). States providing committee representatives include New York, New Jersey, Texas, California, Minnesota, Illinois, Connecticut, and Vermont. Private companies with representatives include Allied Signal Corporation, Exxon Corporation, and Olin Chemical Company. Other organizations with representatives include the American Industrial Hygiene Association (AIHA), American College of Occupational and Environmental Medicine (ACOEM), American Association of Poison Control Centers (AAPCC), and the AFL-CIO. In addition, the committee membership includes individuals from academia, a representative of environmental justice, and other organizations in the private sector. A current list of the NAC/AEGL Committee members and their affiliations is shown in Appendix A of this SOP manual. At present, the Committee is comprised of 32 members.

Recently, the Organization of Economic and Cooperation Development (OECD) and various OECD member countries have expressed an interest in the AEGL Program. Several OECD member countries such as Germany and the Netherlands have been participating in the Committee's activities and actively pursuing formal membership on the NAC/AEGL Committee It is envisioned that the Committee and the AEGL Program in general will progressively expand its scope and participation to include the international community.

The Director of the AEGL Program has the overall responsibility for the entire AEGL Program and the NAC/AEGL Committee and its activities. A Designated Federal Officer (DFO) is responsible for all administrative matters related to the Committee to insure that it functions properly and efficiently. These individuals are not voting members of the Committee. The NAC/AEGL Committee Chair is appointed by EPA and is selected from among the committee members. In concert with the Program Director and the DFO, the Chair coordinates the activities of the Committee and also directs all formal meetings of the Committee. From time to time, the members of the Committee serve as Chemical Managers and Chemical Reviewers in a collaborative effort with assigned scientist-authors (non-Committee members) to develop AEGLs for a specific chemical. These groups of individuals are referred to as the AEGL Development Teams and their function is discussed in Section 4.8 of this manual..

SELECTION OF CHEMICALS FOR AEGL DEVELOPMENT

A master list of approximately 1,000 acutely toxic chemicals was initially compiled through the integration of individual priority lists of chemicals submitted by each U. S. federal agency placing a representative on the Committee. The master list was subsequently reviewed by individuals from certain state agencies and representatives from organizations in the private sector and modified as a result of comments and suggestions received. The various priority chemical lists were compiled separately by each federal agency based on their individual assessments of the hazards, potential exposure, risk, and relevance of a chemical to their programmatic needs. A list of approximately 400 chemicals representing the higher priority chemicals was tentatively identified from the original master list. It was acknowledged that this list was subject to change based on the changing needs of the stakeholders.

On May 21, 1997, a list of 85 chemicals was published in the Federal Register. This list identified those chemicals from the list of approximately 400 chemicals considered to be of highest priority across all U. S. federal agencies and represented the selection of chemicals for AEGL development by the NAC/AEGL Committee for the first two to three years of the program. The Committee has now addressed these chemicals and they are presently in the Draft, Proposed, Interim, or Final stages of development. Certain chemicals did not contain an adequate database for AEGL development and, consequently, are on hold pending decisions regarding further testing This initial "highest" priority list of 85 chemicals is shown in Appendix B.

A second "working list" of approximately 100 priority chemicals is being selected from (1) the original master list, (2) the intermediate list of approximately 400 chemicals (which is a subset of the master list) and (3) from new, high priority candidate chemicals submitted by U. S. Agencies and organizations and OECD member countries that are planning to participate in the AEGL Program. Although "working lists" will be published in the U. S. Federal Register and elsewhere from time-to-time to indicate the NAC/AEGL Committee's agenda, the priority of chemicals addressed, and , hence, the "working list" is subject to modification if priorities of the

NAC/AEGL Committee or individual stakeholder organizations, including international members, change during that period.

SCIENTIFIC CREDIBILITY OF AEGLS

The scientific credibility of the AEGL values is based on adherence to the National Academy of Sciences 1993a guidelines for developing short-term exposure limits, the comprehensive nature of data collection and evaluation, the consistency of the methods and procedures used to develop the values, the potential of acute toxicity testing in cases of inadequate data, and the adoption of the most comprehensive peer review process ever used to establish short-term exposure limits for acutely toxic chemicals.

The comprehensive data gathering process involves literature searches for all relevant published data and the mobilization of all relevant unpublished data. Data and information from unpublished sources is obtained through individual companies in the private sector and the cooperation of trade associations. The completeness of the data searches is enhanced through the oversight and supplemental searches conducted by individual Committee members and interested parties during the peer review process.

Data evaluation and selection is performed by scientists with expertise in toxicology and related disciplines from staff at the organization which drafts Technical Support Documents and the assigned members of the NAC/AEGL Committee. Additionally, input on data evaluation and selection is provided by interested parties who participate in the open meetings of the Committee or who formally comment on the Federal Register notices of Proposed AEGL values.

The work of the NAC/AEGL Committee adheres to the 1993a NRC/NAS publication *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances*. Since this guidance document represents a more general guidance for methods and procedures, the NAC/AEGL Committee interprets and develops greater detail related to the methodologies and procedures that it follows. These Standing Operating Procedures (SOPs) are documented by the SOP Workgroup and represent a consensus or two-thirds majority vote of the NAC/AEGL Committee. SOPs also represent concurrence of the National Academy of Sciences' Subcommittee on Acute Exposure Guideline Levels (NAS/AEGL Subcommittee). Therefore, each step of the AEGL development process follows specific methodologies, criteria or other guidelines to insure consistent, scientifically sound values.

In instances where AEGL values cannot be developed because of poor data or no data, the chemical may be subjected to appropriate acute toxicity testing. The AEGL program is committed to insuring that AEGL values are derived from adequate data and information based on a consensus or two-thirds majority vote of the NAC/AEGL Committee and concurrence of the NAS/AEGL Subcommittee.

To further assure the scientific credibility of the AEGL values and their supporting rationale, the most comprehensive peer review process ever employed in the development of short-term exposure limits has been established (see next section). This review process has been designed to effectively, yet efficiently, encourage and enable the participation of the scientific community and other interested parties from the public and private sectors in the development of the AEGLs. Further, the review process utilizes an expert committee of the National Academy of Sciences, the NAS/AEGL Subcommittee as the final scientific review . Hence, the final judgement of scientifically credible values rests with the United State's ultimate scientific body, the NAS. A detailed summary of the AEGL development process is presented in the next section.

THE AEGL DEVELOPMENT AND PEER REVIEW PROCESS

The process that has been established for the development of the AEGL values is the most comprehensive ever employed for the determination of short-term exposure limits for acutely toxic chemicals. A summary of the overall process is presented in diagram form in Appendix C. The process consists of four basic stages in the development and status of the AEGLs and they are identified according to the review level and concurrent status of the AEGL values. They include (1) "Draft" AEGLs, (2) "Proposed" AEGLs, (3) "Interim" AEGLs and (4) "Final" AEGLs. The entire development process can be described by individually describing the four basic stages in the development of AEGL values.

Stage 1: "Draft" AEGLs

This first stage begins with a comprehensive search of the published scientific literature. Attempts are made to mobilize all relevant, non-published data through industry trade associations and from individual companies in the private sector. A more detailed description of the published and unpublished sources of data and information utilized is provided in Section 2.3 of this document which addresses search strategies. The data are evaluated following the guidelines published in the NRC/NAS guidance document and this SOP manual and selected data are used as the basis for the derivation of the AEGL values and the supporting scientific rationale. Data evaluation, data selection, and the development of a technical support document are all performed as a collaborative effort among the Staff Scientist at the organization which drafts Technical Support Documents, the Chemical Manager, and two Chemical Reviewers. This group is referred to as an "AEGL Development Team". NAC/AEGL Committee members are specifically assigned this responsibility for each chemical under review. Hence, a separate team comprised of different Committee members is formed for each chemical under review The product of this effort is a technical support document (TSD) that contains "Draft" AEGLs. The Draft TSD is subsequently circulated to all other NAC/AEGL Committee members for review and comment prior to a formal meeting of the Committee. Revisions to the initial TSD and the

"Draft" AEGLs are made up to the time of the NAC/AEGL Committee meeting scheduled for formal presentation and discussion of the AEGL values and the documents. Following deliberations during the committee meeting, an attempt is made to reach consensus, or the minimum of a two-thirds majority of a quorum present, to elevate the AEGLs to "Proposed" status. If agreement cannot be reached, the Committee conveys its issues and concerns to the AEGL Development Team and further work is conducted by this group. After completion of additional work, the chemical is resubmitted for consideration at a future meeting. If a consensus or two-thirds majority vote of the Committee cannot be achieved because of inadequate data unrelated to the completeness of the data search, the chemical becomes a candidate for appropriate toxicity studies.

Stage 2: "Proposed" AEGLs

Once the NAC/AEGL Committee has reached a consensus, or the minimum two-thirds majority vote, on the AEGL values and supporting rationale, they are referred to as "Proposed" AEGLs and are published in the Federal Register for a thirty (30) day review and comment period. Following publication of the "Proposed" AEGLs in the Federal Register , the Committee reviews the public comments, addresses and resolves relevant issues and seeks a consensus or minimum two-thirds majority of those present on the Committee on the original or modified AEGL values and the accompanying scientific rationale.

Stage 3: "Interim" AEGLs

Following resolution of relevant issues raised through public review and comment and subsequent approval of the Committee, the AEGL values are classified as "Interim". The "Interim" AEGL status represents the best efforts of the NAC/AEGL Committee to establish exposure limits and the values are available for use as deemed appropriate on an interim basis by federal and state regulatory agencies and the private sector. The "Interim" AEGLs, the supporting scientific rationale, and the TSD, are subsequently presented to the National Academy of Sciences (NAS/AEGL Subcommittee) for its review and concurrence. If concurrence cannot be achieved, the NAS/AEGL Subcommittee will submit its issues and concerns to the NAC/AEGL Committee for further work and resolution.

Stage 4: "Final" AEGLs

When concurrence by the NAS/AEGL Subcommittee is achieved, the AEGL values are considered "Final" and published by the U. S. NAS. Final AEGLs may be used on a permanent basis by all federal, state and local agencies and private sector organizations. It is possible that from time to time new data will become available that challenges the scientific credibility of

"Final" AEGLs. If this occurs, the chemical will be resubmitted to the NAC/AEGL Committee and recycled through the review process.

OPERATION OF THE COMMITTEE

The NAC/AEGL Committee meets formally four (4) times each year for two and one-half (2-1/2) days. The meetings are scheduled for each quarter of the calendar year and are generally held in the months of March, June, September, and December. Based on overall cost considerations, the meetings are generally held in Washington, D.C. However, from time to time, committee meetings may be held at other locations for justifiable reasons.

At least 15 days prior to the committee meetings, a notice of the meeting is published in the Federal Register together with a list of chemicals and other matters to be addressed by the Committee and provides dates, times and location of the meetings. The agenda is finalized and distributed to committee members approximately one week prior to the meeting. The agenda also is available to other interested parties at that time, upon request, through the Designated Federal Officer (DFO).

All NAC/AEGL Committee meetings are open to the public and interested parties may schedule individual presentations of relevant data and information by contacting the DFO to establish a date and time. Relevant data and information from interested parties also may be provided to the Committee through the DFO during the period of development of the Draft AEGLs so that it can be considered during the early stage of development. Data and information also may be submitted during the Proposed and Interim stages of AEGL development as well.

The NAC/AEGL Committee meetings are conducted by the Chair who is appointed by the U.S. Environmental Protection Agency in accordance with the Federal Advisory Committee Act (FACA). At the time of the meeting, both the Chair and all other committee members will have received the initial draft and one or more revisions of the Technical Support Document (TSD) and "Draft", "Proposed", or "Interim" AEGL values for each chemical on the agenda. Reviews, comments, and revisions are continuous up to the time of the meeting and committee members are expected to be familiar with the "Draft", "Proposed", or "Interim" AEGLs, supporting rationale, and other data and information in each TSD and to participate in the resolution of residual issues at the meeting. Procedures for the AEGL Development Teams and the other Committee members regarding work on AEGLs in the Proposed or Interim status are similar to those for Draft AEGLs.

All decisions of the NAC/AEGL Committee related to the development of Draft, Proposed, Interim, and Final AEGLs and their supporting rationale are made by consensus or a minimum of two-thirds (2/3) majority of a quorum of committee members. A quorum of the NAC/AEGL Committee is defined as fifty-one percent (51%) or more of the total NAC/AEGL

Committee membership in attendance.

The highlights of each meeting are recorded by the scientists who draft the Technical Support Documents and written minutes are prepared, ratified and maintained in the Committee's permanent records. Deliberations of each meeting also are tape-recorded when possible and stored in the Committee's permanent records by the Designated Federal Officer (DFO) for future reference as necessary.

All Proposed AEGL values and supporting scientific rationale are published in the Federal Register. Review and comment by interested parties and the general public are requested and encouraged. The Committee's response to official comments on Federal Register notices on Proposed AEGL values consists of an evaluation of the comments received, discussions and deliberations that take place at Committee meetings regarding the considerations of elevation of AEGLs from "Proposed" to "Interim" status, and changes to the Technical Support Documents as deemed appropriate by the NAC/AEGL Committee. This information is reflected on the tapes and in the minutes of the meetings and will be maintained for future reference.

As previously mentioned a "Standing Operating Procedures" Workgroup (SOP Workgroup) was established in March, 1997 to document, summarize, and evaluate the various procedures, methodologies, and guidelines employed by the Committee in the gathering and evaluation of scientific data and information and the development of the AEGL values. The SOP Workgroup performs a critical function by continually providing the Committee with detailed information on the Committee's interpretation of the NAS guidelines and the approaches the Committee has taken in the derivation of each AEGL value for each chemical addressed. This documentation enables the Committee to continually assess the basis for its decision-making, insure consistency with the NAS guidelines, and maintain the scientific credibility of the AEGL values and accompanying scientific rationale. This ongoing effort is continuously documented and is identified as the "SOP Manual".

VALUE OF A COLLABORATIVE EFFORT IN THE AEGL PROGRAM

The value of a collaborative effort in the AEGL Program is related primarily to the pooling of substantial resources of the various stakeholders and the direct or indirect involvement of a significant portion of the relevant scientific community from both the public and private sectors. These factors, in turn, promote greater productivity, efficiency and cost effectiveness of such an effort and greatly enhance the scientific credibility of the Acute Exposure Guideline Levels (AEGLs) that are developed by the Committee.

The formation of the Federal Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) with approximately 30 to 35 members has provided an important forum for scientists, clinicians, and others to develop the AEGLs and

related scientific issues. The composition of the Committee represents a balanced cross-section of relevant scientific disciplines and a balance of U. S. federal and state agencies, academia, the medical community, private industry, public interest groups, and other organizations in the private sector. This mutual participation of stakeholders, including the regulators and the regulated community, in the development of the AEGLs promotes the acceptance of the AEGLs by all parties involved. Additionally, the diverse composition of the committee represents the nucleus of a broad network of scientists, clinicians, and other technical personnel that fosters information and data exchange and the resolution of relevant scientific and technical issues well beyond the committee membership. This network also facilitates the identification of national and international experts with particular expertise that may provide important data, information or insight on a specific chemical or scientific issue.

The collaborative effort also results in greater scientific credibility of the exposure values developed. The pooling of resources enables a very comprehensive gathering and evaluation effort of both published and unpublished data and information. Collaboration provides a broad base of relevant scientific knowledge and expertise that is highly focused on the chemicals and issues addressed by the Committee. This approach provides sufficient scientific and technical resources for the SOP Workgroup to document and evaluate procedures and methodologies that instill rigor and consistency into the process and the resultant AEGL values. The documentation of these procedures and methodologies are contained in this Standing Operating Procedures Manual (SOP Manual). Finally, the collaborative effort has enabled the establishment of the most comprehensive peer review process ever implemented for the development of short-term exposure limits.

Recently the AEGL Program has extended invitations to all OECD member countries to participate on the NAC/AEGL Committee and the program activities in general. It is believed that expanding the scope of the AEGL Program to include the international community will be of great benefit. Their participation will provide even greater resources, further broaden the base of scientific and technical expertise, provide new toxicological data and insights, and foster the harmonization of emergency exposure limits at the international level.

In summary, the establishment of a collaborative effort, with its pooling of resources, represents the most productive, efficient, and cost-effective approach to the development of exposure guideline levels. Further, the effort results in the development of uniform values for a wide range of applications. This eliminates inconsistencies and confusion among individuals and organizations involved in emergency planning, response and prevention of chemical accidents. In global terms, the NAC/AEGL Committee represents an approach to unifying the international community in the development and use of chemical emergency exposure limits. In the interest of multinational companies seeking uniform operating parameters and the mandates placed on federal agencies to achieve international harmonization of standards and guidelines, the participation of the international community in the AEGL Program represents an important goal of the AEGL program.

APPLICATIONS OF THE AEGL VALUES

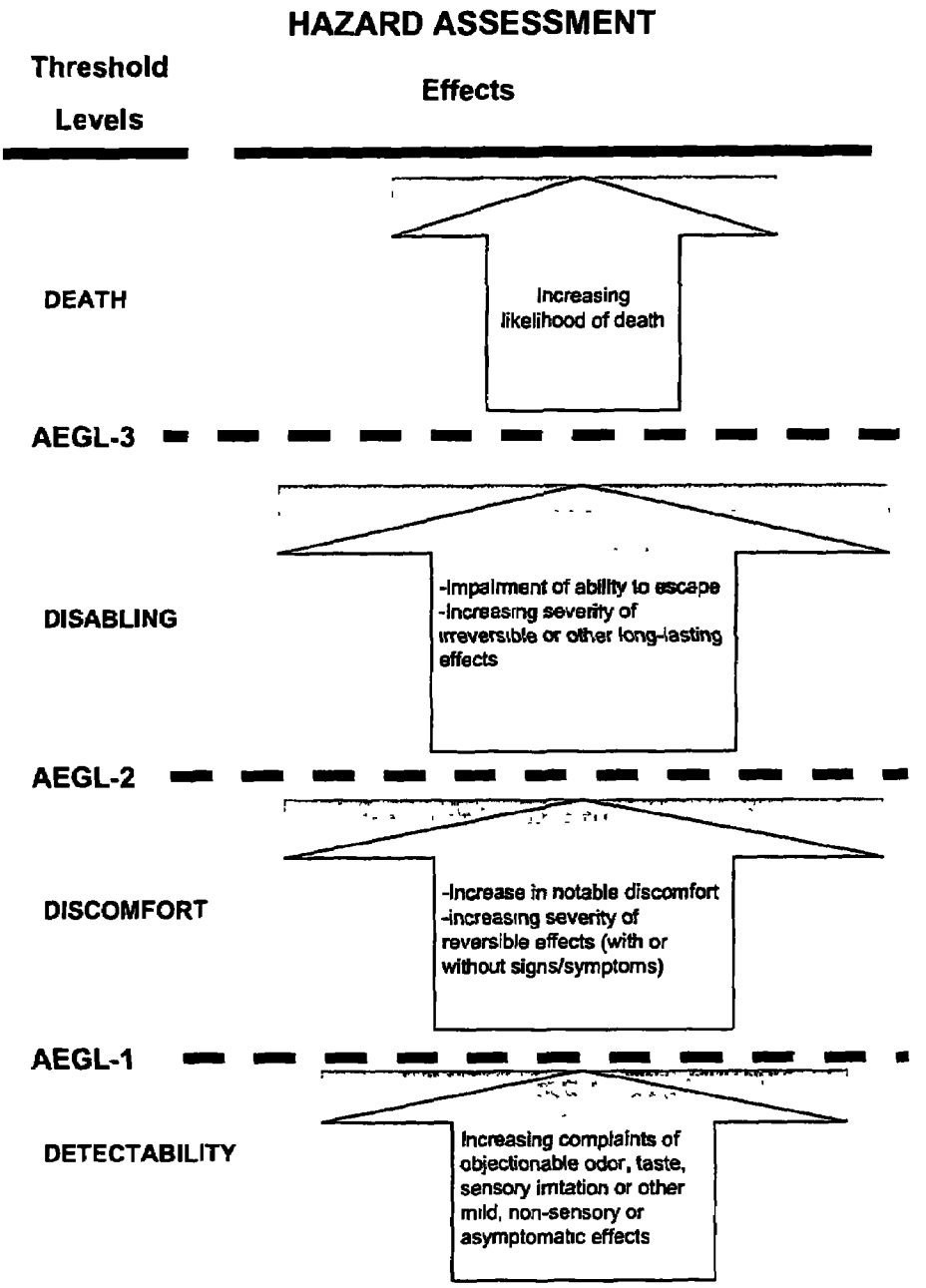
As previously stated, it is anticipated that the AEGL values will be used for both regulatory and non-regulatory purposes by federal and state agencies in conjunction with chemical emergency prevention, preparedness, and/or response programs. This includes the implementation of these chemical emergency activities at the local community level.

More specifically, the AEGL values will be used for conducting various risk assessments to aid in the development of emergency preparedness and prevention plans, as well as real-time emergency response actions, for accidental chemical releases at fixed facilities and from transport carriers. The AEGL values, which represent defined toxic endpoints, are used in conjunction with various chemical release and dispersion models to determine geographical areas, or "vulnerable zones", associated with accidental or terrorist releases of chemical substances. By determining these geographical areas, and the presence of human populations and facilities within these zones, the potential risks associated with accidental chemical releases can be estimated. For example, the release and dispersion models, which take into account the quantity and rate of release of the chemical, the volatility of the substance, the wind speed and wind stability at the time of the release, and a consideration of the topographical characteristics in the area of the release, will define the geographical areas exposed, and quantitatively, the airborne concentration of the "plume" or the chemical cloud as it is dispersed. By comparing the projected airborne concentrations of the chemical substance in question with the exposed populations, human health risks associated with a chemical release can be estimated. Using these risk estimates, emergency response personnel can make effective risk management and risk communication decisions to minimize the adverse impact of the release on human health. Figure 1-1 is a summary diagram that indicates the overall effects that are expected to occur above each of the three AEGL threshold tiers, as well as sensory and non-sensory or asymptomatic effects below the AEGL-1 threshold level. Figure 1-1 also indicates the expected increase in occurrence and severity of the various adverse health effects as the airborne concentration increases beyond each of the three AEGLs.

Because of the complex nature of chemical accidents, the populations at risk, the variable capabilities among emergency response units, and many other considerations related to a specific event, it is beyond the scope of this document to discuss or speculate on specific actions that should or could be taken at any point in time or at a given level of exposure to a specific chemical. However, it is known by emergency responders and planners that various options are available, depending upon the circumstances, for reducing or even preventing the adverse impacts of chemical releases. In general they include public notification and instruction, sheltering-in-place, selective of major evacuation procedures, procedures to enable or facilitate medical attention or some combination of these approaches. These are important decisions best left to local emergency planners and responders to be addressed on a case-by-case basis. Further, information regarding the applications of short-term exposure limits such as AEGLs may be

obtained in Technical Guidance for Hazards Analysis (U.S. EPA, 1987).

1 **FIGURE 1-1 HAZARD ASSESSMENT**
2



2. DERIVATION OF AEGL VALUES

2.1 DEFINITIONS OF AEGL-1, AEGL-2 AND AEGL-3

AEGL severity levels represent short-term exposure values which are a threshold for specific biological effects for the general public and are applicable to specified exposure durations. The values for these specified durations are "... ceiling exposure values for the public (i.e., a ceiling is a concentration of a substance that should never be exceeded)..." (NRC 1993a, p2). Three AEGLs are developed for each of five exposure durations (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. AEGLs for 10 minute durations will be developed for the chemicals included in the first publication of AEGLs by the National Academy of Sciences at a future date.

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above

which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

2.2 EMPIRICAL TOXICOLOGIC ENDPOINTS, AND METHODS FOR DETERMINING EXPOSURE CONCENTRATIONS USED TO DERIVE AEGL-1,2, AND 3 LEVELS

The selection of the biological endpoints that serve as the thresholds for each of the AEGL severity levels are based on the definitions for the Community Emergency Exposure Levels (CEELs) that were published in the 1993a National Academy of Sciences' (NAS) guidelines for developing short-term exposure limits. The AEGLs address the same defined population as the NAS CEELs. The NAS definitions of the 3 CEEL tiers have been modified slightly by the NAC/AEGL Committee only to improve the clarity of description of the threshold levels. Hence, the defined threshold levels for CEELs and AEGLs are the same.

The NAS guidelines describe CEELs (or AEGLs) as ceiling exposure values (i.e., a concentration of a substance that should never be exceeded) that are applicable to emergency exposures to hazardous substances for a specified duration (NAS, 1993). The NAS guidance further states that the CEELs (or AEGLs) must be set low enough to protect most of the population that might be exposed, including those with increased susceptibilities such as children, pregnant women, asthmatics and persons with other specific illnesses (NAS, 1993). The NAS definition of CEELs/AEGLs for each of the three different tiers of adverse health effects states that the adverse effects for each CEEL/AEGL tier is not likely to occur below that level for a specified exposure duration, but becomes increasingly likely to occur at concentrations above that level in a general population, including susceptible individuals. For this reason the NAS also refers to the CEELs/AEGLs as threshold levels (NAS, 1993).

Because the data and methodologies used to derive AEGLs or any other short-term exposure limits are not sufficiently precise to make a distinction between a ceiling value and a threshold value, no distinction has been made with respect to AEGL values. No fine line can be drawn to precisely differentiate between a ceiling level, which represents the highest exposure concentration for which an effect is unlikely to occur, and a threshold level, which represents the lowest exposure concentration for the likelihood of onset of a given set of effects. Hence, AEGLs are not true effect levels. Rather, they are considered threshold levels that represent an estimated point of transition and reflect the best efforts to quantitatively establish a demarcation between one defined set of symptoms or adverse effects and another defined set of symptoms or adverse effects. Therefore, in the development of AEGLs the NAC/AEGL Committee selects the highest exposure level from animal or human data where the effects used to define a given AEGL tier are not observed.

2.2.1 SELECTION OF THE HIGHEST EXPOSURE LEVEL WHERE THE EFFECTS USED TO DEFINE AN AEGL LEVEL WERE NOT OBSERVED

Traditionally, when setting acceptable (typically considered "safe") levels of exposure the evaluator will select the highest experimental exposure which does not cause an adverse effect (No Observed Adverse Effect Level - NOAEL) in an experiment which demonstrated a graded exposure response from no effect to adverse effects. In standard risk assessment practice (NRC, 1993a), the exposure level identified as the NOAEL would then be divided by appropriate uncertainty factors and modifying factors to derive an acceptable exposure level for humans However, there are a number of limitations in this methodology. It does not consider the number of animals used in the experiment and the associated statistical uncertainty around the experimental exposure level chosen. It does not consider the slope of the exposure-response relationship and subjects the evaluator to use the possibly arbitrarily selected exposure levels which were chosen in the face of an unknown exposure-response relationship. Under some conditions, especially a small number of animals exposed per exposure, the NOAEL could be a level associated with significant adverse health effects (Leisenring and Ryan 1992). In recent years Crump (1984), Barnes et al. (1995), US EPA (1995a), Faustman et al. (1994), Gaylor et al. (1998), Gaylor et al. (1999), and Fowles et al. (1999) addressed these problems by using the concept of analyzing all of the data to statistically estimate a benchmark concentration (BMC). The BMC is a statistical estimate of an exposure which will cause a specified incidence of a defined adverse health effect. The BMC is commonly defined as the 95% lower confidence limit (LCL) on the exposure causing a specified level of response (typically 1% to 10%). This exposure is intended to replace the NOAEL and is used like the NOAEL when setting acceptable exposure levels.

The BMC methodology has a number of advantages over the traditional NOAEL approach. The BMC is derived from a statistical analysis of the exposure-response relationship and is not subject to investigator selection of exposure levels. It is a reflection of the exposure response curve. Although the number of animals used in a study will impact the NOAEL and BMC estimates, the BMC, when compared to the maximum likelihood estimate (MLE), will explicitly reflect the variability in the study and the uncertainty around the number of subjects. The greater the variability and uncertainty, the greater the difference between the BMC and the MLE. The BMC calculation allows for the statistical estimation of a BMC in the absence of an empirical NOAEL.

The data most relevant to the development of AEGL-3 values and most amenable to a benchmark concentration analysis are inhalation LC_{50} data. Fowles et al. (1999) analyzed 120 inhalation animal lethality data sets using the BMC methodology. The analyses provide the basis for the application of the BMC approach used by the NAC/AEGL Committee in the development of AEGL values. Benchmark concentrations (95% LCL) and maximum likelihood estimates were developed for the 1, 5, and 10% response levels using log probit and Weibull models. Species tested included rats, mice, guinea pigs, hamsters, rabbits, and dogs. Exposure times ranged from 5 minutes to 8 hours. Each data set consisted of at least 4 data points. The BMC and MLE values were compared with the empirical NOAEL (highest exposure which did not cause death in the experiment) and LOAEL (lowest exposure which killed at least one animal).

The curve generated by the statistical models was subjected to a chi-squared goodness of fit test ($P>0.05$). For statistical and data presentation reasons, 100 studies were analyzed with the probit analysis and 93 with the Weibull model. Most of the studies reported NOAELs (81/100 which were considered for the probit analysis and 74/93 considered for the Weibull analysis).

The benchmark concentrations were generally lower than the NOAELs when analyzed with either statistical estimate. The mean NOAEL/BMC ratios for the 1, 5, and 10% response were 1.60, 1.16, and 0.99 when using a probit analysis and 3.59, 1.59, and 1.17 when using the Weibull analysis. It is interesting to note that comparable means from a Weibull analysis of developmental toxicity data were considerably greater, the developmental toxicity means of the NOAEL/BMC ratios were 29, 5.9, and 2.9 (Allen et al., 1994).

The proportion of times that the NOAEL exceeded the BMC for the 1, 5, and 10% response was 89, 65, and 42% for the probit analysis and 95, 80, and 54% for the Weibull analysis. In all cases the LOAEL/BMC ratio exceeded 1 for the probit and Weibull analysis of the 1 and 5% response but not always for the 10% response (99%). For this reason the BMC_{10} may be too high a response rate to use to predict a NOAEL. In contrast the corresponding 1 and 5% response ratios were always greater than 1.

The ratios of the MLE/BMC were not great, ranging from a mean of 1.39 for a probit analysis of the 10% response to 3.02 for a Weibull analysis of the 10% response. It is important to note that using the probit analysis the LOAEL/MLE ratios were equal to or greater than 1 in 99, 94, and 71% of the cases for the 1, 5, and 10% responses. The MLE would probably be protective at the 1% response level but not for the 5 and 10% response levels. Similar numbers of 99, 97, and 76% were observed for the Weibull analysis.

The BMC approach can provide a more refined assessment of the prediction of the empirical NOAEL. It must be emphasized that even the empirical NOAEL may represent a response level which is not detected. When 5 to 10 animals are used in an experiment a 10 to 20% response can be missed (Leisenring and Ryan, 1992) and even a BMC_{10} is similar to a LOAEL with dichotomized data (Gaylor, 1996). It is expected that the BMC is less than the empirical LOAEL. In the Fowles et al. (1999) analysis of the data the BMC_{05} and BMC_{01} values were always below the empirical LOAEL for the studies analyzed. The probit analysis of the data by Fowles et al. (1999) provided a better fit with the data as measured by the "chi-squared goodness-of-fit test, mean width of confidence intervals, and number of data sets amenable to analysis by the model."

It is interesting to note that the BMC_{05} is very close to the MLE_{01} in the Fowles et al. (1999) evaluation of inhalation acute toxicity data. Through 1999 the NAC/AEGL Committee has used the MLE_{01} to estimate the highest exposure at which lethality is not likely to be observed in a typical acute exposure study. Given the analysis by Fowles et al. (1999) and for the above reasons, the NAC/AEGL Committee will generally use the BMC_{05} (lower 95% confidence

limit (LCL) of the exposure required to produce a 5% response to exposure to chemicals) in the future for this estimate although, the MLE_{01} will also be calculated and considered. This incorporates the uncertainties due to the number of animals used in an experiment, the experimental variability observed, utilizes all of the data and the slope of the exposure response curve, and provides for a reasonable estimate of a predicted experimental NOAEL. In all cases the MLE and BMC at specific response levels will be considered when setting AEGL levels. Statistical models in addition to the log-probit will also be considered. Since goodness of fit tests consider an average fit, they may not be valid predictors of the fit in the low exposure region of interest. In this case the output of the different models will be plotted and compared visually with the experimental data in selection of the most appropriate model.

It should be emphasized that these methodologies will generally be considered for an acute lethal endpoint. Their use to set AEGL-1 and AEGL-2 levels will be considered on a chemical-by-chemical basis. Different endpoints may require the use of different data sets in different or the same species, a different benchmark dose approach, or identification of a different response level. These factors will be considered for specific chemicals and toxicological endpoints.

The preferred approach will be to use the BMC approach to identify the highest exposure at which the toxicologic effects used to define an AEGL tier were not observed. If the data are insufficient to use that approach then the level will be determined empirically from experimental data.

2.2.2 SELECTION OF HEALTH EFFECTS ENDPOINTS FOR AEGL-1, AEGL-2, AND AEGL-3

In addition to the working definitions of the three AEGL tiers, this section includes a summary of the specific biologic endpoints used to establish the AEGL levels for individual chemicals. Also included are general principals for selection of AEGL health effect endpoints that have been derived from the Committee's selections on a chemical-by-chemical basis. Since ideal data sets for certain chemicals are not available, extrapolation methods and the Committee's scientific judgement are often employed to establish threshold values. In the absence of adequate data, no AEGL value is established. The basis for this decision is the failure to achieve a minimum two-thirds majority of a quorum of the Committee that is in favor of establishing a value, or a formal decision by two-thirds of the Committee not to establish a value.

Under ideal circumstances the specific health effects would be identified that determine each of the AEGL levels. A search of the published literature would be performed for data on the chemical, and AEGL levels would be generated from that data. However, data relating exposure and effect do not always follow an ideal paradigm and may lead to apparent inconsistences in the use of endpoints to set AEGL levels. The general principles laid down in

the NRC (1993a) guidance for evaluating data and selecting appropriate health effects, combined with professional judgement, are used to establish AEGL levels. From the evaluations of the first 5 chemicals in this publication, and experience with data sets on chemicals currently under review, the following refinements to the NAS guidelines have been adopted by the NAC/AEGL Committee to set AEGL levels. Following the guidelines are elements of the rationale to capture in the Technical Support Document.

For the reasons discussed in the introduction to this section, the NAC/AEGL Committee generally selects the highest experimental concentration that does not elicit the symptoms or effects defined by the AEGL tier in question. This concentration represents the starting point for AEGL development. In instances where appropriate data are available, the BMC methodology may be considered and used to select the AEGL endpoints.

2.2.2.1 AEGL-1 Endpoints

The NRC 1993a guidelines discuss the definition of the AEGL-1 endpoint on pages 10, 12, and 21. Above the AEGL-1 level, discomfort becomes increasingly likely. Below the AEGL-1 level (detectability) "Exposure insufficient to cause discomfort or adverse health effects might be perceived nevertheless by means of smell, taste, or sensations (mild sensory irritation) that are not uncomfortable. The awareness of exposure might lead to anxiety and complaints and constitutes what is termed here detectability." (NRC, 1993a, p21).

Thus at concentrations below the AEGL-1 level there may be specific effects such as the perception of a disagreeable odor, taste, or other sensations (mild sensory irritation). In some people that could result in mild lacrimation or coughing. Since there is a continuum in which it is difficult to judge the appearance of "discomfort" in animal studies and human experiences, the NAC/AEGL Committee has used its best judgement on a case by case basis to arrive at appropriate and reasonable AEGL-1 values.

One additional factor to consider is that the three tiers of AEGL values "...provide much more information than a single value because the series indicates the slope of the dose-response curve" (NRC, 1993a). If an accident occurs and people smell or otherwise "detect" a chemical, the extent of the concentration range between the AEGL-1 and AEGL-2 levels provides information and insight into the estimated margin of safety between a level of detection or mild sensory irritation (AEGL-1) and a level that may impair escape or lead to a serious long-term or irreversible health effect (AEGL-2). In cases where the biological criteria for the AEGL-1 value would be close to, or exceed the AEGL-2 value, the conclusion is reached that it is "Not Recommended" (NR) to develop AEGL-1 values. In these cases, "detectability" by itself would indicate that a serious situation exists. In instances where the AEGL-1 level approaches or exceeds the AEGL-2 level, it might erroneously be believed that people experiencing mild irritation are not at risk when in fact they have been exposed to extremely hazardous or possibly

lethal concentrations.

Since a comparison of the AEGL-1 and AEGL-2 levels indicates the slope of the dose-response curve which may be of value in emergency response, planning, or prevention, the NAC/AEGL Committee also attempts to establish AEGL-1 endpoints for adverse effects that are asymptomatic or non-sensory. Examples of such effects include significant (measurable) levels of methemoglobin, elevated blood enzyme levels, or other biological markers related to exposure to a specific chemical. By establishing an AEGL-1 value in these instances, important information on the toxicological behavior of a specific chemical is available to emergency responders and planners.

The following criteria have been used by the NAC/AEGL Committee to select endpoints for use in setting the AEGL-1 values.

2.2.2.1.1 No Value Established - AEGL-1 Exceeds AEGL-2

1. What aspects of the chemical toxicity profile make it inadvisable to generate an AEGL-1 value.

For example, the AEGL-1 value was not established because levels which are "detectable" are close to, or exceed, an AEGL-2 level. These materials have poor warning properties.

2.2.2.1.2 No Value Established - Insufficient Data

Insufficient data were available.

2.2.2.1.3 Highest Experimental Exposure Without an AEGL-1 Effect

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

The highest experimental exposure levels which did not cause sensory irritation, pulmonary function, and narcosis in humans have been used to set AEGL-1 levels.

2.2.2.1.4 Effect Level for a Response

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

For example, levels for odor detection in humans, mild sensory irritation, asymptomatic

or non-sensory effects such as methemoglobin formation (22%), and pulmonary function (transient changes in clinically insignificant pulmonary functions of a sensitive individual) have been used as AEGL-1 endpoints.

2.2.2.2 AEGL-2 Endpoints

NRC (1993a) discussed the AEGL-2 definition on pages 10, 12, and 21. The AEGL-2 exposure level is the threshold between reversible effects which cause discomfort, and serious or irreversible health effects or effects which impair escape. Above the AEGL-2 level there is an increasing likelihood people may become disabled or are increasingly likely to experience serious or irreversible health effects. "The term disability is used here to indicate the situation where persons will require assistance or where the effects of exposure will be more severe or prolonged without assistance." (NRC, 1993a, p21). In developing AEGL-2 levels the NAC/AEGL Committee has defined a NOEL for serious or irreversible effects or effects which impair escape. It must be emphasized that reversible clinical toxicity may be observed below the AEGL-2 level. If minor reversible effects are seen at one level of exposure and disabling effects at a higher exposure, the former is used to set the AEGL-2 level. If the exposure associated with disabling effects cannot be determined from experimental data, then the highest level causing reversible effects/discomfort may be used to set the AEGL-2 level.

The following criteria have been used by the NAC/AEGL Committee to date to select endpoints for use in setting the AEGL-2 values.

2.2.2.2.1 Highest Experimental Exposure Without an AEGL-2 Effect

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

The highest experimental exposure levels which did not cause decreased hematocrit, kidney pathology, behavioral changes or lethality (effects observed at higher exposures were above the definition for AEGL-2) have been used as the basis for determining AEGL-2 levels.

2.2.2.2.2 Effect Level for a Toxic Response Which was Not Incapacitating or Not Irreversible

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

For example, strong irritation, dyspnea, pulmonary function, provocation of asthma episodes, pathology (respiratory tract, mild narcosis, methemoglobin formation (41%) have been used to set AEGL-2 levels.

2.2.2.2.3 A Fraction of the AEGL-3 Level

1. State the rationale for using a fraction of the AEGL-3.
2. State why the specific fraction chosen is scientifically justified.

In the absence of specific data used to determine an AEGL-2 value, 1/3 of the AEGL-3 value has been used to establish the AEGL-2 level. This approach can only be used if the data indicate a steep exposure-response relationship from serious to no-effects.

2.2.2.3 AEGL-3 Endpoints

NRC, (1993a) discussed the AEGL-3 definition on pages 10, 12, and 21. The AEGL-3 tier is the threshold exposure level between serious long lasting or irreversible effects or effects which impair escape and death or life-threatening effects. Above the AEGL-3 there is an increasing likelihood of death or life threatening effects occurring. In determining AEGL-3 levels, the NAC/AEGL Committee defined the highest exposure which does not cause death or life threatening effects. It must be emphasized that severe toxicity will be observed at the AEGL-3 level. In cases where data to determine the highest exposure level which does not cause life-threatening effects are not available, levels which cause severe toxicity without producing death have been used.

The following criteria have been used by the NAC/AEGL Committee to date to select endpoints for use in setting the AEGL-3 values.

2.2.2.3.1 Highest Exposure Level Which Does Not Cause Lethality - Experimentally Observed Threshold (AEGL-3 NOEL)

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

Where experimental lethality data have been insufficient to statistically determine a benchmark concentration, the highest experimental exposure which did not cause lethality in an experiment in which death was observed was used to set the AEGL-3 level.

2.2.2.3.2 Highest Exposure Level Which Does Not Cause Lethality - Estimated Lethality Threshold - 1/3 of the LC_{50}

1. State the species, effect, and concentration and exposure time to cause the effect.
2. Describe the toxicologic endpoint of concern.
3. If an exposure which does not produce death is estimated by dividing an LC_{50} value by 3 (or some other divisor), give the slope of the exposure response curve or enough

data points to support the division by 3 (or some other divisor).

Where experimental lethality data have been insufficient to statistically determine an LC_{01} value, but an LC_{50} value was determined, and all exposure levels caused lethality, a fraction of the LC_{50} value was used to estimate the threshold for lethality. In all cases the exposure response curve was steep and the LC_{50} value was divided by three. The Fowles et al. (1999) analysis of inhalation toxicity experiments revealed that for many chemicals, the ratio between the LC_{50} and the experimentally observed non-lethal level was on average a factor of approximately 2, the 90th percentile was 2.9, and the 95th percentile was 3.5. There was a range of ratios from 1.1 to 6.5.

2.2.2.3.3 Highest Exposure Level Which Does Not Cause Lethality - Benchmark Exposure Calculation of the 5 % and 1% Response

1. State the species, effect, and concentration and exposure time to cause the effect.
2. Describe the toxicologic endpoint of concern.
3. State the statistical methodology used to derive a BMC_{05} and the MLE_{01}.

Where sufficient information was available, the preferred method through 1999 was a probit analysis (Finney, 1971) to determine the LC_{01}. Actual calculations were performed using the Number Cruncher Statistical System - Version 5.5. This is a probit analysis of the response - log exposure curve. The Maximum Likelihood Estimate (MLE) was used for the LC_{01} value. The method of Litchfield and Wilcoxon (1948) has also been used.

In the future both the BMC_{05} and MLE_{01} for lethality will be determined, presented and discussed. Results from the above models will be compared with the log probit U. S. EPA (2000) Benchmark Dose Software (http://www.epa.gov/ncea/bmds.htm). In all cases the MLE and BMC at specific response levels will be considered. Other statistical models such as the Weibull may also be considered. Since goodness of fit tests consider an average fit, they may not be valid predictors of the fit in the low exposure region of interest. In this case the output of the different models will be plotted and compared visually with the experimental data to determine the most appropriate model. The methodology which results in values consistent with the experimental data and the shape of the exposure-response curve will be selected for AEGL derivations.

Because of uncertainties that may be associated with extrapolations beyond the experimental data range, the estimated values are compared with the empirical data. Estimated data which conflicts with the empirical data will generally not be used.

2.2.2.3.4 Effect Level for a Response

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

Where the data were insufficient to estimate the highest exposure which does not cause lethality, exposures which caused severe intoxication in the absence of lethality were used in the selection of exposure levels to set AEGL-3 values. The endpoints of concern included decreased hematocrit, methemoglobin formation (70-80%), cardiac pathology, and severe respiratory pathology.

2.3 GUIDELINES/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 U. S. and foreign countries, including references on toxicology, regulatory initiatives, and general chemical information; (3) data from private industry on other private sector 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 U. S. National Library Medicine's TOXNET:

TOXLINE covers the toxicological 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.

TOXLINE65 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 the about the chemical.

PUBLIC MEDLINE (PUBMED):

PUBMED includes MEDLINE and PREMEDLINE. MEDLINE, the U. S. National Library of Medicine's (NLM) 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 of 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 US 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 NASA, DDC, DOE, HUD, 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)

Data from US 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)

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.

U S. ORNL IN-HOUSE DATABASES

CHEMICAL UNIT RECORD ESTIMATES (CURE)

The CURE database contains selected information from the U.S. Environmental Protection Agency 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

fifteen years. These range from Toxicity Summaries to journal articles. This list provides good references for chemicals which overlap the AEGL priority list.

(2) PUBLISHED BOOKS AND DOCUMENTS FROM THE PUBLIC AND PRIVATE SECTORS

GENERAL REFERENCES FOR TOXICOLOGY AND CHEMICAL INFORMATION

U. S. ATSDR (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
U. S. NTP (National Toxicology Program) Div. 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

U. S. AIHA (American Industrial Hygiene Association) Emergency Response Planning Guidelines
(ERPGs) and Workplace Exposure Level Guides (WEELs)
U. S. 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
U. S. NAAQS National Ambient Air Quality Standards
U. S. NIOSH Documentation of IDLH's
U. S NIOSH (National Institute for Occupational Safety and Health) Pocket Guide to Chemical Hazards
U. S. NIOSH Recommendations for Occupational Safety and Health, Compendium of

Policy Documents and Statements
U. S. OSHA (Occupational Safety and Health Administration) Limits for Air Contaminants
U. S. SMACS Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Committee on Toxicology, Commission on Life Sciences, and National Research Council, sponsored by NAS
U. S. EPA Health Effects Documents

(3) UNPUBLISHED DATA FROM PRIVATE INDUSTRY AND OTHER PRIVATE SECTOR ORGANIZATIONS OF ALL NATIONS

Reports and data not published in peer reviewed scientific journals that is relevant to the development of AEGLs. Most often this represents 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 at some later date.

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, conduct searches using chemical nomenclature and common chemical name(s) in addition to the CAS number. Searches by chemical name(s) also should be made if limited 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
acute
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 might not achieve a consensus of the

NAC/AEGL Committee. If a consensus or 2/3 majority of the Committee cannot agree on the adequacy of the data, the chemical may be placed in a cue 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 U. S. NAS (NAS, 1993a) guidelines, U. S. EPA's National Advisory Committee on Acute Exposure Guideline Levels (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 AEGL Committee is intended to provide technical support document (TSD) 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 method for selecting key studies used to calculate an AEGL value. Additionally, the system will allow linkage to 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 from which Committee members can function. The NAC/AEGL Committee has the concurrence of the U. S. National Academy of Sciences (NAS) on these guidelines, as well as all other guidelines published in this manual.

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 U. S. EPA and OECD guidelines are used as the basis for future studies conducted 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 AEGL values without conforming completely to a standard of detailed methodology, data analysis and results reporting. 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 1) uses scientifically valid methods, 2) contains adequate and reliable data and 3) presents defensible conclusions relevant to the AEGL process, it may be included in the technical support document and used to support the AEGLs.

It is important to emphasize that only toxicity data obtained directly from a primary reference source is 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 is obtained solely from the primary references. This includes data 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 non-toxicological or epidemiological information on a chemical. Secondary references also may be used to present background information on the toxicity or toxicological characteristics of a chemical and any other information not important or directly relevant to the actual derivation of, or the supporting rationale for, the AEGL values. Finally, data and information from secondary references should not be included in data summary tables presented in the Technical Support Documents.

The evaluation guidelines are more credible if they are drawn from a widely accepted prescription for study protocol design. The list of guidelines for AEGL study evaluation should be based upon 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 NRC (1993a), the OECD's Guidelines for the Testing of Chemicals, and U. S. EPA (Health Effects Test Guidelines) as a basis for selection.

The NAS (1993a) guidance provides only limited guidance on the use of toxicological data from routes of exposure other than inhalation. The guidance states that the bioavailability and differences in the pharmacokinetics from the different exposure routes of the chemical in question must be considered. Because of these complex biological 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 from alternate routes of exposure will not be included in discussions in the Technical Support Documents unless it is considered important for the support of relevant pharmacokinetics or metabolism data or mechanisms and observed effects 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 toxicological value is obtained for use in AEGL calculations. "Supporting Studies" are the human and/or animal studies which are used to support the toxicological 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 which 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 measurement 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 to be reliable. The list of Elements for Evaluation also is used for initial review of all studies evaluated for possible inclusion in the TSD in instances where they are germane to the selection of studies.

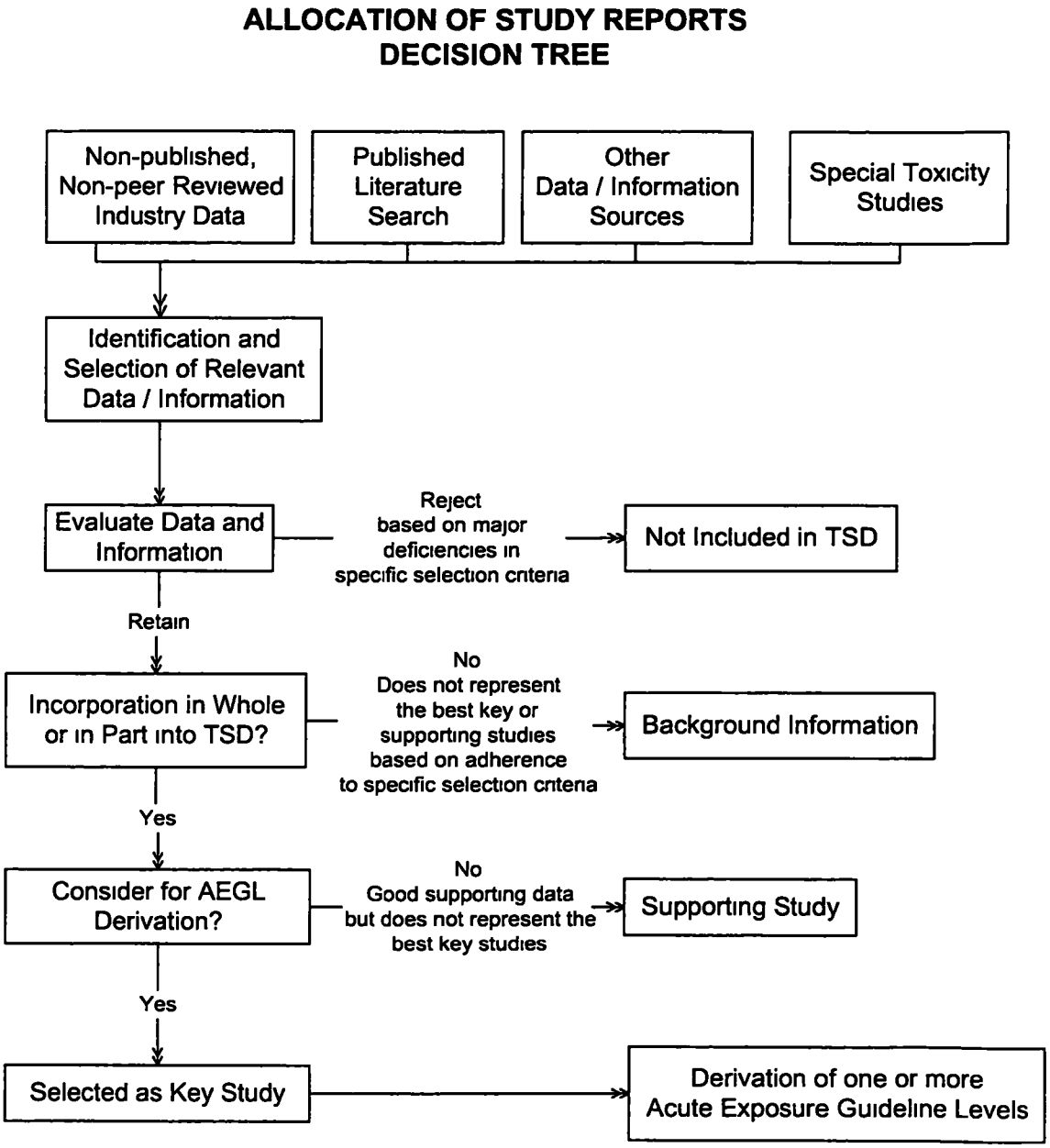
The NAC/AEGL Committee is dependent upon existing human studies published in the literature for data on humans Many of these studies do not necessarily follow current guidelines on ethical standards which require that effective, documented, informed consent from participating humans subjects be required. Further, recent studies which 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 insure 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 judgement to determine whether the human studies were ethically conducted and that the human subjects were likely to have provided their informed consent. Additionally, human data from epidemiological 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 as published in the Code of Federal Regulations (40 CFR Part 26 [*The Common Rule*], 2000).

In addition to the discussion of the Elements for Evaluation in the individual studies section of the Technical Support Document (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 Executive Summary 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 Executive 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. These 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 which reflects the investigations conducted on the chemical and the properties of the chemical. This section reflects a "best professional judgement" approach in the evaluation of the data adequacy and future research needs.

A diagram of the decision process for the selection of key studies and supporting studies

is shown on the following page. 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.

1 **FIGURE 2.3-1 ALLOCATION OF STUDY REPORTS DECISION TREE**



2
3
4

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" toxicological 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 non-toxicological data such as physical/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. Route of exposure. The inhalation route is preferred. Where the endpoint of concern is systemic intoxication and the first pass effect is not significant, oral exposure may be considered. In the absence of scientifically sound data with high confidence in a valid route-to-route extrapolation, routes of exposure other than inhalation will not be used for AEGL derivation.

5. Scientifically credible exposure concentration and exposure duration are provided.

6. Analytical procedures used to determine chamber concentration for inhalation exposure in controlled studies and detailed, scientifically credible methods, procedures, and data used to measure chemical concentration in epidemiological or anecdotal cases (accidental chemical releases). For oral exposure, dose may be determined from the amount of test chemical placed into the subject.

7. Number of subjects. The number 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. Species studied. Humans are most relevant. 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. Presence of a concurrent control group 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/dose selection that establishes a clear dose-response relationship.

11. Observation period. The period is variable based on the time of onset of the toxic effect. If it is rapid (minutes to 2-3 hours) 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 intoxication noted during and after exposure and reported separately by sex and concentration or dose.

13. For animal studies, body weights should recorded throughout the study.

14. For repeated concentration/dose studies, establishment of the highest estimated or experimental (empirical) level of no effect 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.

17. If a NOEL 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. Record of time of death if applicable.

19. For animal studies, necropsy conducted with at least gross effects noted.

20. As available, data (e.g. histopathological 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. Statistical treatment of data generated from study.

23. An evaluation of all relevant data should be performed and summarized in the Technical

Support Document in order 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 and/or studies for each tier, the data adequacy should be addressed separately for AEGL-1, -2, and -3 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 Executive Summary and the Derivation Summary Tables. The summary statements also 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 often an issue of concern. For inhaled toxicants the target tissue is either some component of the respiratory system and/or other tissue or organ. A number of methods have been proposed to adjust for differences in the dose to target tissue in the respiratory system (U.S. EPA, 1994b) and those located systemically (U. S. EPA, 1994b; NRC, 1993a). The concern has been the lack of validated methodologies that would provide scientifically sound values for gases, vapors and aerosols. This is particularly true where the methodology may predict levels for humans that may not be sufficiently protective. Both methodologies referenced above have not been validated for gases with experimental data, especially in the higher dose ranges required to produce toxicity with acute exposures. Another possible dosimetry correction, using the inhaled dose against the body weight raised to the 3/4 power has support based upon an analysis of chronic toxicity studies (U.S. EPA, 1992). However, this adjustment may not be relevant for acute lethality studies (Wolff and Rhomberg, 1998). Therefore, no dosimetry adjustments have been made to date by the NAC/AEGL Committee for attaining human-equivalent doses in the development of AEGLs for gases, vapors and aerosols.

If AEGL values are developed for particulates, the methodology developed by the U. S. Environmental Protection Agency, and validated with experimental data on particulate matter, will be reviewed and applied on the basis of the individual material (U. S. EPA, 1994b). Where specific data and validated models are available for chemicals inhaled as gases, a dosimetry correction will be made by the NAC/AEGL Committee.

2.4.1 Discussion of Potential Dosimetry Correction Methodologies for Gases

2.4.1.1 The Respiratory System as a Target Organ

The RfC (Reference Concentration) methodology for chronic exposure to gases was proposed by U.S. EPA (1994b) as an approach to the dosimetry correction for effects on the respiratory system. This method has not been used by the NAC/AEGL Committee for the following reasons: (1) The RfC dosimetry corrections from animal to man are based upon theoretical constructs which have not been confirmed and validated with experimental data; (2) Some of the RfC assumptions are questionable and can have a significant impact upon the calculated dosimetry correction between animal and human. Below is a discussion of two key examples and their impact upon the dosimetry adjustment. The assumptions are the requirement of uniform deposition in compartments and equivalent percent of deposition in animals and humans

For Category 1 gases (highly water soluble and/or rapidly irreversibly reactive) the RfC methodology assumes that for each respiratory compartment (extrathoracic, tracheobronchial, and pulmonary), the deposition of chemical is equivalent throughout the compartment. This fails to take into account major differences in anatomical structure and deposition (dose) as the gas, vapor or aerosol progresses from proximal to distal regions within any one compartment. The dosimetric adjustment from rodent to man for the extrathoracic region predicts a 5-fold higher delivered dose to humans compared to rodents at equivalent exposures. However, a number of investigators have shown that treating the entire extrathoracic region as a single homogeneous compartment is incorrect. The use of sophisticated computational fluid dynamics computer modeling, correlated with analysis of patterns of lesions induced by chemical exposure, demonstrate that the degree of deposition of chemicals varies greatly in different extrathoracic regions in rats (Kimbell et al., 1993; Kimbell et al., 1997a; Kimbell et al., 1997b) and the monkey (Kepler et al., 1998). Specific areas such as the olfactory epithelium will receive different regional doses in the rat and humans because of differences in surface area, susceptible location, and degree of ventilation (Frederick, et al., 1998). A recent estimate of a dosimetric adjustment for vinyl acetate toxicity to the olfactory epithelium was performed using multiple compartments and a physiologically based pharmacokinetic model (PBPK). Bogdanffy et al. (1999) predicted that a time adjusted exposure of 8.7 ppm in the rat would result in the same damage in a human exposed to 10 ppm. In this case the application of the RfC methodology overestimates the risk to humans.

In the RfC methodology the proportion deposited in each region for Category 1 gases is assumed to be the same in animals and humans. Where the deposition is less than 100% this assumption is incorrect when one considers a rodent breathing at 100 times a minute vs 15 breaths a minute for a human. The residence time for the chemical in a rodent lung is approximately 0.6 seconds while it is approximately 4 seconds in a human or about 6 times as long. All things being equal, the longer residence time in the human respiratory system will mean that the human extracts a greater percent of inspired chemical per breath than a rodent. Another factor to consider is that at high exposure levels, a steady state can be rapidly achieved in which relatively little chemical is deposited in each breath so that the concentration becomes the determining factor.

Of concern is the fact that when dosimetry adjustments are made between rodents and humans for toxicity to the pulmonary region, the delivered dose to the human is predicted to be about 3-times less than the mouse for an equivalent nominal exposure concentration. Using this methodology in the absence of supporting empirical data could seriously underestimate human sensitivity. For example, at lethal concentrations fluorine toxicity is due to pulmonary intoxication in all species tested (Keplinger and Suissa, 1968) Further, the empirically derived LC_{50} values for the mouse, rat, rabbit, and guinea pig are essentially identical. However, the minute volume to surface area ratio for the pulmonary region of the guinea pig closely resembles the human. If the RfC dosimetry procedure were correct, the LC_{50} for the guinea pig should be 2-3 times higher than that observed for the rat and mouse, yet the empirical data were essentially

identical for all three species. Using the RfC methodology to extrapolate a dosimetric correction to humans in this case would seriously underestimate the risk by a factor of 3 from the mouse data. This problem is compounded by the fact that the RfC methodology calls for the use of a lower interspecies uncertainty factor when the dosimetry correction is used.

2.4.1.2 Systemic Toxicity

Most systemic toxicants would fall under the definition of a Category 2 gas in the EPA methodology (U.S. EPA, 1994b). Category 2 gases are moderately water soluble and intermediate in their reactivity such that they would be distributed throughout the respiratory tract and absorbed readily into the blood stream. In the case of Category 2 gases, the RfC dosimetry procedure predicts that the human receives a dose ranging from 6,000 to 50,000 times higher than a rodent (depending upon the species) for an equivalent exposure. These numbers do not appear to be biologically reasonable or scientifically credible. Because of the potential errors, the methodology for category 2 gases has not been used. When a corrected methodology is published it will be evaluated for use by the NAC/AEGL Committee.

For systemic toxicants, the NRC (1993a), proposed that dosimetry correction be conducted by adjusting for minute volume to body weight ratios. It is assumed for this calculation that 100 percent of the chemical, or that equal percentages of the chemical, are absorbed. Given that assumption, the correction is a reasonable approach and may be valid for low concentrations of chemicals. Most animal to human extrapolation is done using mouse or rat data. Using certain typical minute volume and body weight parameters, it is possible to calculate an adjustment factor or multiplier in order to derive an equivalent dose in a human from animal data. The multiplier is approximately 6 for the mouse and 3.5 for the rat. Thus, if the exposure of interest in mice or rats is 100 ppm, then an equivalent internal dose in humans would be predicted to be induced by exposure to 600 ppm and 350 ppm from these two species respectively. Therefore, in order to induce an acutely toxic systemic effect in humans, people would have to be exposed to a concentration 6 times greater and 3.5 times greater than the nominal exposure required to induce the effect in mice or rats respectively.

If, on the other hand, less than 100 percent of the inspired chemical is absorbed with each breath, the human and animal would absorb a different fraction of the chemical in each minute (see discussion above). As the percent absorbed approaches 0 the multiplier would approach 1. In the example above the multiplier for human dosimetry correction would go from 6 to 1 in the case of mice and 3.5 to 1 in the case of rats as the percent absorbed approaches 0.

AEGL-2 and AEGL-3 levels represent relatively high exposure concentrations where absorption may not be complete. If the minute volume to body weight correction for dosimetry which assumes 100 percent absorption were used in these cases, the estimated human exposure equivalent to the rodent would be too high, leading to an underestimate of the toxicity and the derivation of AEGL values that are not protective to the human population

Another approach to dosimetry correction might be that used by the U.S. Environmental Protection Agency when extrapolating from animal cancer bioassays to theoretical excess human cancer risk levels for lifetime exposures (U.S. EPA, 1992) The cross species scaling factor used is based upon an equivalence of $mg/kg^{3/4}$/day. There is reasonable scientific support for utilizing this approach based upon an analysis of a number of multiple exposure studies across a number of animal species (U.S. EPA, 1992) One might assume that the total amount of chemical inhaled is equivalent to the dose (NRC, 1993a) and adjust that across species using the equivalence of $mg/kg^{3/4}$/day. However, Vocci and Farber (1988) point out the power law of $(body\ weight)^{3/4}$ holds for the ventilation rate such that on a weight to weight basis, the rat receives about 4 times the delivered dose of a human for the same exposure concentration. When this adjustment for breathing rate is combined with the adjustment for toxicity (U.S. EPA, 1992), the two cancel each other out and one is left with the conclusion that equivalent exposure concentrations result in equivalent outcomes in animals and humans.

The situation is further complicated by an analysis of oral acute toxicity experiments by Rhomberg and Wolff (1998) using pair-wise comparisons of LD_{50} values for different species for a large number of chemicals on the RTECS database. Their findings contrast with the U.S. EPA (1992) findings, which largely evaluated multiple exposure studies, in that the best correspondence of toxicity across species for LD_{50} values was found when doses were expressed as mg/kg. This finding might argue for the NRC (1993a) recommendation to scale doses across species based upon minute volume to body weight ratios. However, this conclusion would be based upon an evaluation of oral toxicity studies, most of which were probably by gavage. Bolus doses result in a high peak body dose, in contrast to the inhalation of a chemical over a number of hours with a more constant body burden over time. The question then becomes, does inhalation exposure on the order of hours mimic the toxic response seen with multiple exposures (U.S. EPA, 1992) or the acute bolus doses used in the Rhomberg and Wolff (1998) analysis? If the former situation prevails then the rationale by Vocci and Farber would argue for no dosimetry corrections being made. On the other hand, the latter case would argue for the use of the NRC (1993a) methodology.

2.4.2 Current Approach of the NAC/AEGL Committee to Dosimetry Corrections

Given the large amount of uncertainty surrounding this issue, and the fact that the use of no dosimetry corrections for gasses across species would be the most conservative approach, the NAC/AEGL Committee has chosen not to use dosimetry corrections across species. However, as the science surrounding this issue progresses the NAC/AEGL Committee will continue to re-evaluate it's conclusions. If data are available, on a chemical-by-chemical basis, which would scientifically support dosimetry corrections for gases in the development of AEGL values, they will be used to do so.

As AEGL values are developed for particulates, the methodology developed by the U. S

Environmental Protection Agency, and validated with experimental data on particulate matter, will be reviewed and applied on the basis of the individual material (U. S. EPA, 1994b).

2.5 GUIDELINES/CRITERIA FOR SELECTION OF UNCERTAINTY FACTORS TO ADDRESS THE VARIABILITY BETWEEN ANIMALS AND HUMANS AND WITHIN THE HUMAN POPULATION

2.5.1 Introduction

The variation in the toxicological response of organisms to chemical exposures is well known. This variability can be expressed across species and among individuals within the same species. Lack of knowledge about the range of variability introduces uncertainties into any estimate of AEGL values based upon biological data. To account for known and unknown variability in response, the value derived from experimental data is adjusted by a value that reflects the degree of uncertainty. This value is referred to here and by most agencies and organizations as the uncertainty factor (UF). If an extrapolation is being made from animal data to humans the total UF is a composite of an interspecies UF to account for possible differences between animal and human response to the chemical, and an intraspecies UF to account for differences in response to the chemical within the human population. The intraspecies UF is needed to account for possible variabilities in response by "... those at either extreme of age, those with poor nutritional status, those with preexisting diseases, such as certain heart diseases, that are fairly widespread in the general population, those with enhanced hereditary susceptibility, or those who are overexposed because of unusual physical exertion." (NRC 1993a, p88).

Inter- and intraspecies uncertainty factors have been used in the development of "safe" or threshold exposure levels for chronic, non-cancer toxicity by health organizations throughout the world. Examples include the acceptable daily intake (ADI) (Lu, 1988; Truhaut, 1991; Lu and Sielken, 1991), the tolerable daily intake (TDI) or tolerable concentration (TC) (Meek et al., 1994; IPCS, 1994), the minimal risk level (MRL) (Pohl and Abdin, 1995), the reference dose (RfD) (Barnes and Dourson, 1988; Dourson, 1994), and the reference concentration (RfC) (U. S. EPA, 1994b; Jarabeck, 1994). The importance of using distribution based analyses to assess the degree of variability and uncertainty in risk assessments has been emphasized in recent trends in risk analysis. This will enable risk managers to make more informed decisions and better inform the public about possible risks and the distribution of those risks among the population (Hattis and Anderson, 1999). These techniques can be used to assess variability from differences in individual exposure and susceptibility for specific risk assessments in order to reduce the uncertainty in estimating the real variability which exists in a population (Hattis and Burmaster, 1994; Hattis and Barlow, 1996).

The use of uncertainty factors in the development of AEGL values is designed to protect the general public, including sensitive subpopulations, from short-term exposures to acutely toxic chemicals. However, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience adverse effects at concentrations below the corresponding AEGL level. "In the case of CEEL-2 *(AEGL-2)*, uncertainty factors must be balanced against the

Barnes and Dourson (1988) described the U.S. EPA's approach and rationale to assessing non-carcinogenic health risks from chronic chemical exposure. The U. S. EPA approach follows the general format as set forth by the National Research Council (NRC, 1983). The conceptual difference between "safety" and "uncertainty" is discussed within the context of the terms safety factor (SF) versus uncertainty factor (UF) and acceptable daily intake (ADI) versus reference dose (RfD). The authors state that "safety factor" suggests the notion of absolute safety and that the ADI is generally and erroneously interpreted as a strict demarcation between what is "acceptable" and what is "safe" in terms of chronic exposure. In reality, the ADI represents an estimate of a level where the probability of adverse effects is low but a level where the complete absence of all risk to all people cannot be assured. Consequently, the RfD and UF terminology was developed and adopted by the U. S. EPA. The U. S. EPA considers the RfD to be an estimate (with uncertainty spanning perhaps an order of magnitude of a daily exposure to a human population, including sensitive subpopulations), that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Dourson, et al. (1992) conducted an analysis of chronic and subchronic toxicity data on 69 pesticides obtained from EPA's Integrated Risk Information System (IRIS) to determine the potential impact of missing studies on the quality of the RfD values derived. Certain of these data proved useful in determining interspecies variations in toxic response to long term oral ingestion of a wide range of pesticides. The authors' analyses of 1- to 2- year studies indicated that the probability of the rat NOAEL for each of 67 pesticides exceeding the dog NOAEL by greater than 3.16-fold was 28 percent and the probability of the rat NOAEL exceeding the dog NOAEL by greater than 10-fold was 10 percent. Also, the probability of the dog NOAEL in the same studies exceeding the rat NOAEL by greater than 3.16-fold was 19 percent and the probability of the dog NOAEL exceeding the rat NOAEL by greater than 10-fold was 4 percent. These data support the value of using uncertainty factors (UFs) derived from data in developing RfDs and suggests that UFs between species may be significantly less than 10-fold for a wide range of structurally diverse chemicals.

Renwick (1993) considered the expression of toxicity to be the combined result of toxicokinetics (all processes contributing to the concentration and duration of exposure of the active chemical toxicant at the target tissue) and toxicodynamics (mode or mechanism of action of the active toxicant at the target tissue site). Therefore, he reasoned that since both toxicokinetics and toxicodynamics contribute quantitatively to the uncertainty factor, it is necessary to subdivide each of the 10-fold UFs (inter- and intraspecies) into these two components to effectively accommodate differences in contributions made by toxicokinetic and toxicodynamic factors. Hence, for any chemical, appropriate data may be used to derive a specific data-derived factor for that component. The overall inter- and intraspecies UFs would subsequently be determined as the product of the known data-derived factor or factors and the "default" values for the remaining unknown factors. The author evaluated published data for parameters that measure interspecies differences in plasma kinetics (physiological changes, differences in rates of absorption, biotransformation, and elimination) in laboratory animals and

little or no evaluation of scientific data to support or reject the use of this value. Today there is greater knowledge and insight and defined methods to evaluate sensitivity or variability in responses and selecting or deriving more scientifically credible UFs.

Dourson and Stara (1983) introduced the concept that empirical data are available to support the use of UFs for both inter- and intraspecies adjustment. This was followed by the publication of an analysis of the chronic and subchronic toxicity data obtained from U. S. EPA's Integrated Risk Information System (IRIS). Certain of these data proved useful in determining the extent of interspecies variations in toxic response to long-term oral ingestion of a wide range of pesticides. More recently the concept of data-derived UFs has been introduced (Renwick, 1993; Dourson et al., 1996). Finally, the concept of dividing, evaluating, and quantifying separately the toxicokinetic and toxicodynamic factors from each of the inter- and intraspecies UFs has been proposed (Renwick, 1993).

One important consideration in the selection or derivation and use of UFs for the development of AEGLs is the nature of the toxicant and the exposure period. Much of the data, information, and emphasis to date on non-carcinogenic and non-mutagenic substances has addressed chronic effects from long-term or life-time exposures. Certain of the reports discussing the toxicokinetic and toxicodynamic factors as related to variability of response have drawn on carcinogenic or mutagenic mechanisms as a basis for scientific support. By contrast, the AEGL values address relatively high concentration, short-term exposures to threshold effects of acutely toxic chemicals. In attempting to draw on the scientific foundations upon which UFs are being selected for use in developing chronic guideline levels such as RfDs and RfCs, it is important to maintain an awareness of certain potential differences when considering acute guideline levels such as AEGLs. Responses to chronic exposures may be greater between species or between individuals as compared to responses to acute exposures. For example, the impact of individual differences in absorption, excretion, metabolism, rate of repair or accumulation of unrepaired damage may be magnified through exposure to lower concentrations over extended time periods. The higher concentrations associated with acute exposure may tend to overwhelm existing defense mechanisms, possibly ameliorating certain differences in response among species and among individuals within the same species. The higher concentrations associated with single exposures, together with the short-term nature of the exposure period, may nullify existing differences in absorption, metabolism, and excretion of a substance, as well as differences in repair mechanism rates, and other factors. Hence, acute exposure to acutely toxic substances in some instances may reduce the variability in response between species and among individuals of the same species depending upon the mode of action of the chemical. Additionally, the fact that AEGLs are based on, and intended for, inhalation exposure adds one more important dimension to the complexity of differences between individuals and species.

Based on the considerations presented above, the acceptance and use of default UFs based upon chronic exposure data should be carried out only after careful evaluation of chemical specific data for single exposures. However, the concepts, ideas, and approaches to developing

UFs that have emanated from the chronic exposure studies of the past 10 years is of substantial value in the development of AEGLs and will be employed as appropriate in the selection or derivation of UFs used in the AEGL program.

2.5.3.1 Interspecies Uncertainty Factors - Use in the Development of AEGL Values - Discussion

Where data are insufficient to determine the relative sensitivity of animals to man, an uncertainty factor of 10 has been used by U. S. EPA, U. S. ATSDR, Health Canada, International Program on Chemical Safety (IPCS), and Rijksinstituut voor Volksgesondheid en Milieu (RIVM) when developing the equivalent of reference doses for chronic exposure to chemicals (Dourson et al, 1996). When extrapolations are made from animals to humans based upon mg/kg of body weight the factor of 10-fold is usually adequate to account for differences in response. Dourson and Stara (1983) found that a factor of 10 accounted for many of the animal to human differences observed when the dose was adjusted for differences between human and animal body weights and body surface areas.

Brown and Fabro (1983) compared the lowest effective dose to cause teratogenicity in animals (mouse, rat, rabbit, cat, monkey) and humans for 8 chemicals (methyl mercury, diethyl stilbesterol, methotrexate, aminopterin, PCBs, thalidomide, phenytoin, alcohol). The LOAEL ratios ranged from 1.8 to 50 with a geometric mean of 7. Humans were generally more sensitive on an administered oral dose/body weight basis but by less than an order of magnitude. This analysis is complicated by the fact that the criteria and confidence in determining the lowest effective dose are not discussed, and the 8 chemicals may represent potent developmental toxicants in humans since their effect in humans represented the basis for their selection. The potency estimates in humans may represent only the sensitive part of the distribution of human response to exposure. The animal response dose may be closer to the mean response level, and therefore presents a higher LOAEL for the species. However, the retrospective nature allows the choice of the most sensitive animal species. In most instances the animal database is incomplete. Thus, this analysis may represent the spectrum of results in which humans are more sensitive than animals to developmental toxicants.

Renwick 1993 subdivided the inter- and intraspecies UFs into two components to address toxicokinetics and toxicodynamics separately. Although the supporting data for this concept is from chronic animal feeding studies and in vitro cell cultures, the concept of considering the kinetics and dynamics separately across species has relevance to UFs for AEGLs. Renwick proposed specific quantitative values of 4-fold and 2.5-fold for the kinetics and dynamics components, respectively. Although this approach has merit, the NAC/AEGL Committee does not make such a precise quantitative differentiation. To date the NAC/AEGL Committee uses only general information on the kinetic and dynamic components of toxicity to adjust the interspecies uncertainty factor from 10 to 3 or 1. This approach is also consistent with the recommendation by Dourson et al. (1996) to use data-derived uncertainty factors when

appropriate data are available. This approach is in keeping with the U. S. EPA's general approach in the development of RfDs. For example in the case of Aroclor 1016 the default interspecies UF of 10 was reduced to 3 because of the similarity with which monkeys and humans respond to, and metabolize PCBs (toxicokinetics) and the physiologic similarity (toxicokinetics) between the two species (U. S. EPA, 1996b).

Comparisons of the current approach to determine UFs for AEGLs with other short-term exposure limits has not altered the current thinking of the NAC/AEGL Committee. In the development of Emergency Exposure Guideline Levels (EEGLs) by the National Research Council (NRC, 1986) a factor of 10-fold was used for interspecies extrapolation. However, no EEGLs have been developed in the last 15 years so it is not known if different uncertainty factors might be used in light of the more recent concepts and data on interspecies differences.

The NAS Guidelines for Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants (SMACs) states that uncertainty factors between 1- and 10-fold are used for each source of uncertainty (NRC, 1992a). The sources include intraspecies (human) response variabilities, interspecies variabilities, the extrapolation of a LOAEL to a NOAEL, and the extrapolation from an inadequate or incomplete data base. For 1 hour SMACs the NAS employed an overall (combined intra- and interspecies) UF of 10-fold when only animal data were available or when the route of human exposure differed from the study. However, the population for which SMACs is intended does not include infants, children, the elderly, or the infirm and is, therefore, a more homogeneous and healthier subpopulation.

The National Research Council (NRC, 1993a) recommended the use of an interspecies uncertainty factor (UF) within the range of 1- to 10-fold to account for differences between animals and humans. The guidance suggests that the UF should be based on the quality of the data available. In this regard, the NAC/AEGL Committee evaluates data on a chemical-by-chemical basis, considers the weight of evidence, and uses scientific judgement in the selection of interspecies UFs. As data become available, the NAC/AEGL Committee will use data-derived interspecies uncertainty factors.

Information bearing on the toxicokinetics and toxicodynamics of the chemical under consideration, as well as structurally related analogues and/or chemicals which act by a similar mechanism of action, will be used to derive an appropriate interspecies factor which may range from 10 to 3 or 1. In the absence of information on a subject, or analogous, chemical to set data-derived uncertainty factors, the use of a default uncertainty factor of 10 is considered to be protective in most cases. As always, all information on the chemical, its mechanism of action, structurally related chemical analogs, and informed professional judgement will be used when determining appropriate uncertainty factors and evaluating the resultant AEGL values.

2.5.3.2 Interspecies Uncertainty Factors - NAC/AEGL Committee Guidelines

General guidelines followed by the NAC/AEGL Committee to select UFs are presented below. In each section there is a list of questions which should be addressed to support the rationale for the choice of the uncertainty factor used. The guidelines are organized into categories for convenience. However, more than one guideline may be applied to the selection of any one uncertainty factor.

2.5.3.2.1 Most Appropriate Species Used

In cases where there is little interspecies variability (e.g., within a factor of 3), and/or the most sensitive species is selected, and/or a species closely related to humans was selected, the interspecies uncertainty factor is typically reduced from 10 to 3. It should be noted that in these cases the mechanism of action can be identified and there is evidence that it is not expected to vary significantly between species.

THE RATIONALE FOR THE SELECTION OF AN UF SHOULD INCLUDE:

1. The species tested.
2. The toxicologic endpoint used for the AEGL derivation.
3. The qualitative and quantitative range of response of the species tested.
4. Discussion of why the species/study chosen was the most appropriate.
5. Discussion of the variability among studies with the same species or among strains.

2.5.3.2.2 Most Sensitive Species Not Used

In instances where the most sensitive species is not used, an uncertainty factor of 10 is generally used.

THE RATIONALE FOR THE SELECTION OF AN UF SHOULD INCLUDE:

1. The species tested.
2. The toxicologic endpoint used for the AEGL derivation.
3. The qualitative and quantitative range of responses of the species tested.
4. Discussion of why the most sensitive species was not used, and/or why the less sensitive species was selected.

2.5.3.2.3 Mechanism of Action is Unlikely to Differ Among Species

If evidence is available indicating the mechanism of action, such as direct acting irritation or alkylation is not expected to differ significantly between species an interspecies uncertainty factor of 3 is generally used.

THE RATIONALE FOR THE SELECTION OF AN UF SHOULD INCLUDE:

1. A description of the mechanism of action.
2. A discussion of why the mechanism of action is unlikely/likely to differ? Is bioavailability/metabolism/detoxification/elimination likely to be an issue?

2.5.3.2.4 Mechanism of Action is Unknown

In cases where the mechanism of action is unknown, or insufficient data between species are available, or there are likely to be substantial (but inadequately quantified) differences in metabolic and physiological response between species, an interspecies uncertainty factor of 10 is applied.

THE RATIONALE FOR THE SELECTION OF AN UF SHOULD INCLUDE:

1. Description of the toxicological effects observed.
2. Description of the range of uncertainty in toxicologic response and how that relates to this assessment.
3. Discussion of what is known/unknown about the mechanism of action.
4. Discussion of the extent of data available among species.

2.5.3.2.5 Variability in Response Between Species

When there is a wide degree of variability between species, or strains or experiments which cannot be adequately explained, an interspecies uncertainty factor of 10 is applied.

THE RATIONALE FOR THE SELECTION OF AN UF SHOULD INCLUDE:

1. Description of the response.
2. Discussion of the differences or similarities in pharmacokinetic parameters (absorption/metabolism/detoxification/elimination) among species.
3. Discussion of the range of dose-dependent response(s) of the species tested and the qualitative and quantitative aspects of the data.

2.5.3.2.6 Humans More Sensitive than Animals

Where published data show humans are more sensitive than animals, an interspecies uncertainty factor of 10 is used unless published results demonstrate otherwise.

THE RATIONALE FOR THE SELECTION OF AN UF SHOULD INCLUDE:

1. Description of the toxicologic endpoints for which humans and animals show differential sensitivity.
2. Discussion of the factors where humans are thought to be more/less sensitive than animals.

3. State which species were tested.
4. Discussion of the range of response of the species tested. This discussion should address qualitative and quantitative aspects of the data.
5. Discussion of why humans are more susceptible than test animals.

2.5.3.2.7 Use of an Uncertainty Factor of 10

The uncertainty factor for interspecies response adjustment is 10 when there is insufficient information about the chemical or its mechanism of action to justify a lower UF, or if data are available suggesting a high degree of variability between species

THE RATIONALE FOR THE SELECTION OF AN UF SHOULD INCLUDE:

1. Discussion of why an uncertainty factor of 10 is chosen. For example, the analysis may depend upon data collected in only one species, high variability of response, uncertainties in exposure measurement, etc. This statement could point to data gaps which could be filled if the need exists.

2.5.3.2.8 A Selected Uncertainty Factor Applied to Animal Data Would Drive the AEGL-2 or -3 Level to a Value Which Humans can Tolerate without Lethal or Serious Adverse Effects

Where the application of an interspecies uncertainty factor of 10 reduces the AEGL-3 level, the threshold for lethality, or the AEGL-2 level, the threshold for irreversible or disabling effects, to an exposure concentration which humans are known to tolerate without adverse effect, the interspecies uncertainty factor is reduced to 3 or 1.

THE RATIONALE FOR THE SELECTION OF AN UF SHOULD INCLUDE:

1. Citations and explanations of the human data and how it relates to the AEGL value derived with an UF selected on the basis of the existing guidelines.

2.5.3.2.9 A multiple exposure study was used to set the level.

In cases where a single exposure AEGL value is derived from a multiple exposure study because the acute data set for a single exposure is lacking, the multiple exposure data are considered an inherently conservative estimate because a biological organism is expected to have greater tolerance to a single exposure as compared to multiple exposures to the same chemical. If the adverse effect identified in the multiple exposure study is cumulative for the AEGL level of concern, the interspecies uncertainty factor used to adjust the multiple exposure animal data might be reduced to 1 or 3. Careful judgement should be used when making this assessment. If a chemical is cleared very rapidly, or there is evidence that the concentration causing the effect does not vary with duration or number of exposures, then the animal may be able to sustain

repeated insult at a level close to a single acutely toxic exposure. Thus in these instances the reduction of the uncertainty factor based on multiple exposures versus a single exposure would not be justified.

THE RATIONALE FOR THE SELECTION OF AN UF SHOULD INCLUDE:

1. A description of the study.
2. Discussion of the known or suspected clearance rate and other toxicokinetic properties of the chemical. For example, does the concentration causing the effect vary significantly with time or number of exposures?

2.5.3.3 Intraspecies Uncertainty Factors - Use in the Development of AEGL Values - Discussion

Intraspecies uncertainty factors (UFs) are used to address the variability in biological response that exists within a human population exposed to a toxic agent. Their use represents an important step in the AEGL development methodology and is designed to account for the differences which can occur within the general population.

The National Research Council, National Academy of Sciences' guidelines for developing emergency exposure limits state that the exposure limits are "designed to protect almost all people in the general population..." (NRC, 1993a). The NRC guidelines state that, although the levels "...are designed to protect 'sensitive' individuals, some hyper-susceptible individuals might not be protected...". This distinction is based on the premise that emergency exposure limits must be set low enough to protect the general population but must also be set at levels that minimize the risks associated with inappropriate or unwarranted response to chemical emergencies as a result of rare or exceptional circumstances. Consequently, the AEGL values may not be expected to necessarily protect certain individuals with unique or idiosyncratic susceptibilities. This consideration is clearly communicated in the NAC/AEGL Committee's definition of the AEGLs.

When data are insufficient to determine the relative sensitivity of individuals in a human population exposed to a specific chemical, a default uncertainty factor of 10 has been used by U. S. EPA, U. S. ATSDR, Health Canada, IPCS, and RIVM when developing the equivalent of reference doses for chronic exposure to chemicals (Dourson et al, 1996). This value of 10 is generally applied to the NOAEL (the highest observed or calculated dose which did not cause an adverse effect in an experiment). A number of studies have tried to address the issue of the reasonableness or validity of this factor. Under ideal circumstances an analysis would provide information on the ratios of the experimentally observed NOAELs for different human groups within a population for a wide range of defined exposures to chemicals. Groups would be identified based upon biochemical or physiological differences which might cause members of the group to respond to chemical exposure in a fundamentally different manner - either quantitatively or qualitatively. Sample sizes would be large and include a wide variety of genetic backgrounds. Such examples would include differences among newborns, infants, children, adults, the elderly, the infirm, and those compromised by illness, including asthmatics. The NOAELs also would represent a distinct relationship between dose level and response. These data would encompass all variables due to the toxicokinetics and toxicodynamics factors. Such data are not available, even in carefully controlled, double blind clinical trials for new therapeutic drugs. However, surrogates have been developed which provide information on the reasonableness of the choice of the intraspecies uncertainty factor of 10 or less. This approach is referred to as the use of data-derived uncertainty factors.

Dourson and Stara (1983) analyzed the slopes of 490 adult p.o. rat LD_{50} studies reported

by Weil (1972). They calculated the intraspecies adjustment factor required to reduce the dose 3 standard deviations below the median LD_{50} response using a probit, log-dose analysis. This gives a z value of 0.4987 from the mean or a calculated response of 1.3/1000 (Spiegel, 1996). This was used to predict the response of a sensitive subgroup in the population. An adjustment factor of 10 was adequate to reduce the response from a dose killing 50% of the animal population to a level which would kill only the most sensitive members of the inbred rat population in 92% of the chemicals studied. These data support the contention that a 10-fold uncertainty factor is adequate in many instances to account for intraspecies differences in response to acute exposures. However, in some instances this UF may not protect the more sensitive members of the population. The extrapolation reported here represents a measure of 3 standard deviations from the median response data points. Statistically, an extrapolation of 3 standard deviations from the mean includes more than 99 percent of the population in question, or approximately 999 individuals out of a population of one thousand. The extrapolation of three standard deviations as performed by Dourson and Stara (1983) includes a similar proportion of the population in question, 998.7 out of 1000. It is interesting to note that the Fowles et al. (1999) analyses of inhalation toxicity experiments revealed that for many chemicals, the ratio between the LC_{50} and the experimentally observed non-lethal level was on average a factor of approximately 2, the 90^{th} percentile was 2.9, and the 95^{th} percentile was 3.5. There was a range of ratios from 1.1 to 6.5. Therefore, the use of an UF of 3-fold with a NOAEL for lethality can achieve the same reduction in acute lethality as that reported by Dourson and Stara (1983). The 490 LD_{50} studies with rats were undoubtedly based on a wide range of chemical substances exhibiting many different toxicological mechanisms. Hence, the variability due to chemical-specific properties was included in this evaluation and was accounted for by an adjustment factor of 10-fold in 92 percent of the chemicals tested. This type of statistical analysis makes the untested hypothesis that the slope of the dose response was the same in the experimental dose range and at the untested tails of the experiment. It also reflects the response in a homogeneous (inbred) adult animal population and does not measure the difference in values between potentially sensitive subgroups such as adult vs newborn.

A number of authors have presented data and analyzed adult:newborn LD_{50} ratios to assess the differential sensitivity of young and adult animals. Done (1964 as cited in NRC, 1993b) compiled LD50 ratios between immature and mature animals. He found that for 34 of 58 chemicals the immature animals were more sensitive that adults, and for 24 of 58 chemicals the adults were more sensitive than the immature animals (NRC, 1993b). A similar compilation of newborn/neonate and adult LD_{50} ratios for rat and mouse was done by Goldenthal (1977) on data submitted to FDA in drug applications. This included a broad range of chemicals such as analgesics, bronchodilators, CNS depressants and stimulants, anti-depressants, tranquilizers, etc. NRC (1993b) analyzed these data and found that about 225 of the compounds were more toxic to neonates and 45were more toxic to adults. Almost all of the age related differences from the Done (1964 as cited in NRC 1993b) and Goldenthal (1977) data collections were within a factor of 10 of each other and most of the ratios were within a factor of 3 (NRC, 1993b). Sheenan and Gaylor (1990) analyzed adult:newborn LD_{50} ratios for 238 chemicals. The median ratio of the

LD_{50} values between age groups was 2.6. Approximately 86% of the ratios were less than 10 indicating that this factor is adequate to account for differences in response to chemical exposure between adult and young in most cases but may be insufficient for 14% of the cases. In these studies the comparison was made from the median response.

Another indirect approach to quantify biological uncertainty is to measure the observed variability in human populations. Calabrese (1985) examined a number of parameters related to toxicokinetics (metabolism, binding of chemicals to protein and DNA, and activity levels of enzymes). In studies which included between 10 and 349 subjects he concluded that generally 75-95% of the population fell within a range of 10-fold. However, his conclusion was based on the supposition that the 10-fold factor was to account for the total range of human variability as opposed to the range from an experimental NOEL to the most sensitive person. In a similar study, Hattis et al. (1987) evaluated toxicokinetic parameters in 101 data sets (5 or more healthy adults) on 49 chemicals (primarily drugs). They found that 96% of the variation was within a factor of 10. However, this analysis also measured the total range of human variability. These analyses measured the range of responses for toxicokinetic parameters and give some sense of the variability in an adult population only and not in a potentially sensitive subpopulation. They do not measure how far the tail for response goes beyond the lowest dose/activity in the population measured, nor the response of different populations. Another consideration is the fact that these data represent measures of toxicokinetic variables which may not directly reflect the threshold of toxicologic response to chemical exposure.

Ideally, one would like to be able to compare NOAEL levels observed in an experiment to the tail of the NOAEL distribution in order to assess the actual frequency of response in the total human population when the intraspecies uncertainty factor of 10 is applied and obtain a measure of the sensitive person. Determining the experimental NOAEL is fraught with problems of sample size and dose selection. The response of the sensitive population at a dose 10 fold lower than the experimental NOAEL will never be known. Hattis et al. (1999) performed statistical modeling analyses designed to determine the efficacy of applying the intraspecies uncertainty factor of 10 to a NOAEL. They statistically analyzed clinical studies on humans which measured parameters related to toxicokinetics and toxicodynamics. The studies had at least 5 subjects each and included approximately 2700 data points for the toxicokinetic endpoints. They demonstrated that the population distribution of the data were lognormal in the data region and assumed that they were lognormally distributed out to the extreme tails. From the data, and assuming a lognormal distribution, they calculated the dose required to produce an incidence in 5% of the population. This is essentially an experimental NOAEL which is divided by the intraspecies uncertainty factor when a risk assessment is performed. The dose at the 5% incidence level was divided by 10 and the response at that dose calculated, assuming a lognormal distribution of data, to the extreme tails. This approach was used to assess the response rate when a 10 fold uncertainty factor is applied to a NOAEL. They found that "...acting by itself, a 10-fold reduction in dose from a 5% effect level could be associated with effect incidences ranging from slightly less than one in ten thousand for a median chemical/response to a few per

thousand for chemicals and responses that have more human interindividual variability than 19 out of 20 typical chemicals/responses." The analysis did not include sensitive subpopulations so the variability seen could be greater. This type of analysis assumes a lognormal distribution of the data to the extreme tails. It does not allow for a threshold which is generally assumed to be true for non-cancer effects. Thus, the calculated response at doses 10-fold less than the 5% response level may be overly conservative. There are no data, human or animal, that far out in the tail of the distribution curve. The analysis by Hattis et al. (1999) indicates that a human intraspecies UF of 10 would be protective of sensitive individuals and may be overly conservative in many instances.

Another approach to measuring variability between different groups of a human population is to compare maximum tolerated doses (MTDs) or effect levels between groups. Reports comparing the MTDs of chemotherapeutic agents in child and adult cancer patients indicate that most of the substances studied were tolerated as well, and, in many instances, tolerated better by children than by adults when the dose was expressed as mg/kg body weight or mg/m^2 (Glaubiger et. al., 1982; Marsoni, et. al., 1985). In those instances where children demonstrate a greater response at equivalent dose to these substances, the differences were less than a factor of two-fold. Although MTDs are not entirely a precise measure of a toxicological threshold, they represent a credible parameter by which relative toxicities between groups can be measured in humans. It is important to acknowledge that although the substances studied represent a diverse group of chemical classes, these substances exhibit similar mechanisms of cytotoxicity. Therefore, the results observed cannot be applied to a large number of other chemicals with different mechanisms of action. In addition, only MTDs were reported, not the variability within each group in response to the drugs. Thus, this type of study gives a measure of response between groups within a population but not the variability within each group.

Other studies regarding differences in sensitivities between specific groups in humans to various anaesthetic gases have been reported. These studies indicate children, particularly infants, are more resistant than adults to the effects of various volatile anesthetics (Gregory, et. al , 1969; Katoh and Ikeda, 1992; Lerman et. al., 1983; Matthew, et al., 1996; Stevens, et al., 1975; LeDez and Lerman, 1987). The susceptibility of individuals of different ages has been extensively studied in the anesthesia literature where the concentrations of various anesthetic gases in the lung which produce "anesthesia" (ie lack of movement) have been measured. The results are usually reported as the Mean Alveolar Concentration (MAC) which produces lack of movement in 50% of persons exposed to that concentration. Occasionally the ED_{95} - the alveolar concentration which prevents movement in 95% of those exposed is also reported. MACs for several anesthetic gases have been measured as a function of age. The results consistently show a pattern with maximal sensitivity (lowest MAC values) in newborns, particularly prematures, pregnant women, and the elderly. The least sensitive (highest MAC values) occur in older infants, toddlers and children as compared to adults. The total range of sensitivity was 2-3 fold. Many organic solvents for which AEGLs are developed can also produce anaesthesia in humans at high doses. As previously stated, this type of study gives a measure of response between

groups within a population but not the variability within each group.

Intraspecies uncertainty factors (UFs) are used to address the variability in biological response that exists within a human population exposed to a toxic agent. Their use is designed to account for the range of response to exposure by individuals within the general population. As the studies above demonstrate, an uncertainty factor of 10 is adequate to account for variability in the majority of cases and a factor of 2-3 is often adequate.

It has been proposed that data on the differences in kinetics and dynamics be used to modify the uncertainty factors from defaults of 10 (Renwick, 1993; Dourson et al., 1996). Renwick (1993) proposed dividing inter- and intraspecies uncertainty factors into two components. Toxicity is considered to be the combined function of toxicokinetics (all processes contributing to the concentration and duration of exposure of the active chemical toxicant at the target tissue) and toxicodynamics (mode or mechanism of action of the active toxicant at the target tissue site). If data are available on the differences between or within species on one or both of these two processes, then it should be possible to reduce the total uncertainty factor by developing a data derived uncertainty factor. This approach has in fact been taken by the U. S. Environmental Protection Agency in the examples below.

The U. S. EPA (1996b) reduced the default intraspecies uncertainty factor of 10 to 3 for Aroclor 1016 because data from animal and human studies indicate that infants who were exposed transplacentally represent a sensitive subpopulation and this information (toxicity in monkeys) was used to derive the RfD value (toxicodynamics).

In the case of methyl mercury toxicodynamics data were used to reduce the intraspecies UF to 3 (U. S. EPA, 1995b). The RfD was based upon a benchmark dose computed lower 95% confidence limit on the 10% increase over the background for human childhood neurological abnormalities (this level has been used to represent the NOAEL) in the sensitive subpopulation (the developing fetus). Therefore, the default intraspecies uncertainty factor of 10 was reduced to 3. Since the sensitive subpopulation had been identified, the toxicodynamic part of the uncertainty factor had been addressed. However, variability due to toxicokinetics was maintained with the use of the 3 fold uncertainty factor.

For styrene the default intraspecies UF of 10 was reduced to 3 in the calculation of the RfC value because the lower 95% limit of the exposure extrapolation for a NOAEL in a human cross-sectional study was used and the biological exposure index had been shown to account for variation in pharmacokinetic and physiological measures such as the alveolar ventilation rate (U. S.EPA, 1993).

In the absence of information to set data derived uncertainty factors, an uncertainty factor of 10 is considered to account for intraspecies variability in most cases. When information is available about the response of a sensitive population, mechanism of action in different species

and/or subgroups within an exposed population, toxicokinetics or toxicodynamics, it will be factored into the development of a data derived uncertainty factor which may vary between 10, 3, or 1. All information on the chemical, its mechanism of action, structurally related chemical analogs, a discussion of the weight of evidence and informed professional judgement are used when determining appropriate uncertainty factors.

2.5.3.3.1 Range of Susceptibility

The National Research Council, National Academy of Sciences' guidelines for developing emergency exposure limits state that the exposure limits are "designed to protect almost all people in the general population..." (NRC, 1993a). The NRC guideline levels "...are designed to protect 'sensitive' individuals, some hyper-susceptible individuals might not be protected...". This distinction is based on the premise that emergency exposure limits must be set low enough to protect most of the general population but must also be set at levels that minimize over-response to chemical emergencies as a result of rare or exceptional circumstances. Consequently, the AEGL values may not necessarily protect certain individuals with unique or idiosyncratic susceptibilities. This consideration is clearly communicated in the definitions of the three AEGL tiers.

The definition, and intended application of AEGL values make distinctions between susceptible and "hypersusceptible" individuals. It is important to characterize these two terms and the potential subpopulations they may represent for purposes of uncertainty factor selection . It is also important to distinguish between these two populations for purposes of risk communication to emergency planners, emergency responders, and to the public.

Individual susceptibility within a population will vary according to both individual determinants and the specific properties of a given chemical. The origins of susceptibility are multifactorial and distributed across populations. According to the U. S. Presidential/Congressional Commission of Risk Assessment and Risk Management, "Genetic, nutritional, metabolic, and other differences make some segments of a population more susceptible than others...susceptibility is influenced by many factors" (P/CC, 1997). The factors are based on intrinsic and/or acquired differences among individuals and may include age, gender, genetic factors, ethnicity and race, quality of life and life-style considerations. The latter considerations may be further classified as preexisting illnesses, prior exposure(s), nutritional status, personal behavior (e.g. occupation, smoking, alcohol, obesity, etc.), and socio-economic factors. The NRC also characterizes such determinants: "[S]ome of the individual determinants of susceptibility are distributed bimodally...other determinants seem to be distributed more or less continuously and unimodally" (NRC, 1994).

Hypersusceptibility describes extreme examples of responses. Hypersusceptibility may represent biological reactions that are unique, idiosyncratic and/or stem from determinants that

are generally discontinuous with, and lay outside of, the range of distributions expected for the general population.

The determination of susceptibility entails the presence of observable changes in biochemical or physiological processes reflecting dose-response relationships unique to a chemical (e.g., sulfur dioxide) or class of chemicals (e.g., acid aerosols). Susceptibility and hypersusceptibility are not meaningful concepts outside of the context of specific exposures; "Dose-response relationships are chemical-specific and depend on modes of action; people are not hyper-susceptible to all kinds of exposures" (P/CC, 1997).

Susceptibility and hypersusceptibility may reflect transient, rather than permanent states. For example, infants are susceptible to some chemicals (e.g. ingested nitrates and nitrites as a result of their relatively high gastric pH), but lose that susceptibility as they mature. Susceptible populations may also experience transient periods of hypersusceptibility. For example, asthmatics represent 5 to 10 percent of the general population and can be more susceptible than non-asthmatics to challenge by respiratory irritants. Moreover, at any given time some asthmatics may be suffering acute asthmatic attacks, which might lead to a hypersusceptible condition, just prior to an irritant exposure. Based on the transient condition, these individuals might not be accounted for in the published AEGL values. Similarly, otherwise normal individuals may suffer transient periods of hypersusceptibility during periods of illness. For example, following very severe, acute respiratory infections, many non-asthmatic individuals will experience several weeks or more of bronchiolar hyper-reactivity and bronchospasm following non-specific exposure to respiratory irritants. This condition can be considered an example of transient hypersusceptibility. In general, since there is little or no information regarding the responses of transiently hypersusceptible individuals to chemical exposures, the corresponding AEGL values might not be protective for this group.

During the past 15 years, a wide range of symptoms and complaints in patients thought to be related to extreme sensitivity to low-levels of diverse and often non-quantifiable chemical exposures have been reported by clinicians and researchers. This syndrome has been referred to as "Multiple Chemical Sensitivity" or MCS (Cullen, 1987). MCS has been characterized as the heightened, extraordinary, or unusual response of individuals to known or unknown exposures whose symptoms do not completely resolve post exposure and/or whose sensitivities seem to spread to other chemicals (Ashford, 1999). The syndrome is thought by Ashford to be a 2-step process with an initial acute exposure to high concentrations of a substance and the subsequent triggering of symptoms at extraordinarily low-levels of exposure to the same substance or different substances. He believes that repeated or continuous lower level exposures may also lead to the same type of sensitization. Ashford and Miller (1998) also postulate that this sensitivity may be the consequence of a variety of disease processes resulting from "toxicant-induced loss of tolerance" (TILT) - described as "a new theory of disease providing a phenomenological description of those disease processes".

In response to the increasing public demand for government attention to a problem frequently identified as MCS, the Environmental Health Policy Committee (EHPC) of the U.S. Public Health Service (USPHS), formed the Interagency Workgroup on MCS in 1995 to address this issue. The workgroup's charge was to review the scientific literature on MCS, consider the recommendations from various expert panels on MCS, review current and past federal actions, and make recommendations to policy makers and researchers at government agencies concerned with evaluating public health issues that might relate to MCS-like syndromes. The Workgroup comprised scientists from the U. S. federal agencies, including, ATSDR, DOD, DOE, DVA, NCEH (CDC), NIEHS (NIH), and EPA. The original draft report was peer reviewed by 12 independent experts in occupational and/or environmental medicine, toxicology, immunology, psychology, psychiatry, and physiology. A Predecisional Draft Report was issued for public comment on August 24, 1998 (U. S. PHS, 1998). Although a final report has not yet been issued, the Draft Report concluded that MCS remains a poorly defined problem where the experts disagree on possible causes (e.g., physical or mental) while the sufferers complain of a wide range of symptoms (not associated with any "end-organ" damage) that may result from a disruption of homeostasis by environmental stressors.

In addition to the EHPC Interagency Workgroup on MCS, the U. S. National Academy of Sciences (NRC, 1992b, 1992c), professional organizations (ACOEM [McLellan et al., 1999]; AAAI, 1986; AAAAI, 1999;), and others (Kreutzer, et al., 1999; Kipen and Fiedler, 1999; Graveling, et al, 1999) have attempted to address this issue. Despite these attempts, the diagnosis, treatment and etiologic assessment of MCS has remained a troublesome medical and social concern for individuals, physicians, government and organizations (McClellan et al., 1999). No consensus has yet been reached for a case definition (U. S DHHS, 1995; ACOEM [McLellan et al., 1999]; Graveling, et al, 1999), diagnostic methods (U. S. DHHS, 1995; AAAAI, 1999; ACOEM [McLellan et al., 1999], or treatment (AAAAI, 1999). Further, despite extensive literature on the existence of MCS, "there is no unequivocal epidemiological evidence; quantitative exposure data are lacking; and qualitative exposure data are patchy" (Graveling et al., 1999). Although most reviewers contend that symptoms characteristic of chemical sensitivities exist, they agree that symptoms may be exaggerated and may be "differentially precipitated by psycho social events or stress, or by different physical or chemical exposures" (Ashford, 1999). All researchers and clinicians familiar with the problem agree more work must be done to understand the unexplained symptoms that are attributed to MCS (Kipen and Fiedler, 1999).

The American College of Occupational and Environmental Medicine (ACOEM), the American Academy of Allergy, Asthmatics, and Immunology (AAAAI) and the International Programme on Chemical Safety (IPCS) have all recommended that the term "idiopathic environmental intolerance" be used to replace the term MCS (McClellan et al., 1999; IPCS, 1996; AAAAI, 1999). These authors believe that the term MCS incorrectly implies that the condition affects the immune system and that chemical exposure is its sine qua non (McLellan et al., 1999). No immunological dysfunction has been identified in these patients (Graveling, et al.,

1999; AAAAI, 1999). Further, they concur with other prominent medical organizations in maintaining that evidence does not exist to define MCS as a distinct entity (ACOEM [McLellan et al., 1999]).

While some clinicians hold that MCS occurs as a result of environmental exposures, mechanism(s) by which this may take place have not been proven scientifically. No single widely accepted test of physiologic function can be shown to correlate with observed symptoms (U. S. PHS, 1998; Brown-DeGagne and McGlone, 1999; AAAAI, 1999; McLellan et al., 1999). Immunologic, allergic, neuropsychological, and traditional psychiatric disorders have all been postulated to cause MCS, but to date, they have not been supported by well designed studies (U. S. PHS, 1998; McLellan et al., 1999; Brown-DeGagne and McGlone, 1999).

As a result of the considerations presented here, it is not believed that MCS represents a viable scientific basis for developing AEGL values, including further adjustments for sensitive subpopulations, at this time. However, the need for scientific research on this proposed syndrome that may help explain and describe its features, enable scientifically valid approaches to hazard or risk assessment, and define appropriate clinical interventions is recognized. Also, the NAC/AEGL Committee will remain vigilant and will consider any new data or information that is scientifically credible and relevant to the development of AEGL values.

2.5.3.3.2 Selection of Intraspecies Uncertainty Factors

To meet the AEGL definitions that protect susceptible individuals but not necessarily hypersusceptible individuals, the NAC/AEGL Committee evaluates two separate considerations regarding susceptibility. First, evidence is reviewed to attempt to distinguish "susceptible" from "hypersusceptible" individuals for each chemical of concern. Second, estimation of the range of response variability in the general population that includes susceptible (but not necessarily hypersusceptible) individuals and selection of appropriate intraspecies uncertainty factor(s) for development of the AEGL values(s) is carried out.

2.5.3.3.3 Distinguishing Susceptible and Hypersusceptible Individuals

A clear distinction between susceptible and hypersusceptible individuals in all cases for all chemicals is not achievable with the clinical and toxicological information available to date. However, the NAC/AEGL Committee has identified specific categories and populations that may be considered sensitive and part of the general population that the AEGL values are intended to protect. These categories include children and infants, the elderly, asthmatics, pregnant women and the fetus, and individuals with preexisting illnesses, diseases or metabolic disorders who would not ordinarily be considered in a severe or critical medical condition. Examples of sensitive individuals based on preexisting illnesses include those with compromised pulmonary function (typical respiratory infections, smokers, immunologically sensitized due to prior

exposures, etc.), hepatic function (alcoholism, hepatitis, prior chemical exposures, etc.), cardiac function (dysrhythmias), and those with impaired renal function.

Hypersusceptible individuals are considered as those individuals whose reactions to chemical exposure are unique and idiosyncratic, lie outside of the range of distributions expected for the general public, including sensitive individuals, and constitute a relatively small component of the general public. For example, the AEGLs are intended to be protective of mild to moderate asthmatics, but may not necessarily be protective of severe asthmatics. Additionally, there are some asthmatics who, at any given time, could be coincidentally suffering acute asthmatic episodes at the time of a chemical emergency. Such individuals may be considered transient hypersusceptible individuals and would not necessarily be protected by the published AEGLs. Examples of hypersusceptible individuals might include those with severely debilitating pulmonary, hepatic, or renal disorders or diseases, the elderly with serious debilities of primary physiological systems, and those individuals with unique hypersensitivities to specific chemicals or chemical classes such as the isocyanates.

Certain otherwise healthy individuals in the general population also may suffer transient periods of hypersusceptibility as a result of highly severe, but reversible, short-term illnesses. For example, during recovery from a severe episode of acute upper respiratory infection, many non-asthmatic individuals will experience several weeks or more of bronchiolar hyper-reactivity and bronchospasm following non-specific exposure to respiratory irritants. This reversible condition is considered an example of transient hypersusceptibility and it is acknowledged that the AEGL values may not be protective of individuals in such circumstances.

The nature of the dose-response relationships among sensitive and hypersensitive individuals is highly complex and not well-understood. In almost all instances there is no clear line of demarcation that distinguishes susceptible individuals from hypersusceptible individuals and there is no generic or medical guidance that can be followed for a wide range of chemical exposures. However, since most biological responses are chemical-specific and are dependent on the mode of action of the substance in question, the issue of identifying and protecting groups or populations of sensitive individuals is addressed by the NAC/AEGL Committee on a chemical-by-chemical basis. The Committee uses all available data on the properties of the chemical and their relationship to both normal and compromised biochemical, physiological, and anatomical systems in humans to identify and protect sensitive populations. In the absence of data on the chemical in question, the use of structurally related chemicals and scientific judgement may be employed to select uncertainty factors that provide protection for the public health.

2.5.3.3.4 Estimating the Range of Variability in a Human Population

The NAC/AEGL Committee estimates the range in variability of response to specific chemical exposures primarily on the basis of quantitative human data. Acceptable experimental

data are more likely to be available for AEGL-1 and AEGL-2 endpoints than for AEGL-3 endpoints. For example, numerous studies have considered induction of bronchospasm after controlled exposures to sulfur dioxide in asthmatics and non-asthmatics. There is marked individual variability in the severity of reaction to inhalation of low concentrations of sulfur dioxide. Asthmatics, individuals with hyper-reactive airways, smokers and those with chronic respiratory or cardiac disease react to relatively lower concentrations (Aleksieva, 1983; Simon, 1986). Susceptibility may also be increased in people over 60 years of age, but reports have not been consistent (Rondinelli et al., 1987; Koenig, et al., 1993). By contrast, comparable human data for AEGL-3 tier concentrations are limited to anecdotal case reports.

For example, during the course of the Committee's deliberations on phosphine AEGL development, the possibility that children are more susceptible to phosphine exposure was suggested by two case reports describing the deaths of children, but not adults, after "comparable" phosphine exposures. As with most case reports, the exposure concentrations were not quantified. However, both the children and the adults in question were present in somewhat restricted environments, suggesting comparable exposure levels. Based on these case reports, the Committee concluded that children may be more sensitive to phosphine exposure and selected uncertainty factors that would provide additional protection for children.

In cases where quantitative human data are lacking for specific chemicals, but adequate data can be found for structurally or mechanistically similar agents, uncertainty factors may be selected by analogy to structurally similar chemicals and/or mechanism of action. For example, asthmatics are particularly sensitive to sulfur dioxide. Declines of >20% in FEV1 have been documented after inhalation of 0.4-1 ppm for 2-15 minutes. The effects of sulfur dioxide exposure are enhanced in normal and asthmatic individuals by moderate exertion (ventilation >40 l/m with mouth breathing), hyperventilation, and use of oral airways (Horstman, et al., 1988; Frank, 1980; Koenig, et al., 1981; Koenig, et al., 1982; Balmes, et al., 1987; Linn, et al., 1987; Roger, et al., 1985). Duration of bronchospasm is generally limited and these patients may develop tolerance with prolonged or repeated exposure. These studies suggest that mouth-breathing asthmatics exposed to sulfur dioxide develop bronchospasm at levels of approximately 33 percent of comparably exposed non-asthmatics. Accordingly, the Committee generally has used an uncertainty factor of 3 when considering the differences in human susceptibility to most respiratory irritants. However, the NAC/AEGL Committee is aware that the variation in response of asthmatics may differ among respiratory irritants ranging from mild to severe in their effects. The most appropriate uncertainty factor will be considered based upon the degree of severity of the irritant chemical and the biological data available, for known or suspected differences among humans.

Children and infants are often considered as susceptible populations. There is a general belief that children and infants are more susceptible to the effects of toxic substances than adults. Much of this belief is predicated upon the fact that children, and particularly infants, possess immature or developing biochemical, physiological, and anatomical systems that are not

adequate to combat the adverse affects of toxic chemicals. Further, it is believed that in certain instances, the toxic effects of chemicals may permanently damage or alter the growth and function of developing organs and organ systems in the young. The potential for greater sensitivity to chemical substances by children and infants has been reviewed by the National Research Council of the National Academy of Sciences (NRC, 1993b). The report indicates that there are limited data on the relative toxicity of pesticides and other xenobiotic compounds in immature and mature humans. Consequently, the NRC focused on laboratory animal studies, age-related pharmacokinetic and pharmacodynamic differences, and pharmacological data from controlled clinical investigations with humans. The NRC concluded that the mode of action is generally similar in mammalian species and across age and development stages within species. They also concluded that children may be more sensitive or less sensitive than adults to pesticide toxicity, depending on the chemical, but that the quantitative differences in toxicity between the age groups are usually less than a factor of approximately 10-fold.

Although many reports have been published on the pharmacokinetic differences of pharmacologic agents and other chemicals in children and adults, the data cannot be translated into meaningful dose-response relationships to make valid quantitative comparisons in the absence of specific biologically relevant endpoints. Bruckner and Weil (1999) summarized the biological factors which may influence the responses of adolescents to chemical exposure.

Based on the limited data available, the extent to which significant differences in the susceptibility of children/infants and adults exists is largely unknown. However, the difference is generally considered to be within a factor of 10-fold (NRC, 1993b) with most of the differences in susceptibility on the order of 2-3 fold. It is highly probable that any differences are chemical-specific and also related to specific developmental stages of children and infants. Within the context of the AEGL program, this issue is further complicated by the consideration of once-in-a-lifetime inhalation exposures of 1 hour or less to 8 hours. The discussion at the beginning of this section indicates that there is a paucity of data on age related differences and the young can be more or less susceptible than adults to exposure to chemicals, depending upon the chemical or chemical class in question. However, it is believed that uncertainty factors applicable to other sensitive subpopulations are adequate to protect children and infants with decisions based on a weight-of-the-evidence on a chemical-specific basis. It is important that all of the relevant information on the chemical be considered when making judgements about selection of the appropriate uncertainty factors for age differences and all other factors that contribute to differences in susceptibility.

In summary, the maximum variation in responses of susceptible populations are believed to generally range within 3 to 10-fold of a for healthy individuals. All information on the chemical, including its mechanism of action, the biological responses, and data on structurally related chemical analogs is considered as well as informed professional judgement when determining appropriate uncertainty factors. Information about similarities and differences in toxicokinetics and toxicodynamics are used where available to modify as necessary the

qualitatively and quantitatively as compared to non-sensitive individuals.

2.5.3.4.3 Age/Life Stage/Condition Differences

When available data indicate certain age groups may be uniquely sensitive as contrasted to the general population, an intraspecies uncertainty factor of 10 is generally used.

THE RATIONALE FOR THE SELECTION OF THIS UF SHOULD INCLUDE:

1. Description of the toxicologic endpoints which differ between humans of different age groups.
2. Discussion of the magnitude of this difference. For example, quantitatively, how much does the response differ, or what qualitative information indicates there may be differences among age groups?

2.5.3.4.4 Response by Normal and Sensitive Individuals to Chemical Exposure is Unlikely to Differ for Mechanistic Reasons

In cases where the mode or mechanism of action is such that the response elicited by exposure to the chemical by different subpopulations is unlikely to differ, an intraspecies uncertainty factor of 3-fold is generally used. Typically this involves a direct acting mechanism of toxicity where metabolism is unlikely to play a major role. A steep dose response curve may also be an indication of little variation within a population, and is factored into the weight-of-evidence considerations for UF determination.

THE RATIONALE FOR THE SELECTION OF THIS UF SHOULD INCLUDE:

1. Description of the mechanism of action.
2. Discussion of why the response to chemical exposure is unlikely to differ and whether metabolism/detoxification is likely to be an issue.

2.5.3.4.5 Mode or Mechanism of Action is Unknown

When the mode or mechanism of toxic action is uncertain, or unknown metabolic factors may play an important role, and/or a broad range of responses to chemical exposure is observed, there is concern that there may be large differences in susceptibility between individuals. In these cases an intraspecies uncertainty factor of 10 may be applied.

THE RATIONALE FOR THE SELECTION OF THIS UF SHOULD INCLUDE:

1. Description of the toxicity reported and the uncertainty associated with the chemical's mechanism of action or other factors.
2. Statement as to why the effects seen add uncertainty to the assessment.

2.5.3.4.6 Uncertainty Factors Which Result in AEGL Values That Conflict with Actual Human Exposure Data

When AEGL values are initially proposed, the candidate range of values are compared to the known spectrum of supporting data on the chemical. In a weight-of-the-evidence approach, conflicts between the candidate AEGLs (generally derived from animal data) and the supporting data (either animal data or human data) may lead to the conclusion that the uncertainty factors utilized in the calculations are inappropriate because they conflict with other specific and highly relevant data. In this case, the candidate AEGLs are revised to reflect the supporting data. In other cases where the AEGL may conflict with an existing standard or guideline, the comparative basis of the two values may be evaluated to see if the discrepancy is justified or resolvable.

THE RATIONALE FOR THE SELECTION OF THIS UF SHOULD INCLUDE:

1. A statement on why the use of uncertainty factors initially selected conflict(s) with the published evidence.

2.6 GUIDELINES/CRITERIA FOR SELECTION OF MODIFYING FACTORS

2.6.1 Definition

In addition to the uncertainty factors discussed above, an additional Modifying Factor may be necessary when an incomplete data base exists. Hence, the modifying factors represent an adjustment for uncertainties in the overall database or for known differences in toxicity among structurally similar chemicals. The modifying factor "... reflects professional judgment of the entire data base available on the specific agent" and is applied on a case by case basis (NRC, 1993a, p88). The Modifying Factor may range from 1to 10-fold. The default value is 1-fold.

2.6.2 Use of Modifying Factors to Date in the Preparation of AEGL Values

Modifying factors have been used for chemicals currently published "Final" by the U. S. National Academy of Sciences. Modifying factors of 2 or 3 are under consideration for chemicals currently undergoing review to account for (1) a limited data set, (2) instances where the adverse effects used to set the AEGL level are more severe than those described in the AEGL definition, and (3) to account for the differential toxicity of chemical isomers.

2.7 GUIDELINES/CRITERIA FOR TIME SCALING

Acute Exposure Guideline Levels (AEGLs) are derived for 30-minute, 1-hour, 4-hour, and 8-hour exposure durations to meet a wide range of needs for government and private sector organizations. AEGLs for 10 minute exposure durations will be developed for all future chemicals addressed by the NAC/AEGL Committee, and 10 minute AEGLs will be developed for the first six chemicals published by the U. S. NAS in the near future. Experimental animal and controlled human exposure-response data and data from human exposure incidents often involve exposure durations differing from those specified for AEGLs. Therefore, extrapolation from the reported exposure duration and chemical concentration of a toxic endpoint to an equivalent concentration for an AEGL-specified period is usually required. The discussion in this section covers the concept, the published scientific literature, the methodologies used for extrapolation, and examples of the application of these methodologies to specific chemicals for the development of AEGL values.

2.7.1 Overview

In accordance with the needs of stakeholders, AEGLs are derived for 30-minute, 1-hour, 4-hour, and 8-hour exposure durations. Stakeholders have requested that the NAC/AEGL Committee also develop 10 minute AEGL values. AEGL values for 10 minute durations will be developed for chemicals in future U. S. NAS publications. Experimental exposure-response data from animal studies or human exposure incidents often involve exposure durations differing from AEGL-specified durations or may coincide with only one or two AEGL exposure durations. Therefore, extrapolation from a reported toxic endpoint concentration and exposure duration to an equivalent concentration for an AEGL-specified exposure period is usually required.

The 1993a NRC/NAS guidelines for developing short-term exposure limits address the extrapolation of the effects of genotoxic carcinogens from long-term to short-term exposures. Only limited NRC/NAS guidance is provided for approaches or methodologies for the extrapolation of reported acutely toxic effects to shorter or longer durations of exposure. Therefore, the NAC/AEGL Committee and ORNL have reviewed the scientific literature related to time exposure relationships and current approaches and methodologies used for time-scaling. Documented here are the NAC/AEGL Committee's approaches to making exposure duration adjustments to develop of AEGL values from 10 minutes to 8 hours. This approach also has been reviewed by scientists representing certain OECD-member countries.

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law (NRC, 1993a) or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept

states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs t (see Curve Fitting and Statistical Testing of the Generated Curve below). Ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals (See Table 2.7-1). Hence, these workers showed that the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where n = 1. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

In cases where adequate data are available, the NAC/AEGLCommittee conducts an analysis of chemical-specific toxicity and exposure data to derive a chemical-specific and health effect-specific exponent (n) for use in extrapolating available exposure data to AEGL-specified exposure durations. If data are not available for empirically deriving the exponent n, the NAC/AEGL Committee identifies the most appropriate value for n by comparing the resultant AEGL values derived using n=1 and n=3. The value of n=1 has been used historically by others and results in rapid reductions in concentrations when extrapolations are made to longer exposure periods and rapidly increasing concentrations when extrapolated to shorter exposure periods. Based on the work of ten Berge et. al. (1986), 1 represents the estimate of the lower boundary of the value of n. The value of n=3, an estimate of the upper boundary of the value of n (ten Berge, 1986), results in less rapid rates of decrease in estimated effect concentrations when extrapolations are made to longer exposure periods and to less rapid rates of increase in estimated effect concentrations when extrapolated to shorter exposure periods. This range of values in n from 1 to 3 encompasses approximately 90 percent of the chemicals examined by ten Berge et al. (1986). In selecting a value for n when the derivation of n is not possible, the NAC/AEGL Committee evaluates the resultant AEGL values determined with either the upper or the lower boundary value of n (1 or 3) within the context of other supporting data to determine the reasonableness of the extrapolated AEGL value. A value of n=1 is used when extrapolating from shorter to longer exposure durations and a value of n=3 when extrapolating from longer to shorter durations. The resultant AEGL value is then compared to supporting data to determine the scientific reasonableness of the derived AEGL value. A consensus of the Committee generally favors the use of a value for n that results in an AEGL value that best fits the supporting data.

In summary, analyses of relevant data, together with scientific judgement are used to determine the extent of temporal extrapolation and its validity in AEGL derivations. For example, extrapolation of 10-minute exposure data to a 4 or 8-hour AEGL value requires more supporting data and or/assumptions than the extrapolation of 10-minute exposure data to a 30-minute or 1-hour AEGL. Errors in the estimated exposure concentration-exposure duration relationship (i.e., the value of n) will progressively increase the magnitude of the error of the derived AEGL value as the time from the empirical data point to the extrapolated data point increases. Since toxicity data are often not available for any or all of the AEGL-specified time periods, temporal extrapolation is usually necessary to generate scientifically credible values for the AEGL time points.

2.7.2 Summary of Key Publications on Time Scaling

Several investigators have studied the relationship of exposure duration and exposure concentration as related to the toxic response to airborne chemicals (Haber, 1924; Flury, 1921; Rinehart and Hatch, 1964; ten Berge et al., 1986; ECETOC, 1991, and Pieters and Kramer, 1994).

Based on observations and studies with chemical warfare gases such as phosgene, Haber (1924) found that for certain chemicals the product of the exposure duration multiplied by the exposure concentration was constant for a specific response or toxic endpoint (i.e., lethality). In experiments with cats, Haber found that a specific concentration x time product would result in 100% lethal response and that as long as this product value was maintained, regardless of the specific exposure concentration or duration, the response was consistent. This linear relationship became known as Haber's Rule; or $C \times t = k$ where C = concentration of the chemical of the chemical in question, t = exposure duration, and k = a cumulative exposure constant. Similarly, Flury (1921) found that inhalation of phosgene exhibited a linear relationship, $C \times t = E$, where E represents the onset of pulmonary edema. Obviously, the cumulative exposure constant may relate to any number of responses or toxic endpoints. However, the information reported by Haber is limited to a small number of chemicals or chemical classes and substantial quantitative data derived from controlled studies is lacking.

Historically Haber's Rule has been used for time concentration extrapolations U. S. EPA (1994b). This relationship assumes that each unit of damage is irreversible, that no repair takes place during the exposure period and, therefore, that each unit of exposure is 100 percent cumulative. However, this is generally not the case for acutely toxic responses to short-term exposures. The relationship between concentration and duration of exposure as related to lethality was examined by ten Berge et al. (1986) for approximately 20 irritant or systemically-acting vapors and gases. The authors subjected the entire individual animal data set to probit analysis with exposure duration and exposure concentration as independent variables. They used the methodology of Finney (1971) to investigate the fit of the data into a probit model on the basis of a maximum likelihood estimate. In re-evaluating the raw data for these chemicals, it was

found that the linear relationship described by Haber's, $C \times t = k$, was not always a valid predictor of lethality. An exponential function ($C^n \times t = k$), where the value of n ranged from 0.8 to 3.5 for different chemicals, was a more accurate quantitative descriptor These authors derived empirically-based, chemical-specific regression coefficients for exposure duration and exposure concentration, as well as chemical-specific values for *n*. The values for *n* for the 20 chemicals studied ranged from 0.8 to 3.5. The analyses indicated that the concentration-duration relationship for lethality was described more accurately by the exponential function ($C^n \times t = k$) and that Haber's Rule was appropriate for only a limited number of the chemicals. Based upon the results of the analyses, ten Berge et al. (1986) concluded that the concentration-time relationship (i.e., value for *n)* should be determined empirically from acute inhalation exposure toxicity data on a chemical-specific basis.

2.7.3 Summary of the Approaches that may be Taken for Time Scaling

A tiered approach to generating toxicity values for time scaling is taken by the NAC/AEGL Committee to derive AEGL values from empirical data. This approach is summarized below. Each of the approaches and the circumstances under which they are, or could be, used are discussed subsequently in this section of the SOP Manual.

(1) If appropriate toxicological data for the exposure concentration-exposure duration relationship of a specific health effect endpoint are available for the AEGL-specified exposure periods, use the empirical data directly.

(2) If empirical exposure concentration-exposure duration relationship data are available, albeit they do not coincide with AEGL - specified exposure periods, use the available data to derive values of n and extrapolate the AEGL values using the equation $C^n \times t = k$.

(3) If no empirical exposure concentration-exposure duration relationship data are available to derive a value of n, a value of n=1 for extrapolating from shorter to longer exposure durations, and a value of n=3 for extrapolating from longer to shorter exposure durations, should be selected initially. The scientific reasonableness of the selection of the estimated lower and upper boundaries of n (n=1 and n=3) is then evaluated by comparing the resultant AEGL values with all other supporting data. If appropriate, the final value(s) of n may be modified to reconcile differences between extrapolated AEGL values and the supporting data.

(4) If there are no supporting data to evaluate selected values of n, a value of n=1 for extrapolating from shorter to longer exposure periods and a value of n=3 for extrapolating from longer to shorter exposure periods should be selected. In the absence of other data, the resultant AEGL values are thought to be protective and scientifically credible.

The balance of this section of the guidance will provide more detailed information on the

approaches stated above.

2.7.4 Use of Empirical Data that is Available for AEGL-Specified Exposure Durations

If toxicity data are available for all four AEGL-specified exposure periods, there is no need to derive values of n and the data for each exposure period can be used directly. However, it is rare that toxicity data are sufficiently comprehensive to encompass all of the AEGL-specified exposure periods from 10 minutes to 8 hours. Further, there are instances where empirical data are not available to estimate n and predict the exposure concentration-exposure duration relationship using $C^n \times t = k$. Therefore, the sequential approaches used by, or available to the NAC/AEGL Committee to establish AEGL values for the specified exposure periods are discussed in the following sections.

2.7.5 Derivation of Values of n When Adequate Empirical Data are Available for Other than the AEGL-Specified Exposure Durations

A key element in the procedure of time-scaling is the use of a value or values for n in the equation $C^n \times t = k$. If empirical data for exposure durations other than the AEGL-specified exposure periods are available to quantify the exposure concentration - exposure duration relationships for a health effect endpoint, including lethality, the value of n should be derived using the method of calculation described in this section. It is believed empirically derived values of n are scientifically more credible than simply choosing n=1 (Haber's Rule) or attempting to select some other value of n.

2.7.5.1 Selection of Appropriate Health Effect End Point for Deriving a Value for n

The first step in any time scaling methodology is the selection of the health effect endpoint of concern. Clearly the health effect endpoint selected should be consistent with the definition of the AEGL tier being determined. Further, the endpoint should be unambiguous and consistently observed at all reported exposure durations. For example, death is an unambiguous endpoint and a quantitatively determined index of toxicity, the LC_{50}, is a response rate which can be compared reliably among exposures at different time periods. The use of the LC_{50} as an index of toxicity is ideal because it is a statistically derived concentration which is not subject to the vagaries of dose selection and exhibits less variability in response than any other experimental endpoint. Death is included in the AEGL-3 definition and is used for estimating the value of n.

A comparable endpoint for the AEGL-1 and AEGL-2 tiers would be an ED_{50} (the dose which causes a specific response in 50 percent of the animals) for a precisely defined toxic or health effect endpoint that is consistent with the definition of the AEGL tier in question. The

actual endpoint is often difficult to determine in most experiments because the observed effects are often a continuum from mild to severe and generally not precise enough to determine an ED_{50} value with reliability. Further, incidence data for non-lethal effects is not always reported. For these reasons, the concentration/response relationship and the value of n derived from lethality data have often been applied to both the AEGL-3 and the AEGL-2 exposure period extrapolations. However, in instances where the mechanism of toxicity causing the health effect of concern at the AEGL-2 tier is thought to be different than that which causes lethality, the value of n derived from LC_{50} data should not be used. Under these circumstances, AEGL-2 values can be developed by selecting the upper and lower boundaries of n (n=3 and n=1) for extrapolation from longer to shorter and shorter to longer exposure periods, respectively. The resultant AEGL-2 values should be evaluated within the context of other supporting data to evaluate the reasonableness of the values of n selected. In the absence of supporting data, the AEGL values determined using n=3 and n=1 should be utilized.

Selection of appropriate endpoints for AEGL-1 values per se represents a unique and often difficult task. Based on the NAC/AEGL Committee's experience to date, no rigorous data for any chemical have been available from which values of n could be derived for the AEGL-1 type of endpoints. The derivation of AEGL-1 values is discussed later in this section.

2.7.5.2 Criteria for Adequate Empirical Data for Deriving Values of n

After determining the health effect endpoint to be used in deriving the value(s) for n, the next step is to evaluate the quality and the quantity of the data to be used in the derivation. Obviously, two data points will define the slope of a curve describing the exposure time/exposure concentration relationship. However, the validity and, hence, the value(s) of n will depend on many factors including the scientific soundness of the concentration exposure-duration data, the length of the empirical exposure duration(s) relative to the AEGL-specified exposure periods, and the known or perceived similarities in effects and mechanism of action of the chemical at the reported exposure concentrations and durations. Generally three empirical data points will improve the scientific validity of the slope and the estimated values(s) for n, and the validity is likely to increase with an increase in the number of empirical data points used to derive n, provided that there is a reasonable fit of these data points.

2.7.5.3 Curve Fitting and Statistical Testing of the Generated Curve

Once the health effect endpoint and data points describing the concentration-exposure duration relationship have been selected, the values are plotted and fit to a mathematical equation from which the AEGL values are developed. There may be issues regarding the placement of the exponential function in the equation describing the concentration-exposure duration relationship (e.g. $C^n x\ t = k$ vs $C\ x\ t^m = k_2$ vs $C^x\ x\ t^y = k_3$). It is clear that the concentration-exposure duration relationship for a given chemical is directly related to its pharmacokinetic and pharmacodynamic properties. Hence, the use and proper placement of an exponent or exponents to quantitatively

describe these properties is highly complex and not well understood.

The quantitative description of actual empirical data of this relationship can be expressed by any of a number of linear regression equations. In the assessment of empirical data reported by ten Berge et al. (1986) these workers quantified the concentration-exposure duration relationship by varying the concentration to the n^{th} power. Since raising c or t or both to a power can be used to quantitatively define the same relationship or slope of the curve, and to be consistent with data and information presented in the peer reviewed scientific literature, the equation $C^n \times t = k$ is used for extrapolation. It must be emphasized that the relationship between C and t is an empirical fit of the log transformed data to a line. No conclusions about specific biological mechanisms of action can be drawn from this relationship.

The preferred method is to use a statistical methodology which utilizes all of the individual animal data and generates a maximum likelihood estimate with 95% confidence limits. Where individual animal data are available, the NAC/AEGL Committee will explore using the methodology of Finney (1971). This methodology has been incorporated into a computer program and provided to the Committee by Dr. ten Berge from the Netherlands.

Unfortunately, the individual animal data are often not available and only LC_{50} values are listed. In this case a linear regression analysis of the log-log transformation of the concentration/time data will be performed as described below.

When time-concentration data are plotted on a log-log plot, they generally fall along a straight line. For that reason a simple linear regression (Alder and Roessler, 1968) is run on the data to generate the mathematical curve. The basic linear regression equation is in the form:

$$Y = a + bX$$

where Y is the predicted value of the dependent variable, X is the value of the independent variable, a is the Y intercept and b is the slope of the line.

This is the form of the log-transformation of the nonlinear $C^n * t = k$ equation to a linear equation (see below):

$$\log C = (\log k)/n + (-1/n) * \log t$$

where C is the predicted value of the concentration to cause an effect at exposure duration t. The $(\log k)/n$ is the Y intercept of the plot of $\log C$ against $\log T$, and $-1/n$ is the slope of the plot of $\log C$ against $\log T$.

$$C^n * t = k$$
$$\log(C^n * t) = \log k$$

$$n * \log C + \log t = \log k$$
$$n * \log C = \log k - \log t$$
$$\log C = (\log k)/n - (\log t)/n$$
$$\log C = (\log k)/n - (1/n) * \log t$$

The regression coefficient or slope, *b*, returns the slope of the linear regression line through data points X and Y. The slope (rate of change along the regression line) is the distance between the Y values of the two points divided by the distance between their respective X values. The regression coefficient is calculated as:

$$b = \frac{N\Sigma XY - (\Sigma X)(\Sigma Y)}{N\Sigma X^2 - (\Sigma X)^2}$$

where N = the number of observations

or

$$-1/n = \frac{N\Sigma(\log t)(\log C) - (\Sigma \log t)(\Sigma \log C)}{N\Sigma(\log t)^2 - (\Sigma \log t)^2}$$

The above is solved in a spreadsheet for n.

The validity of the derived value(s) of n is dependent on the degree of correlation among the various concentration/time data points used to construct the curve and the equation. Normally a coefficient of determination (r^2) is calculated as a measure of how well the generated curve (linear in this case) fits the data points. If $r^2 = 0$ the data do not fit a linear relationship. If $r^2 = 1$ the data exhibit a strong linear relationship. If the number of data points are 3 and the real value of r = 0 "... the chance of obtaining a fairly high correlation coefficient for the sample is greater than the chance of obtaining a small correlation coefficient." (Alder and Roessler 1968, p191) If the number of data points are 4 "... the chance of obtaining a particular correlation coefficient is equal to that of obtaining any other." (Alder and Roessler 1968, p191). Since the number of data points typically available are only in the range of 3 or 4 values, the use of r^2 to measure how well the data fit the generated curve is not a meaningful test to perform. Therefore informed professional judgement is exercised by the NAC/AEGL Committee.

Given the fact that the distribution of r for low numbers of observations (typically 3 or 4 data points for time scaling) cannot be fit to a normal curve, meaningful statistical tests of the fit of the regression line (used to derive n) to the data cannot be performed. Even with these shortcomings, a regression analysis of the data as previously described gives the best fit of a line to the data. A visual inspection of the regression line vs the data also will show the reasonableness of the fit and, hence, the reasonableness of the derived value for n. This is generally the best approach empirical data are used to derive n values for developing AEGL

values for specified exposure durations. As stated earlier, it must be emphasized that: **When deriving or selecting a value for n, the NAC/AEGL Committee evaluates the resultant AEGL values within the context of other supporting data to determine the reasonableness of the extrapolated values. This is true even when the value of n is derived from empirical data that describes the concentration-exposure duration relationship. The NAC/AEGL Committee uses a value for n that results in AEGL values that best fit the supporting data.** Therefore, there is no substitute for informed professional judgement based on careful review, evaluation and discussion of all available data.

2.7.5.4 Examples of NAC/AEGL Committee Derivations of Values of n from Empirical Data

During the course of AEGL development, the NAC/AEGL Committee has used empirically-based derivations of n in the equation $C^n \times t = k$ for time-scaling to AEGL-specified exposure periods. Guidelines have been developed from this experience and are presented in the final part of this section.

2.7.6 Selection of Values of n When Adequate Empirical Data are Not Available to Derive Values for n

When adequate data describing concentration-exposure duration period relationships for a specific chemical and toxic endpoint of interest are not available, an alternative approach to quantitatively estimating this relationship must be followed. The approach used by the NAC/AEGL Committee involves the application of the equation $C^n \times t = k$ and the selection of a value or values of n that results in AEGL values that best fit the supporting data for the chemical and toxic endpoint in question. It is important to distinguish the difference between the derivation of values of n as described in the preceding section and the selection of values of n as described in this section.

An evaluation of the analysis of values of n by ten Berge et al. (1986) served as the basis to select the limits used by the NAC/AEGL Committee.

Table 2.7-1 is a summary of the airborne concentration-exposure duration relationships for 20 chemicals based on their LC_{50} values.

TABLE 2.7-1. VALUES OF n FROM TEN BERGE ET AL. (1986).

SYSTEMIC CHEMICALS	Value of n (ave)
HCN	2.7
H2S	2.2
methyl t-butyl ether	2
methylenechlorobromide	1.6
ethylenedibromide	1.2
tetrachloroethylene	2
trichloroethylene	0.8
carbon tetrachloride	2.8
acrylonitrile	1.1
IRRITANTS	
ammonia	2
HCl	1
chlorine pentafluoride	2
nitrogen dioxide	3.5
chlorine	3.5
perfluoroisobutylene	1.2
crotonaldehyde	1.2
HF	2
ethylene imine	1.1
bromine	2.2
dibutylhexamethylenediamine	1

Range of n	# Chemicals/range	Cumulative # chemicals	
0.8-1.5	8	8	
1.51-2.0	6	14	
2.01-2.5	2	16	
2.51-3.0	2	18	90% with n<3
3.01-3.5	2	20	

The lowest value of n was 0.8 and the highest value of n was 3.5. Approximately 90 percent of the values of n range between n=1 and n=3. Consequently, these values were selected as the reasonable lower and upper bounds of n.

In the absence of data to derive a value for n, the NAC/AEGL Committee selects values for n of 1 and 3, depending on an extrapolation from shorter to longer durations or longer to shorter durations. The value of n is then used in the equation $C^n \times t = k$ to extrapolate from empirically reported concentration and exposure durations to the AEGL-specified exposure duration(s). The Committee then selects the derived AEGL values in accord with the supporting

data.

2.7.6.1 Selection of Values of n When Extrapolating from Shorter to Longer Exposure Periods

As discussed previously, a value of n=1 represents the lower range of the concentration-exposure period relationship. If the exponent n=1 is used in the equation $C^n \times t = k$, there is a rapid decrease in extrapolated values when extrapolations are made from shorter to longer exposure periods (see Figure 2.7-1). The extrapolated values are lower and, hence, represent a conservative estimate of the AEGL value. A value of n=3 represents a value in the upper range for the concentration-exposure duration relationship and results in a less rapid rate of decrease when extrapolating from shorter to longer exposure periods. Therefore, the extrapolated AEGL values for longer exposure periods are higher and, hence, less conservative in terms of protecting human health. See Figure 2.7-1.

When data are not available for deriving a value of n, the NAC/AEGL Committee develops tentative AEGL values from shorter to longer exposure durations using n=1 in the equation $C^n \times t = k$ and evaluates these values with all other supporting data to determine their scientific reasonableness. Therefore a "weight of evidence" test is applied to the tentative AEGLs by comparing these values to the supporting data to determine the most scientifically credible AEGL values. In instances where the supporting data indicate that the tentative AEGL developed using a value of n=1 is too low or too high, the AEGL may be adjusted to scientifically accommodate the supporting data. If there are no supporting data indicating that the derived AEGL should be adjusted, a value of n=1 is used to account for the uncertainty of the concentration-endpoint relationship at longer exposure durations.

2.7.6.2 Selection of Values of n When Extrapolating from Longer to Shorter Exposure Periods

When extrapolating from longer to shorter exposure durations using the equation $C^n \times t = k$ and a value of n=1, there is a relatively rapid increase in the extrapolated values (see Figure 2.7-1). Under these circumstances, the derived AEGL value represents a relatively high estimate of the toxic endpoint concentration at shorter exposure durations and is, therefore, a less conservative value. When extrapolating from longer to shorter exposure durations using a value of n=3, there is a less rapid rate of increase in the derived AEGL value. As a result, the extrapolated AEGL value is more conservative when selecting a value of n=3. See Figure 2.7-1.

Under circumstances where the NAC/AEGL Committee selects a value for n to derive AEGL values from empirical data for longer exposure periods, tentative AEGLs are derived using values for n of 3 and then compared to the derived values with all other relevant data.

Again, this represents a "weight of evidence" approach to selecting a value of n for the most scientifically credible AEGL values. In instances where the supporting data indicate that the tentative AEGL developed using a value of n=3 is too high or too low, the AEGL may be adjusted to scientifically account for the supporting data. If there are no supporting data indicating that the derived AEGL should be adjusted, a value of n=3 should be used to accommodate for the uncertainty of the concentration-exposure duration relationship for the shorter exposure durations.

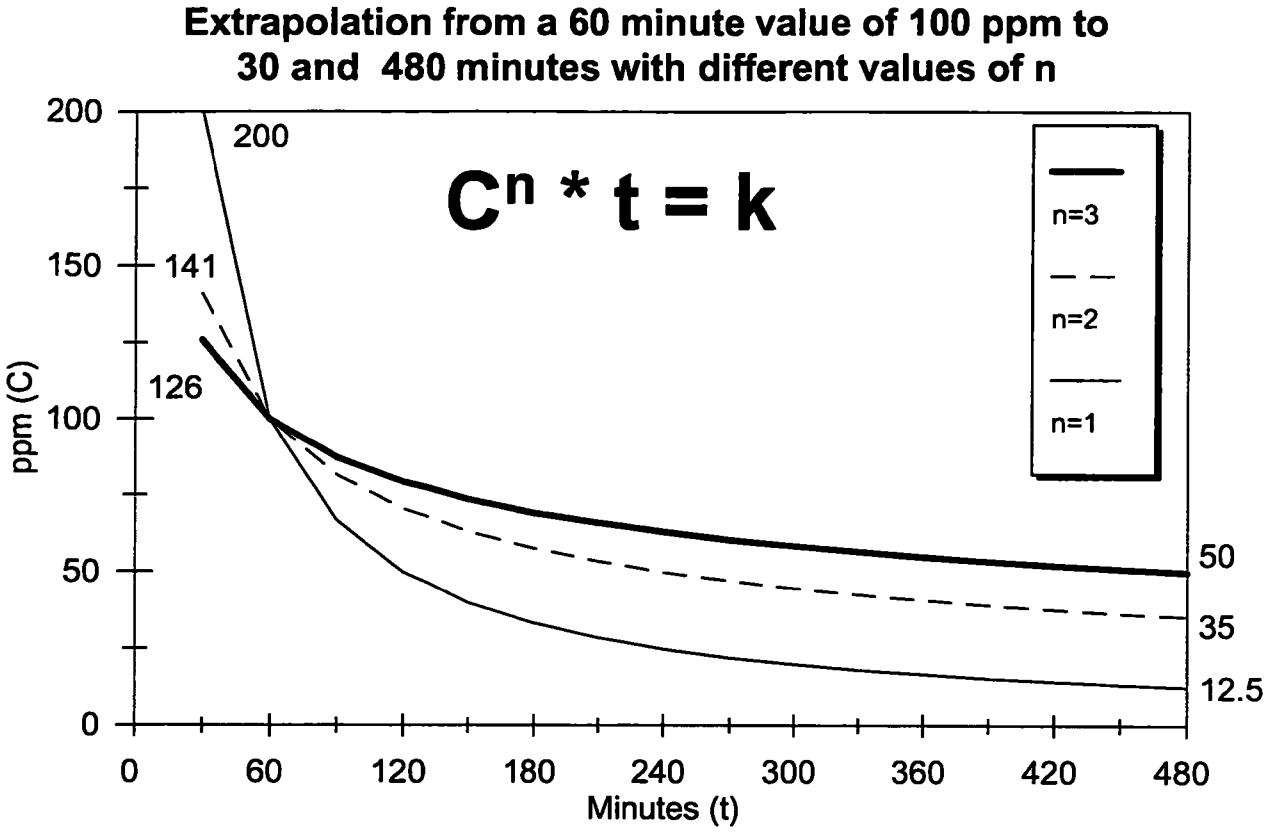


FIGURE 2.7-1 EFFECTS OF VARYING n IN THE EQUATION C^n x t = k

SHORT TO LONG DURATION EXTRAPOLATIONS: Note that when extrapolating from 60 minutes to longer exposure durations, the lower the value of n the lower the extrapolated value Therefore, when extrapolating from short to long exposure durations, a value of n=1 yields a more conservative value than any value of n that is >1

LONG TO SHORT DURATION EXTRAPOLATIONS. Conversely, when extrapolating from 60 minutes to shorter exposure durations, the higher the value of n the lower the extrapolated value Therefore when extrapolating from long to short exposure durations a value of n=3 yields a more conservative value than any value of n that is <3

2.7.7 Special Considerations in the Time Scaling of AEGL-1 and AEGL-2 Values

The previous descriptions of approaches to time scaling for toxic end-point concentrations are most applicable to the derivation of AEGL-3 values. This is because unequivocal data relating the concentration required to cause an effect to the time duration of exposure are LC_{50} data. Lethality is an unambiguous end-point which does not involve gradations of severity or incidence which are often difficult to quantify (e.g., lung congestion, lung edema, irritation in the respiratory tract involving variations in both degree and area affected). With respect to AEGL-2 values, it is far more difficult to quantify and achieve consensus on gradations in non-lethal toxic effects with respect to severity and incidence in a manner that readily results in a simple, quantitative toxic end-point concentration - exposure duration relationship. Further, the LC_{50} is a statistically derived value in the mid-point of the dose-response curve which is less subject to the vagaries in response at the extremes of the exposure regimen. For these reasons, the NAC/AEGL Committee primarily has used LC_{50} data in the derivation of exposure-time scaling relationships. These quantitative relationships have then subsequently been used to derive both the AEGL-2 and the AEGL-3 values, and occasionally the AEGL-1 values. This is believed to be a scientifically credible approach if the mechanism of toxicity for AEGL-2 and AEGL-3 is known or thought to be similar.

It is recognized that the time scaling relationship observed with a lethality AEGL-3 endpoint may not accurately describe the irreversible effects or impairment of escape endpoint used for the AEGL-2 endpoint. However, the NAC/AEGL Committee compares the AEGL-2 values against the supporting data to assess the reasonableness of the AEGL-2 determinations. Based on this assessment, adjustments are made to better fit the supporting data If there are data that suggest different toxicological mechanisms for lethal effects and AEGL-2 health effects, selected values of n should be used for the development of the AEGL values. The upper and lower bounds of n=3 and n=1 should be used for extrapolation from longer to shorter and from shorter to longer exposure periods, respectively. The resultant AEGL-2 values should then be evaluated using all supporting data and adjusted or maintained accordingly.

A difficult application of time scaling is encountered when attempting to derive AEGL-1 values. The AEGL-1 value defines the air-borne concentration that distinguishes detection from discomfort. As a result, the difficulty in attempting to quantify this often subjective level with respect to severity and incidence in a manner sufficient to derive a concentration-exposure duration relationship is greater than in the case of the AEGL-2. This is further complicated by the nature of the biological end-point that one is attempting to quantify. For example, the concentration level for odor detection in a group of individuals may actually decrease over time due to olfactory fatigue. With respect to mild sensory effects, they generally are not cumulative over a range of exposures of 10 minutes to 8 hours. Hence, the same AEGL-1 value may be assigned to all AEGL-specified exposure periods. In certain instances, where experimental data suggest that the sensory effects may increase due to the cumulative dose over time, the 10

minute, 30 minute and 1 hour values may be constant, yet differ from a lower but constant AEGL-1 value that is established for the 4 hour and 8 hour AEGL exposure durations.

In the case of certain sensory irritants, the AEGL values may be constant across all AEGL time periods because this end-point is considered a threshold effect and prolonged exposure will not result in an enhanced effect. In fact individuals may adapt to sensory irritation by these chemicals over these exposure periods such that the warning properties are reduced.

2.7.8 Time Scaling - Guidelines for NAC/AEGL Committee Approach

This section is a compilation of time scaling guidelines which are used when deriving AEGL values for different time periods.

2.7.8.1 Use of Empirical Data to Determine the Exposure Concentration-Exposure Duration Relationship

THE RATIONALE FOR THE SELECTION OF AN EMPIRICALLY BASED TIME SCALING APPROACH SHOULD INCLUDE:

1. The health effect used.
2. The exposure durations for which data were available.
3. Description of the statistical methodology used. If no methodology was used then describe how the value of n was derived.
4. Description of the data used, including durations or the concentration/time values used for extrapolation. Include the formula used.
5. Description of the different values of n that were used from one or more studies and why a specific derived value of n was used.
6. The value of k calculated from $C^n \times t = k$ after the uncertainty and modifying factors have been applied to C.
7. If the value of n is based upon an analysis of the combined data from a number of different studies then provide a description of how the different time/concentration values were combined and why they were used.

2.7.8.2 Estimating the Concentration-Exposure Relationship using a Surrogate Chemical

THE RATIONALE FOR THE SELECTION OF THIS TIME SCALING APPROACH SHOULD INCLUDE:

1. Description of the structure/activity relationships between the two chemicals.
2. The health effect endpoint used.
3. The exposure durations for which data were available.
4. The statistical methodology used or a statement of how the value of n was derived
5. Description of the data from the surrogate chemical used to derive the concentration-exposure duration relationship. If a derived value of n is used, the equation should be included.
6. A description of how the different time/concentration values were combined and why they were used if the value of n is based upon an analysis of the combined data from a number of different studies.
7. The value of k calculated after uncertainty and modifying factors have been applied.

2.7.8.3 Estimating the Concentration-Exposure Duration Relationship when Data are not Available to Derive a Value for n and Supporting Data are Available.

Selection of values for n. In the absence of data to derive a value for n, a value for n of 1 is initially selected when extrapolating from shorter to longer exposure durations and a value for n of 3 is initially selected when extrapolating from longer to shorter exposure durations. The values of n are used with the equation $C^n \times t = k$ to extrapolate from the empirically reported exposure concentrations and exposure durations to the AEGL-specified exposure durations. AEGL values in accord with the supporting data are then selected.

THE RATIONALE FOR THE SELECTION OF THE TIME SCALING APPROACH SHOULD INCLUDE:

1. A presentation of the rationale in the TSD text as follows: The relationship between concentration and duration of exposure as related to lethality was examined by ten Berge et al. (1986) for approximately 20 irritant or systemically-acting vapors and gases. The authors subjected the individual animal data sets to probit analysis with exposure duration and exposure concentration as independent variables. An exponential function ($C^n x\ t = k$), where the value of n ranged from 0.8 to 3.5 for different chemicals was found to be an accurate quantitative descriptor for the chemicals evaluated. Approximately 90 percent of the values of n range between n=1 and n=3. Consequently, these values were selected as the reasonable lower and upper bounds of n. A value of n=1 is used initially when extrapolating from shorter to longer time periods because the extrapolated values represent the most conservative approach in the absence of other data. Conversely, a value of n=3 is used when extrapolating from longer to shorter time periods because the extrapolated values are more conservative in the absence of other data. If supporting data are available (description and references for data should be included) indicating that the AEGL value initially extrapolated is (too high/too

low), the AEGL value has been adjusted to reflect these (data, effects, etc.).

2. Presentation of the AEGL values or exposure concentrations extrapolated from data using a value of n=1 or n=3 and the adjustments made as a result of supporting data..
3. Discussion of the adjustment(s) made and the rationale for making them.

2.7.8.4 Determining Concentration-Exposure Relationships when Data are not Available to Derive a Value for n and no Supporting Data are Available.

In the absence of data to derive a value(s) of n and the absence of supporting data to validate a value of n, the value of n=1 will be selected for extrapolating from shorter to longer exposure durations, and the value n=3 will be selected for extrapolating from longer to shorter expoosure durations.

THE RATIONALE FOR THE SELECTION OF THIS TIME SCALING APPROACH SHOULD INCLUDE·

1. A presentation of the rationale in the TSD text as follows: The relationship between concentration and duration of exposure as related to lethality was examined by ten Berge et al. (1986) for approximately 20 irritant or systemically-acting vapors and gases. The authors subjected the individual animal data sets to probit analysis with exposure duration and exposure concentration as independent variables. An exponential function ($C^n \times t = k$), where the value of n ranged from 0.8 to 3.5 for different chemicals was found to be an accurate quantitative descriptor for the chemicals evaluated. Approximately 90 percent of the values of n range between n=1 and n=3. Consequently, these values were selected as the reasonable lower and upper bounds of n to use when data are not available to derive a value of n. A value of n=1 is used when extrapolating from shorter to longer time periods because the extrapolated values are conservative and therefore, reasonable in the absence of any data to the contrary. Conversely, a value of n=3 is used when extrapolating from longer to shorter time periods because the extrapolated values are conservative and therefore reasonable in the absence of any data to the contrary.

2.7.8.5 AEGL Exposure Values are Constant Across Time.

THE RATIONALE FOR THE SELECTION OF THE TIME SCALING APPROACH SHOULD INCLUDE.

1. The data and mode or mechanism of action of the chemical and its effect on humans that supports the assignment of constant AEGL values across exposure durations.

2.8 GUIDELINES/CRITERIA FOR ADDRESSING SHORT TERM EXPOSURE KNOWN AND SUSPECT CARCINOGENS

Cancer represents a serious adverse health effect. Historically, the concerns for chemically-induced cancers were based on long-term, continuous exposure in controlled animal studies or information derived from clinical or epidemiological studies of continuous or long-term exposures in humans. To conduct quantitative risk assessments for cancer in humans, mathematical (probit-log-dose) models were developed to utilize primarily animal bioassay data and extrapolate from the higher experimental levels to assess the carcinogenic risk to humans at low levels of chemical exposure. The evolution and usefulness of mathematical models to accommodate new understanding or new concepts regarding the mechanisms of carcinogenesis have been summarized in two publications by the National Research Council (NRC), National Academy of Sciences (NAS): Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants (NRC, 1992a), and Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances (NRC, 1993a).

In the United States, some state and federal regulatory agencies conduct quantitative risk assessments on known or suspect carcinogens for continuous or long-term human exposure by extrapolating downward in linear fashion from an upper confidence limit on theoretical excess risk (FDA, 1985; U. S. EPA, 1986). The values derived for a specified "acceptable" theoretical excess risk to the U.S. human population, based on a lifetime of exposure to a carcinogenic substance, have been used extensively for regulatory purposes.

There are no adopted state or federal regulatory methods for deriving such short-term standards on the basis of carcinogenic risk because nearly all carcinogenicity studies in animals and retrospective epidemiologic studies have entailed high-dose, long-term exposures. As a result, there is uncertainty regarding the extrapolation from such studies in animals to the case of brief human exposures. This is particularly problematical because the specific biological mechanisms at the molecular, cell and tissue levels leading to cancer are often not known. It is also possible that the mechanisms of injury that follow brief, high-dose exposures will often differ from those following long-term exposures. To date U.S. federal regulatory agencies have not established regulatory standards based on, or applicable to, less than lifetime exposures to carcinogenic substances.

2.8.1 NRC/NAS Guidance

Guidance on the development of short-term exposure limits, published by the U. S. National Research Council, National Academy of Sciences identified cancer as one of the potential adverse health effects that may be associated with short-term inhalation exposures to certain chemical substances (NRC, 1993a). This guidance document discusses and recommends specific risk assessment methodologies for known genotoxic carcinogens and for carcinogens

whose mechanisms are not well understood. As a first approximation the general approach involves linear low-dose extrapolation from an upper confidence limit on theoretical excess risk. Further, the NRC/NAS guidance states that the determination of short-term exposure limits will require the translation of risks estimated from long-term, continuous exposures to risks associated with short-term exposures. Conceptually, the approach recommended for genotoxic carcinogens is the method developed by Crump and Howe (1984) for applying the multistage model to assessing carcinogenic risks based on exposures of short duration. In the case of non-genotoxic chemical carcinogens, the NRC/NAS guidance acknowledges that the approach is less clear because of the many different modes of action and the complexities of non-genotoxic carcinogenic mechanisms and the paucity of data on chemical-specific mode of action. It is acknowledged also that dose thresholds may exist for certain non-genotoxic, carcinogens. The NRC guidance suggests that, in lieu of linear, low-dose extrapolation, approaches involving non-carcinogen risk assessment techniques or the pure-promoter model from the class of initiation-promotion-progression models be used, provided a known mechanism of action can justify the specific approach. The guidance emphasizes the importance of knowing the underlying biological processes when using any such models.

2.8.2 Precedents for Developing Short-Term Exposure Limits Based on Carcinogenicity

The NRC/NAS guidance (1993a) for assessing the excess risks of genotoxic carcinogens is based on an adaptation of the work of Crump and Howe (1984) by the NAS' Committee on Toxicology (COT). The COT's adaptation of the methodology was made for developing Emergency Exposure Guidance Levels (EEGLs) and Short-Term Public Exposure Guidance Levels (SPEGLs) for the Department of Defense (NRC, 1986). EEGLs represent exposure levels intended to be acceptable for the performance of specific tasks by military personnel during emergency conditions lasting 1 to 24 hours. The SPEGLs represent acceptable ceiling concentrations for a single, unpredicted short-term exposure to the public. The exposure periods range from 1 hour or less to 24 hours and the SPEGLs are generally set at 0.1 to 0.5 times the corresponding EEGL value.

The criteria and methods document prepared by the COT for the development of EEGLs and SPEGLs indicates that theoretical excess carcinogenic risk levels in the range of 10^{-4} to 10^{-6} are acceptable risk levels (NRC, 1986). However, the document states that "The role of short-term exposures in producing cancer is not clear .... any exposure to a carcinogen has the potential to add to the probability of carcinogenic effects .... (but) .... the effects of long or repeated exposures could greatly overshadow brief exposures (up to 24h)." Additionally, the COT states "The assumption that the carcinogenic response is directly proportional to total dose is likely not to hold for all materials and all tissues that these materials affect." However, these concerns not withstanding, the COT set SPEGL values based on the carcinogenic risk assessment methodology previously mentioned for hydrazine, methyl hydrazine, and 1,1-dimethyl hydrazine.

In each case, the excess cancer risk level used was 10^{-4} and the derived values were determined to be lower than corresponding airborne concentration levels that were estimated to cause acute toxicity. SPEGL values for exposure periods of less than 24 hours of other known or suspect human carcinogens were not based on carcinogenicity. These chemicals included benzene, trichloroethylene, ethylene oxide, and lithium chromate.

The National Aeronautics and Space Administration (NASA) requested that the COT develop spacecraft maximum allowable concentrations (SMACs) for space-station contaminants. The COT published guidelines for the development of short-term and long-term SMACs (NRC, 1992a). Short-term SMACs refer to concentrations of airborne substances that will not compromise the performance of specific tasks during emergency conditions lasting up to 24 hours. Because of NASA's concern for the health, safety, and functional abilities of space crews, SMACs for exposure from 1 to 24 hours should not cause serious or permanent effects but may cause reversible effects that do not impair judgement or interfere with proper responses to emergencies. The long-term SMACs are designed to prevent deterioration in space crew performance with continuous exposure for up to 180 days.

The guidelines for determining SMACs for carcinogens recommend the methods proposed by Kodell, et. al., (1987) based on the linear multistage model. The level of excess risk used in the computation is 10^{-4}. The guidelines suggest extrapolations of long-term (often lifetime) exposures to shorter durations such as 1, 30, or 180 days and refer to a single-day exposure as "the case of near instantaneous exposure." Further, the guidance states "It must be remembered that extrapolation from a daily lifetime exposure level and conversion to an instantaneous exposure level using .... (equations presented) .... is an extreme case and is valid only under the assumptions underlying the multistage theory of carcinogenesis." A review of the first three volumes of published SMACs (35 chemicals) including ten (10) known or suspect carcinogens, indicated that an assessment of excess risk for less than a 24 hour exposure period was conducted on only one of the 10 carcinogenic substances. Carcinogenic assessments for excess risk were conducted on all 10 chemicals for 24 hours, as well as 7, 30, and 180 days. The reasons provided in the COT technical support documents for not undertaking a risk assessment on carcinogenic substances for exposure periods of less than 24 hours included: (1) "Data not considered applicable to the exposure time (1 hr.)", (2) "Extrapolation to one hour exposure duration produces unacceptable uncertainty in the values", and (3) "The COT model was not used to calculate acceptable concentrations for exposures shorter than 24 hours" (NRC, 1992a).

As stated previously, to date no U.S. federal or state regulatory agency has promulgated or established regulatory limits for single short-term (less than 24 hours) exposures based on carcinogenic properties.

2.8.3 Scientific Basis for Credible Theoretical Excess Carcinogenic Risk Assessments for Single Exposures of 8 Hours or Less

The NRC/NAS guidance (NRC, 1993a) suggests that AEGLs can be developed using carcinogenic risk assessment methodologies for exposure durations of 1 to 8 hours provided adequate data are available. However, the guidance states that risk assessments on chemical carcinogenicity in humans should be based on all relevant data and embody sound biological and statistical principles. While some of the substances may be considered known human carcinogens, most of the information is based on animal testing information. Additionally, since the mode of action for animal carcinogens are not always the same with respect to biological properties among animal species or strains and humans, a weight-of-evidence evaluation must be carried out on a case-by-case basis. The weight of evidence evaluation considers comparative metabolic disposition, pharmacokinetics parameters, routes of exposure, mechanisms of action, and organ or species differences in response in animals and humans.

Uncertainties regarding lifetime theoretical excess carcinogenic risk assessments increase as shorter durations of a single exposure are considered. Most of these concerns stem from the reliance of both conclusions of carcinogenicity and quantitative assessments on long-term exposures in humans in occupational settings or in test animals. Thus, calculations for short-term risks require substantial extrapolation. At the same time, there are special concerns and unresolved issues regarding short exposures that will require more relevant data before they can be resolved. As evidenced from the actual application of these guidelines, the COT was reluctant in most cases to develop quantitative carcinogenic risk assessments for less than 24 hours exposure in the development of SMACs.

To better understand the empirical data base for single exposures, the U.S. EPA funded a study for the AEGL Program by Dr. Edward Calabrese of the University of Massachusetts to review the published literature and assess the circumstances during which a single exposure of short duration may cause cancer. This effort, referred to as the Single Exposure Carcinogen Database, has been completed and represents a computerized summary that will enable the evaluation of toxicological studies to assist in the NAC/AEGL Committee's assessment as to whether a single exposure to a chemical under consideration for AEGL development could cause tumor development. The data base will contain numerous parameters important to tumor outcome and/or quality of the studies conducted. The database will contain approximately 5,500 "studies" or data sets involving approximately 500 chemicals from nearly 2000 references.

Although a brief overview of the Single Exposure Carcinogen Database has been presented to the NAC/AEGL Committee, at the present time it is not known whether the data available on single exposure of carcinogenic substances will be sufficient to justify their use in the development of AEGL values. First, less than 20 of the 5,500 studies or data sets are based on inhalation exposure. An initial review of the database indicates that only a limited number of short-term cancer studies conducted by the inhalation route are available. Hence, route to route extrapolations would need to be conducted in a manner that would not substantially weaken the

conclusions. This could be done for certain substances using standard U. S. EPA or U. S. NAS procedures if the toxicant is likely to cause tumors at a site other than the port of entry. If the substance causes tumors at the site of application or port of entry in oral or parenteral protocols, extrapolation to the inhalation route of exposure becomes problematic. For this reason the NAC/AEGL Committee in most cases will likely continue to rely on data from long-term human and animal studies as the basis for the quantitative cancer risk assessments it conducts for short-term exposures of 8 hours or less.

The Single Carcinogen Database may prove to be useful in obtaining some important information for AEGL development. The database shows that single exposure to various chemical classes, using various species and strains of animals, can result in tumor formation. Furthermore, chemicals can be selected from the database for which there is dose-response information. Data and information from positive responses of the chemical in the database could be compared between the single dose study and the long-term study.

2.8.4 Practical Issues of Using Quantitative, Carcinogenic Risk Assessments for Developing AEGLs

In addition to the important scientific issues regarding carcinogenic risk assessments in the development of AEGL values, there are important practical issues to be considered by emergency planners and responders regarding AEGL values that would be based on possible carcinogenic effects. The acceptable cancer risk for a lifetime exposure to known or suspect human carcinogens ranges from 10^{-4} to 10^{-6} for the U.S. EPA and most other U.S. federal regulatory agencies (U. S. EPA, 1991). The AEGL values, however, are designed for emergency planning, response, and prevention to accidental releases from chemical accidents. Thus, theoretical excess cancer risk may be accumulated in 30 minutes or in a few hours. In addition to the individual risk of 10^{-4} to 10^{-6} one should also consider a measure of population based risk. Experts in the chemical accident field indicate that the typical U.S. population at risk during most accidental chemical releases is in the range of 1,000 to 5,000. The actual number of individuals exposed depends on many factors, such as population density, quantity released, release rate, prevailing wind direction and velocity, terrain and ambient temperature to name a few. Therefore, a population-based risk range of 10^{-4} to 10^{-6}, assuming a credible carcinogenic assessment can be made, appears to be approaching zero for a population of 1,000 to 5,000 or higher. The consideration of population-based risks by using assessment methods designed for individual risks has precedent in U.S. EPA assessments of new industrial chemicals under TSCA (Toxic Substance Control Act) Section 5 and pesticide chemicals under FIFRA (Federal Insecticide Fungicide and Rodenticide Act).

Implementation of emergency response procedures based on theoretical excess risk values of 10^{-4} to 10^{-6} values may be problematical. For example, if such values were used, they would be based on an anticipated increased cancer risk of 10^{-4} to 10^{-6}, a level consistent with the EPA's

acceptable cancer risk for lifetime exposures to known or suspect human carcinogens. However, the risks associated with evacuation and other response measures might possibly pose greater risks of injury or perhaps death. Thus, setting AEGL values based on a cancer risk may lead to response measures that increase actual or total risk for the exposed population.

2.8.5 Current Approach of the NAC/AEGL Committee to Assessing Potential Single Exposure Carcinogenic Risks

Based on the discussions and considerations presented in the earlier sections of in this chapter on cancer risk assessment, the NAC/AEGL Committee has developed no AEGL values based on carcinogenicity to date. In view of the great uncertainty of the assumptions used in extrapolating from lifetime exposures to 8 hours or less, the paucity of single, inhalation exposure data, the relatively small populations involved, and the potential risks associated with evacuations and other response measures, the Committee does not believe their use in setting AEGL values is justifiable at the present time.

However, the NAC/AEGL Committee will continue to identify and evaluate carcinogenic data during the development of AEGLs on a chemical-by-chemical basis. The scientific parameters which are used in this analysis are presented later in this section. In those cases where, in the judgement of the Committee, it is appropriate, risk assessments for 10^{-4}, 10^{-5}, and 10^{-6} levels of cancer risk will be conducted. It is believed that information on known or suspect human carcinogens should be provided to emergency planners and responders and made available to the public at large even when such information is not used to set AEGL values. Therefore, the Committee will continue to provide data and information on the carcinogenic properties of chemicals in the Technical Support Documents, and in instances where the appropriate data are available, develop quantitative cancer risk assessments at risk levels of 10^{-4}, 10^{-5}, and 10^{-6} in accordance with the NAS guidance (NAS, 1993a). The NAC/AEGL Committee will attempt to limit potential cancer risk to 10^{-4} or less where there is scientifically credible data to support the risk based on a single exposure. If at some future date, substantial and convincing scientific data become available that clearly establishes a relationship between a single, short-term inhalation exposure to a chemical and the onset of tumors that are likely to occur in humans, the carcinogenic risk in the development of the appropriate AEGL values will be considered.

2.8.5.1 Evaluation of Carcinogenicity Data

The evaluation of the carcinogenicity of a chemical in humans should be based on the analysis of all relevant data, both positive and negative responses. Human epidemiologic and clinical studies, as well as accidental exposure reports are considered and used to evaluate the carcinogenic potential of a substance. In the absence of human data, long-term bioassay data from controlled animal studies are used to derive theoretical excess carcinogenic risk estimates for exposed humans. The selection of data for estimating risk is based on the species and strain considered most closely resembling the human response to provide the most accurate estimates.

Data suggestive of a single exposure inducing a carcinogenic response, including related mechanistic data that support such a possibility, will be considered. If highly convincing data become available the Committee will consider the merits of the information in the development of AEGL values. Weight should be given to those studies most relevant to estimating effects in humans on a case-by-case basis. Data for assessing the strength of conclusions drawn from controlled animal studies should include information on comparative metabolic pathways, pharmacokinetics, routes of exposure, mechanisms of action, and organ or species differences in response. In general, the NAC/AEGL Committee will follow a weight-of-evidence approach in the evaluation of carcinogenicity that is consistent with the availability and biological variability of the data and its relationship to the likelihood of effects in humans.

2.8.5.2 Methodology Used for Assessing the Carcinogenic Risk of a Single Exposure

Guidance published in 1993a by the Committee on Toxicology, National Research Council, National Academy of Sciences (NAS) states that the setting of AEGLs (CEELs) should involve linear low-dose extrapolation from an upper confidence limit on excess risk for genotoxic carcinogens and for carcinogens with mechanisms of action that are not well understood. More specifically, the NAS guidance suggests an approach utilizing the methods proposed by Kodell et al. (1987) based on multistage models. Although the NAS guidance states that multistage models could be useful for setting AEGL values, the guidance acknowledges that sufficient information may not be available to postulate the total number of stages in the cancer process and the stage(s) that are dose-related. In these instances, the NAS guidance recommends the use of the time-weighted-average dose where the instantaneous dose D at time t_0 is assumed to be the equivalent of the lifetime excess carcinogenic risk as daily dose D up to time t. This equivalence is expressed by the equation $D = d \times t$. As shown by Kodell et al. (1987), the actual risk will not exceed the number of stages in the model (k). In instances where multistage models can be used and prudence dictates conservatism, the NAS guidance suggests reducing the approximation of D by an adjustment factor of 2 to 6, depending on the number of assumed stages in the multistage model employed.

To date the NAC/AEGL Committee has evaluated excess theoretical risk at levels of 10^{-4}, 10^{-5}, and 10^{-6} for a one-time exposure to known or suspect human carcinogens by determining the total cumulative lifetime dose and applying Haber's law (concentration required to produce an effect x time of exposure = constant) for exposure periods ranging from 8 hours to 30 minutes. The resultant doses are then divided by an adjustment factor to account for the multistage nature of carcinogens. See the example below.

2.8.5.2.1 The Determination of an Adjustment Factor Dealing with the Dose-Dependent Stage of Carcinogenesis

There is an extensive body of literature which deals with the concept of malignant tumor development, progression of an initiated cell through successive stages and quantitative risk assessment. Two references, Crump and Howe 1984 and Kodell et al. 1987, are cited in the NRC (1993a), publication. The concept has been further discussed in a number of publications (Goddard et al, 1995; Murdoch et al., 1992; Murdoch and Krewski, 1988). This process is referred to as a cell kinetic multistage model. There are several published variations of the basic tenants in the model. If only one or more stages are dose-dependent and exposure is concentrated in the dose-dependent stage, it is possible to underestimate risk when the risk is based upon lifetime exposure. For example, if the first stage is dose-dependent, and there is a single exposure to an infant, the probability of cancer induction is maximized because the entire lifetime of the individual is available for progression through the remaining stages in the development of the cancer. If the same dose were given to an elderly person, the probability of inducing cancer approaches 0 because there is insufficient time remaining in the life of that individual for the initiated cell to progress through the subsequent stages to a malignant cancer. Kodell et al. (1987) demonstrated that the underestimation of risk which is based upon a lifetime of exposure will not exceed the number of stages in the multistage model. For this reason the NRC (1986) recommends dividing the risk assessment based upon the lifetime exposure by a factor between 2 and 6 to account for the number of stages in the multistage model applicable to the particular chemical of concern.

In addition to the multistage model there have been a number of publications investigating the two stage birth-death-mutation model (Morrison, 1987; Chen et al., 1988; Murdoch and Krewski, 1988; Moolgavkar and Luebeck, 1990; Murdoch et al., 1992; Goddard et al. 1995). This model is similar to the multistage model in which there are two stages. However, the impact of the number of stem cells at the time of chemical exposure is considered as well as the net growth rate of cells which have undergone the first stage of initiation. If the first stage initiating event creates a cell which has a net growth rate greater than that of the stem cell, then the risk of that initiating event will be greater than if the initiated cell grew at the same relative rate as the stem cell. In this case, exposure early in life will cause a greater risk than exposure late in life. Conversely, exposure to a completer (effects only the second stage) late in life will be more effective than early exposure because relatively more initiated cells are present. If this is the only stage effected by the chemical, this situation is the same as 2 stages in the multistage model. However, if the net growth of the initiated cells is 10 times the stem cell rate the relative effectiveness of exposure late in life could be 10 fold (Murcoch and Krewski, 1988) Exposure to promoters between the first and second stage event can have an impact by increasing the net growth rate of initiated cells over that of stem cells. However, for maximum effectiveness the exposure to promoters (generally considered to be non-genotoxic exposure) must encompass multiple events (Chen et al., 1988; Murdoch and Krewski, 1988). Thus, the cancer risk associated with a single exposure to a promoter should not be greater than predicted from multiple exposures and no correction to the estimated risk need be made in this case.

A major impact upon the risk assessment of the two stage model comes from carcinogen exposure in the first stage in which the initiation event creates a cell with a greater net growth rate than the stem cells. Modelers have considered a number of scenarios in which the net growth rate of initiated cells varies from -10 to +10. The greatest increase in risk in the two stage model comes about when the first stage is dose-dependent and the initiating event creates a cell with a net growth rate of +10. In this case the increased risk is 10 fold (Murdoch and Krewski, 1988; Murdoch et al., 1992; Goddard et al., 1995)

Unfortunately, data on the biological plausibility of the maximum value for the net growth rate of initiated cells is lacking (Murdoch et al, 1992). Major data needs for the two stage birth-death-mutation model include the number of stem cells at different times of the life cycle, how fast they divide and differentiate and how they respond to chemical exposure in terms of cell division and mutation rate. This information is also needed for the initiated cell populations (Moolgavkar and Luebeck, 1990). Because of this major uncertainty, the projections made for the two stage model remain more speculative than for the multistage model in which there is general agreement that the number of stages should not exceed 6.

For the above reasons, unless there is evidence to the contrary, the multistage model is used when estimating risks for short-term exposures from lifetime exposure studies. In all of the above referenced publications on the multistage model, the maximum number of stages modeled is 6.

AEGL values are applicable to humans in all stages of life so the maximum risk to an infant must be considered. In this case, the concentration based upon a lifetime exposure study is divided by 6 unless there is evidence that the chemical is a later stage carcinogen or operates by a mechanism different from the multistage model. The NAC/AEGL Committee will use the divisor of 6 in agreement with the 1993a NAS guidance on the development of short-term exposure limits which states that a factor of 6 represents a conservative adjustment factor for a near-instantaneous exposure.

2.8.5.3 Summary of Cancer Assessment Methodology used by the NAC/AEGL Committee

The U.S. EPA q1* values that are listed on the Integrated Risk Information System (IRIS) or the GLOBAL86 generated slope factor values (Howe et al., 1986) are used to compute lifetime risk levels. These values are based upon the guidance in U. S. EPA 1986. The U.S. EPA (1996a) proposed methodology will be considered in the future. These values are used to compute the concentration for a single exposure to the time periods of interest. As discussed in the beginning of this section, these values are typically divided by 6 to account for early exposure to a carcinogen in which the first stage is dose-dependent or late exposure to a carcinogen in which the last stage is dose-dependent. If there is information about the number of stages required for development of the cancer or the stage which is dose-dependent, the divisor will be

modified accordingly. An example of a Carcinogenicity Assessment is given in Appendix I.

The cancer evaluation includes a weight of evidence discussion which considers the following factors:

- Less evidence of carcinogenicity from a short-term exposure
  - No evidence for human carcinogenicity (may or may not lend support of cancer induction from a single exposure but an important consideration)
  - Lifetime or long-term exposure necessary to elicit cancer
  - Positive response only at very high doses
  - Neoplasia appears reversible (when treatment is discontinued)
  - Appears to be a "threshold" carcinogen

- Greater evidence of carcinogenicity from a short-term exposure
  - Proven human carcinogen (may or may not lend support of cancer induction from a single exposure but an important consideration)
  - Short time-to-tumor
  - Evidence for cancer from one to a few exposures
  - Positive response at low doses
  - Complete carcinogen
  - Irreversible (when treatment is discontinued)
  - Strongly mutagenic

2.9 GUIDELINES/CRITERIA FOR MISCELLANEOUS PROCEDURES AND METHODS

2.9.1 Mathematical Rounding of AEGL Values

Given the uncertainties involved in generating AEGL values it could be argued that only one significant figure should be used. However, because of a number of considerations discussed below, numbers will be rounded to 2 significant figures. For example, 1.5, or 23, or 0.35. The value 7.35 would be rounded to 7.4.

Trivial differences in numbers can give large differences if only one significant figure is used. For example, values of 14.9 and 15.1 would yield AEGL values of 10 and 20 respectively. This is a two fold difference for a very small difference in computed AEGL values. Values of 18, 14, 11, and 6 ppm for 30 minute, 1, 4, and 8 hours would give values of 10, 10, 10, and 20 ppm for the time points. It would not give the appearance of a logical progression. These numbers will be used in exposure models to make decisions. The use of 2 significant figures will allow for a more reasonable progression when different exposure scenarios are considered.

Two significant figures may seem overly precise when values less than 1 ppm are presented since those levels may be difficult to measure. However, the AEGL-2 values will often be used to compare with ambient air dispersion modeling projections for planning purposes. In this case the use of 2 vs 1 significant figure could have an impact. Other rounding off schemes may be used on a case by case basis with a justification.

2.9.2 Multiplication of Uncertainty Factors

When uncertainty factors are multiplied together the NAC/AEGL Committee often multiplies two uncertainty factors of 3. Since the value 3 represents the geometric mean of 10 and 1, the actual number is 3.16. Therefore, the product of two different uncertainty factors is not 3 times 3 but 3.16 times 3.16, which equals 10. For simplicities sake 3 times 10 is represented by 30.

3. FORMAT AND CONTENT OF TECHNICAL SUPPORT DOCUMENTS

The Technical Support Document (TSD) is the compilation of all relevant data and information from all key studies/references and the most important supporting studies/references for both human exposures and laboratory animals. Additionally, this support document addresses all methodologies employed in the derivation of the AEGL values in question and the rationale and justifications for why certain data were used in the derivation and why certain studies or data were not selected, why specific methodologies and adjustment factors were or were not used, the scientific evidence supporting the rationale and justification, and the appropriate references to the published scientific literature or sources of unpublished data and information.

Major components to the TSD include 1) the Preface which includes definitions of the AEGL tiers; 2) an Executive Summary which includes a concise summary of toxicity information on the chemical, rationales used for time scaling and selection of uncertainty factors, and a table of AEGL values for the three tiers as well as key references; 3) the main body of the TSD which includes a detailed discussion of the items in listed in 2) and; 4) a Derivation Summary Table which includes a list and discussion of the key data elements and rationale used to derive the AEGL values.

EDITORIAL CONVENTIONS

- Concentrations will be expressed in the units used in the publication. If the data in the publication or other data sources, were expressed in ppm, enter only ppm values. If data, were expressed in mg/m^3 or other units, then state the concentration as expressed in the data source and add ppm in parentheses.

- References to footnotes should be superscript and lower case.

3.1 FORMAT AND CONTENT OF THE TECHNICAL SUPPORT DOCUMENT (TSD)

PREFACE

The AEGL tiers are defined in the Preface of each TSD. See Chapter 2.1 for definitions of AEGL-1, 2, and 3.

TABLE OF CONTENTS

Major headings in the text, tables and figures should be marked with the word processor

indexing tool so that the Table of Contents can be generated by the computer. A sample Table of Contents is presented in Appendix E.

EXECUTIVE SUMMARY

The Executive Summary should include:

The name and CAS number of the chemical being reviewed.

A brief description of the substance, its physical properties, and uses.

A brief statement or overview of the toxicology, including the extent of the data/information retrieved and reviewed, highlights of the most important research and strengths and weaknesses of the database. Discuss data on human exposures and data on laboratory animals.

A brief summary (1 paragraph for each AEGL tier) of the key study (with references), the data used, and the derivation of the AEGL values. Each summary will include:

- Information on the toxic endpoints and exposure levels used as the basis for deriving the AEGL values.
- Exposure level (If the data in the publication are expressed in ppm enter only ppm values. If data were expressed in mg/m^3 or other units then state the concentration as expressed in the publication and add ppm in parentheses).
- Exposure period.
- Why this time-concentration point was selected (include effects observed or not observed, relate to the AEGL level, etc.).
- The species and number of animals used.
- Consistency with human data if appropriate.
- The reference to the key study.
- A statement of uncertainty factors and modifying factors used or not used and why a specific value was chosen.
- A statement of the time scaling method used and why it was selected (include the rationale for the value of n in the time scaling equation).

A brief statement regarding carcinogenicity, if appropriate.

A brief statement on the adequacy of the data (see Section 2.3.3 of this SOP Manual).

A summary table of draft/proposed AEGL values with:

- Values presented in ppm with mg/m in parentheses.
- A rationale and reference for AEGL-1, -2, and -3.

Reasons for no AEGL value.

References

A sample Executive Summary is presented in Appendix F.

OUTLINE OF THE MAIN BODY OF THE TECHNICAL SUPPORT DOCUMENT

1. INTRODUCTION

- General information regarding occurrence, production/use, physical/chemical data (table for physical chemical data)

2. HUMAN TOXICITY DATA

2.1 Acute Lethality - include anecdotal case reports if pertinent
2.2 Nonlethal Toxicity
2.2.1 Acute Studies - include anecdotal case reports if pertinent
2.2.2 Epidemiologic Studies
2.3 Developmental/Reproductive Toxicity
2.4 Genotoxicity
2.5 Carcinogenicity - include EPA and IARC classifications
2.6 Summary - weight-of-evidence approach

As appropriate, data are tabulated within sections and/or in summary

3. ANIMAL TOXICITY DATA

3.1 Acute Lethality - include species/strain, number of animals, exposure concentrations/durations, mortality rates/ratios, time to death. (The order of animals shown should be used. If no data are available for a species, the number should be used for the next species discussed.)
3.1.1 Nonhuman Primates
3.1.2 Dogs
3.1.3 Rats
3.1.4 Mice
3.1.5 Guinea Pigs
3.1.6 Rabbits
3.1.7 Other Species

- Sections to include relevant studies (potential key studies and supporting data) or provide overall picture of toxicity data as appropriate
- Third-level headers to vary dependent upon available data; exclusion of header to imply no data

3.2 Nonlethal Toxicity - include species/strain, no. of animals, exposure concentrations/durations, critical effects, time course data, etc. (The order of animals shown should be used. If no data are available for a species, the number should be used for the next species discussed.)
3.2.1 Nonhuman Primates

3.2.2 Dogs
3.2.3 Rats
3.2.4 Mice
3.2.5 Guinea Pigs
3.2.6 Rabbits
3.2.7 Other Species

- Sections to include relevant studies (potential key studies and supporting data) or provide overall picture of toxicity data as appropriate
- Third-level headers to vary dependent upon available data; exclusion of header to imply no data

3.3 Developmental/Reproductive Toxicity
3.4 Genotoxicity
3.5 Carcinogenicity
3.6 Summary - weight-of-evidence approach

Tabulation of data as appropriate within sections and/or in summary

4. SPECIAL CONSIDERATIONS

4.1 Metabolism and Disposition - general background; interspecies and individual variabilities especially as they pertain to AEGL derivation
4.2 Mechanism of Toxicity - general background; interspecies and individual variabilities especially as they pertain to AEGL derivation
4.3 Structure-Activity Relationships - data relevant to filling data gaps on the chemical
4.4 Other Relevant Information
4.4.1 Species Variability
4.4.2 Concurrent Exposure Issues (potentiation, etc)

- Third-level headers to vary dependent upon available data; exclusion of header implies no data

5. DATA ANALYSIS FOR PROPOSED AEGL-1

5.1 Summary of Human Data Relevant to AEGL-1 - general summary description of selected key and supporting study(ies) if available
5.2 Summary of Animal Data Relevant to AEGL-1 - general summary description of selected key and supporting study(ies) if available
5.3 Derivation of AEGL-1 - key study, critical effect, dose/exposure, uncertainty factor application/justification, temporal extrapolation, assumptions, confidence, consistency with human data if appropriate

6. DATA ANALYSIS FOR PROPOSED AEGL-2

6.1 Summary of Human Data Relevant to AEGL-2 - general summary description of selected key and supporting study(ies) if available

6.2 Summary of Animal Data Relevant to AEGL-2 - general summary description of selected key and supporting study(ies) if available

6.3 Derivation of AEGL-2 - key study, critical effect, dose/exposure, uncertainty factor application/justification, temporal extrapolation, assumptions, confidence, consistency with human data if appropriate

7. DATA ANALYSIS FOR PROPOSED AEGL-3

7.1 Summary of Human Data Relevant to AEGL-3 - general summary description of selected key and supporting study(ies) if available

7.2 Summary of Animal Data Relevant to AEGL-3 - general summary description of selected key and supporting study(ies) if available

7.3 Derivation of AEGL-3 - key study, critical effect, dose/exposure, uncertainty factor application/justification, temporal extrapolation, assumptions, confidence, consistency with human data if appropriate

8. SUMMARY OF PROPOSED AEGLS

8.1 AEGL Values and Toxicity Endpoints

8.2 Comparison with Other Standards and Criteria (summarized in text and presented in a table - see SOP Appendix K for an example)

8.3 Data Adequacy and Research Needs (for content see Section 2.3.3 of this SOP Manual)

9. REFERENCES CITED

10. APPENDICES

APPENDIX A (Derivation of AEGL Values) See SOP Appendix G for an example
APPENDIX B (Time Scaling Calculations) See SOP Appendix H for an example
APPENDIX C (Carcinogenicity Assessment) See SOP Appendix I for an example
APPENDIX D (Derivation Summary) See SOP Appendix J for specific format and an example

APPENDIX D: Format for Derivation Summary

DERIVATION SUMMARY
(CAS NUMBER; CHEMICAL NAME)

	AEGL-1(OR 2 OR 3) VALUES			
10 minutes	30 minutes	1 hour	4 hours	8 hours
ppm	ppm	ppm	ppm	ppm
Reference:				
Test Species/Strain/Number:				
Exposure Route/Concentrations/Durations:				
Effects:				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale:				
Modifying Factor:				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				
Data Adequacy[a]:				

[a] Elements that should be included in the Data Adequacy Section are discussed in Section 2.3.3 of this SOP Manual. If an AEGL-1 value is not recommended, there should be a short discussion of the rationale for that choice. The rationale should include as appropriate a discussion that numeric values for AEGL-1 are not recommended because (1) relevant data are lacking, (2) the margin of safety between the derived AEGL-1 and AEGL-2 values is inadequate, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

3.2 Potential Inclusion of Graphic Descriptions of Data

Graphic descriptions of important and relevant data can be helpful in identifying, understanding and comparing data in terms of similarities and differences, degree of variation, and trends among the values cited. Well prepared graphs provide the reader with a rapid overview of dose-response relationships in terms of both airborne concentrations and exposure periods among various studies and various species. The graphs should supplement the data tables but not replace them. They can be placed in the body of the document or in an appendix. Below are examples of presentations of graphic data.

It is very difficult to keep different times and the toxicity values for those times in one's head when reading the Technical Support Document. Comparisons are difficult to make between times because the values vary according to the time. The old adage "A picture is worth a thousand words" is especially appropriate when analyzing inhalation data. A particularly useful way to present the data is presented in Table 3.2-1 and Figure 3.2-1. It is based upon the concept of placing the toxic response into severity categories (Hertzberg and Miller, 1985; Hertzberg and Wymer, 1991; and Guth et al., 1991). In Table 3.2-1 the severity categories are chosen to fit into definitions of the AEGL level health effects. In the table the category severity definitions for the column headings are 0 = No effect; 1 = Discomfort; 2 = Disabling; 3 = Lethal; NL = Did not die at a lethal conc (at an experimental concentration in which some of the animals died and some did not, the NL label refers to the animals which did not die); AEGL or C = AEGL or censored (severity category could not be established). The effects which will place an experimental result into a particular category will vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. When the exposure concentration is placed into the appropriate column, the graph in Figure 3.2-1 is generated. The doses often span a number of orders of magnitude, especially when human data exist. Therefore the concentration is placed on a log scale. Note that the AEGL values are designated as a triangle without an indication to their level. The AEGL-3 is higher than the AEGL-2, which is higher than the AEGL-1.

This type of plot is useful for a number of reasons and can be used to address the following questions:

- Are the AEGL levels protective?
    - Are the AEGL-3 levels below the concentration causing death in experimental animals? If the answer is no then the question should be raised about the appropriateness of the AEGL-3 value. Is the AEGL-3 level appropriate and the data point anomalous, or should the AEGL-3 value be lowered?
    - Similar questions should be asked about the AEGL-1 and AEGL-2 values.

- Are there data points which appear to be outliers? Why are they outliers? Should they be considered in the development of AEGL values or discarded because of faulty experimental technique.

- Does the spread of data points for a particular severity category indicate major differences between species or are the results from different species congruent.

- Is the time scaling algorithm reasonable consistent with the data? For example, does the plot of the AEGL-3 values using the derived or chosen value of n in the equation $C^n \times t = k$ parallel the slope of the lethality data. Similar questions can be asked about the AEGL-1 and AEGL-2 plots.

- Is there evidence that a different time scaling factor should be used for the AEGL-2?

- What are the most appropriate data points to use for the time scaling?

TABLE 3.2-1 GROUPING DATA INTO CATEGORIES FOR PLOTTING

Reference chemical	Exp	Grp	Species	Sex	# Exposed	ppm	Minutes	ppm 0	ppm 1	ppm 2	ppm	ppm	ppm	Category	GpSize	Incidence	Comments
NAC/AEGL-1						115	30						115	AEGL			
NAC/AEGL-1						82	60						82	AEGL			
NAC/AEGL-1						41	240						41	AEGL			
NAC/AEGL-1						29	480						29	AEGL			
NAC/AEGL-2						267	30						267	AEGL			
NAC/AEGL-2						189	60						189	AEGL			
NAC/AEGL-2						94	240						94	AEGL			
NAC/AEGL-2						67	480						67	AEGL			
NAC/AEGL-3						897	30						897	AEGL			
NAC/AEGL-3						634	60						634	AEGL			
NAC/AEGL-3						317	240						317	AEGL			
NAC/AEGL-3						224	480						224	AEGL			
Baelum et al., 1985			hu			100	390		100					1			sensory irritation, sleepiness, intoxication, manual dexterity, color discrimin
Wilson 1943			hu			200	480		200					1			headache, lassitude, anorexia
Wilson 1943			hu			200	480			200				2			headache, nausea, incoordination, reaction time
						500	480			500				2			headache, nausea, incoordination, reaction time
Wilson 1943			hu			500	480		500					1			headache, nausea, incoordination, reaction time and palpitation, extreme w
Ukai et al., 1993			hu			100	480		100					1			weight loss, dizziness, headache, tightness in chest, dimmed vision
Lee et al., 1988			hu			100	480		100					1			weight loss, dizziness, headache,
Gamberale and Hultengren, 1972			hu			300	20		300					1			reaction time
Gamberale and Hultengren, 1972			hu			700	20		700					1			perceptual speed
von Oettingen et al., 1942			hu			200	480			200				2			muscular weakness, confusion, impaired coordination, and dilated pupils
von Oettingen et al., 1942			hu			200	480			200				2			severe incoordination, confusion, dilated pupils, nausea, and extreme fatigue
						600	480			600				2			severe incoordination, confusion, dilated pupils, nausea, and extreme fatigue
von Oettingen et al., 1942			hu			800	180			800				2			loss of self-control, muscular weakness, extreme fatigue, nausea, and bone
Baelum et al., 1990			hu			100	420		100					1			sensory irritation, altered temp. perception, headache, dizziness, and score
Echeverria et al., 1991			hu			150	420		150					1			performance on spatial and neurobehavioral tasks, headache, eye irritation,
Andersen et al., 1983			hu			40	360		40					1			no effect/sensory irritation, odor
						100	360		100					1			no effect/sensory irritation, odor
Rahil et al., 1996			hu			100	360	100						0			latency on a neurobehavioral task (not a biologically relevant neurobehavior
Dick et al., 1984			hu			100	240	100						0			accuracy on visual-vigilance test (not a biologically
Cherry et al., 1983			hu			80	240	80						0			no impairment on neurobehavioral tasks
Carpenter et al., 1976			hu			220	15		220					1			sensory threshold
Pryor et al., 1978			rat			26700	60				26700			NL			LC50
Pryor et al., 1978			rat			26700	60					26700		3			LC50
Cameron et al., 1938			rat			24400	90				24400			NL			60% mortality
Cameron et al., 1938			rat			24400	90					24400		3			60% mortality
Kojima and Kobayashi, 1973			rat			15000	150				15000			NL			80% mortality
Kojima and Kobayashi, 1973			rat			15000	150					15000		3			80% mortality
Cameron et al., 1938			rat			12200	390				12200			3			100% mortality
Carpenter et al., 1976			rat			8800	240				8800			NL			LC50
Carpenter et al., 1976			rat			8800	240					8800		3			LC50
Smyth et al., 1969			rat			4000	240				4000			NL			16% mortality
Smyth et al., 1969			rat			4000	240					4000		3			16% mortality
Bonnet et al., 1979			mouse			6940	360				6940			NL			LC50
Bonnet et al., 1979			mouse			6940	360					6940		3			LC50
Svirbely et al., 1943			mouse			5320	420				5320			NL			LC50
Svirbely et al., 1943			mouse			5320	420					5320		3			LC50
Moser and Balster, 1985			mouse			38465	10				38465			NL			LC50
Moser and Balster, 1985			mouse			38465	10					38465		3			LC50
Moser and Balster, 1985			mouse			21872	30				21872			NL			LC50
Moser and Balster, 1985			mouse			21872	30					21872		3			LC50
Moser and Balster, 1985			mouse			19018	60				19018			NL			LC50
Moser and Balster, 1985			mouse			19018	60					19018		3			LC50

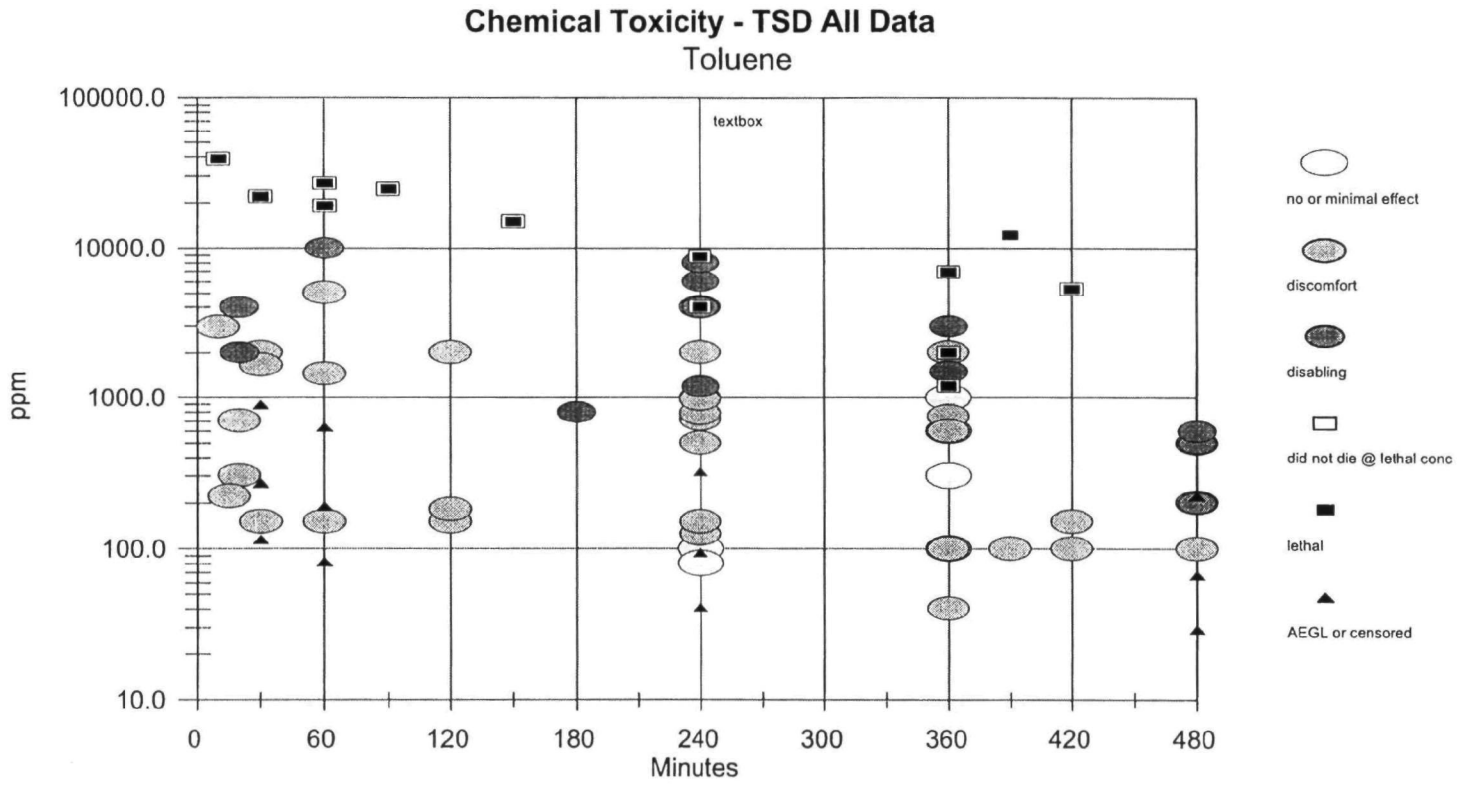


FIGURE 3.2-1 PLOT OF CATEGORIES OF DATA

4. CURRENT ADMINISTRATIVE PROCESSES AND PROCEDURES FOR THE DEVELOPMENT OF AEGL VALUES

The primary purpose of the AEGL Program and the NAC/AEGL Committee is to develop guideline levels for short-term exposures to airborne concentrations of acutely toxic, high priority chemicals. These Acute Exposure Guideline Levels (AEGLs) are needed for a wide range of planning, response, and prevention applications. These applications may include many U. S. initiatives such as the EPA's SARA Title III Section 302-304 emergency planning program, the CAAA Section 112(r) accident prevention program, and the remediation of Superfund sites program; the DOE environmental restoration, waste management, waste transport, and fixed facility programs; the DOT emergency waste response program; the DOD environmental restoration, waste management, and fixed facility programs; ATSDR health consultation and risk assessment programs; NIOSH/OSHA regulations and guidelines for workplace exposure; State CAA Section 112(b) programs and other state programs; the U. S. Chemical Manufacturer's Association (CMA) Chemtrec program; and other chemical emergency programs in the U. S. private sector. From an international perspective, it is anticipated that the AEGLs will find a wide range of applications in chemical emergency planning, response, and prevention programs in both the public and private sectors of member-countries of the Organization for Economic and Cooperation Development (OECD). It is hoped that the AEGLs also will be used by other countries in the international community

A principal objective of the NAC/AEGL Committee is to develop the most scientifically credible, acute (short-term) exposure guideline levels possible within the constraints of data availability, resources and time. This includes highly effective and efficient efforts in data gathering, data evaluation and data summarization, fostering the participation of a large cross-section of the relevant scientific community, both nationally and internationally, and the adoption of procedures and methods that facilitate consensus-building for AEGL values within the NAC/AEGL Committee.

Another principal objective of the NAC/AEGL Committee is to develop AEGL values for approximately 400 to 500 acutely hazardous substances within the next ten (10) years. Therefore, the near-term objective is to increase the level of production of AEGL development to approximately forty (40) to fifty (50) chemicals per year without exceeding budgetary limitations or compromising the scientific credibility of the values developed.

To reach these objectives, the NAC/AEGL Committee must adopt and adhere to specific processes and procedures both scientifically and administratively. This is accomplished through the development and maintenance of a comprehensive "Standing Operating Procedures" Manual (SOP Manual) that addresses both the scientific and administrative procedures required to achieve the objectives of the NAC/AEGL Committee previously mentioned. This section is

devoted to those administrative processes and procedures deemed necessary to achieve the AEGL Program objectives.

4.1 COMMITTEE MEMBERSHIP AND ORGANIZATIONAL STRUCTURE

The NAC/AEGL Committee is comprised of representatives of U. S. federal, state and local agencies, and organizations in the private sector that derive programmatic or operational benefits from the AEGL values. This includes federal representatives from the Environmental Protection Agency (EPA), the Department of Energy (DOE), the Agency for Toxic Substances and Disease Registry (ATSDR), the National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA), the Department of Transportation (DOT), the Department of Defense (DOD), the Center for Disease Control (CDC), the Food and Drug Administration (FDA), and the Federal Emergency Management Agency (FEMA). States providing committee representatives include New York, New Jersey, Texas, California, Minnesota, Illinois, Connecticut, and Vermont. Private companies with representatives include Allied Signal Corporation, Exxon Corporation, and Olin Chemical Company. Other organizations with representatives include the American Industrial Hygiene Association (AIHA), American College of Occupational and Environmental Medicine (ACOEM), American Association of Poison Control Centers (AAPCC), and the American Federation of Labor - Congress of Industrial Organizations (AFL-CIO). In addition, the committee membership includes individuals from academia, a representative of environmental justice, and other organizations in the private sector. A current list of the NAC/AEGL Committee members and their affiliations is shown in Appendix A of this SOP manual. At present, the Committee is comprised of 32 members.

Recently, the Organization of Economic and Cooperation Development (OECD) and various OECD member countries have expressed an interest in the AEGL Program. Several OECD member countries such as Germany and the Netherlands have been participating in the Committee's activities and actively pursuing formal membership on the NAC/AEGL Committee. It is envisioned that the Committee and the AEGL Program in general will progressively expand its scope and participation to include the international community.

The Director of the AEGL Program has the overall responsibility for the entire AEGL Program and the NAC/AEGL Committee and its activities. A Designated Federal Officer (DFO) is responsible for all administrative matters related to the Committee to insure that it functions properly and efficiently. These individuals are not voting members of the Committee. The NAC/AEGL Committee Chair is appointed by EPA and is selected from among the committee members. In concert with the Program Director and the DFO, the Chair coordinates the activities of the Committee and also directs all formal meetings of the Committee. From time to time, the members of the Committee serve as Chemical Managers and Chemical Reviewers in a collaborative effort with assigned scientist-authors (non-Committee members) to develop AEGLs

for a specific chemical. These groups of individuals are referred to as the AEGL Development Teams and their function is discussed in Section 4.8 of this manual..

4.2 THE AEGL DEVELOPMENT AND PEER REVIEW PROCESS

The process that has been established for the development of the AEGL values is the most comprehensive ever employed for the determination of short-term exposure limits for acutely toxic chemicals. A summary of the overall process is presented in diagram form in Figure 4.2-1. The process consists of four basic stages in the development and status of the AEGLs and they are identified according to the review level and concurrent status of the AEGL values. They include (1) "Draft" AEGLs, (2) "Proposed" AEGLs, (3) "Interim" AEGLs and (4) "Final" AEGLs. The entire development process can be described by individually describing the four basic stages in the development of AEGL values.

Stage 1: "Draft" AEGLs

This first stage begins with a comprehensive search of the published scientific literature. Attempts are made to mobilize all relevant, non-published data through industry trade associations and from individual companies in the private sector. A more detailed description of the published and unpublished sources of data and information utilized is provided in Section 2.3 of this document which addresses search strategies. The data are evaluated following the guidelines published in the NRC/NAS guidance document and this SOP manual and selected data are used as the basis for the derivation of the AEGL values and the supporting scientific rationale. Data evaluation, data selection, and the development of a technical support document are all performed as a collaborative effort among the Staff Scientist at the organization which drafts Technical Support Documents, the Chemical Manager, and two Chemical Reviewers. This group is referred to as an "AEGL Development Team". NAC/AEGL Committee members are specifically assigned this responsibility for each chemical under review. Hence, a separate team comprised of different Committee members is formed for each chemical under review. The product of this effort is a technical support document (TSD) that contains "Draft" AEGLs. The Draft TSD is subsequently circulated to all other NAC/AEGL Committee members for review and comment prior to a formal meeting of the Committee. Revisions to the initial TSD and the "Draft" AEGLs are made up to the time of the NAC/AEGL Committee meeting scheduled for formal presentation and discussion of the AEGL values and the documents. Following deliberations during the committee meeting, an attempt is made to reach consensus, or the minimum of a two-thirds majority of a quorum present, to elevate the AEGLs to "Proposed" status. If agreement cannot be reached, the Committee conveys its issues and concerns to the AEGL Development Team and further work is conducted by this group. After completion of additional work, the chemical is resubmitted for consideration at a future meeting. If a consensus or two-thirds majority vote of the Committee cannot be achieved because of inadequate data unrelated to the completeness of the data search, the chemical becomes a candidate for

appropriate toxicity studies.

Stage 2: "Proposed" AEGLs

Once the NAC/AEGL Committee has reached a consensus, or the minimum two-thirds majority vote, on the AEGL values and supporting rationale, they are referred to as "Proposed" AEGLs and are published in the Federal Register for a thirty (30) day review and comment period. Following publication of the "Proposed" AEGLs in the Federal Register , the Committee reviews the public comments, addresses and resolves relevant issues and seeks a consensus or minimum two-thirds majority of those present on the Committee on the original or modified AEGL values and the accompanying scientific rationale.

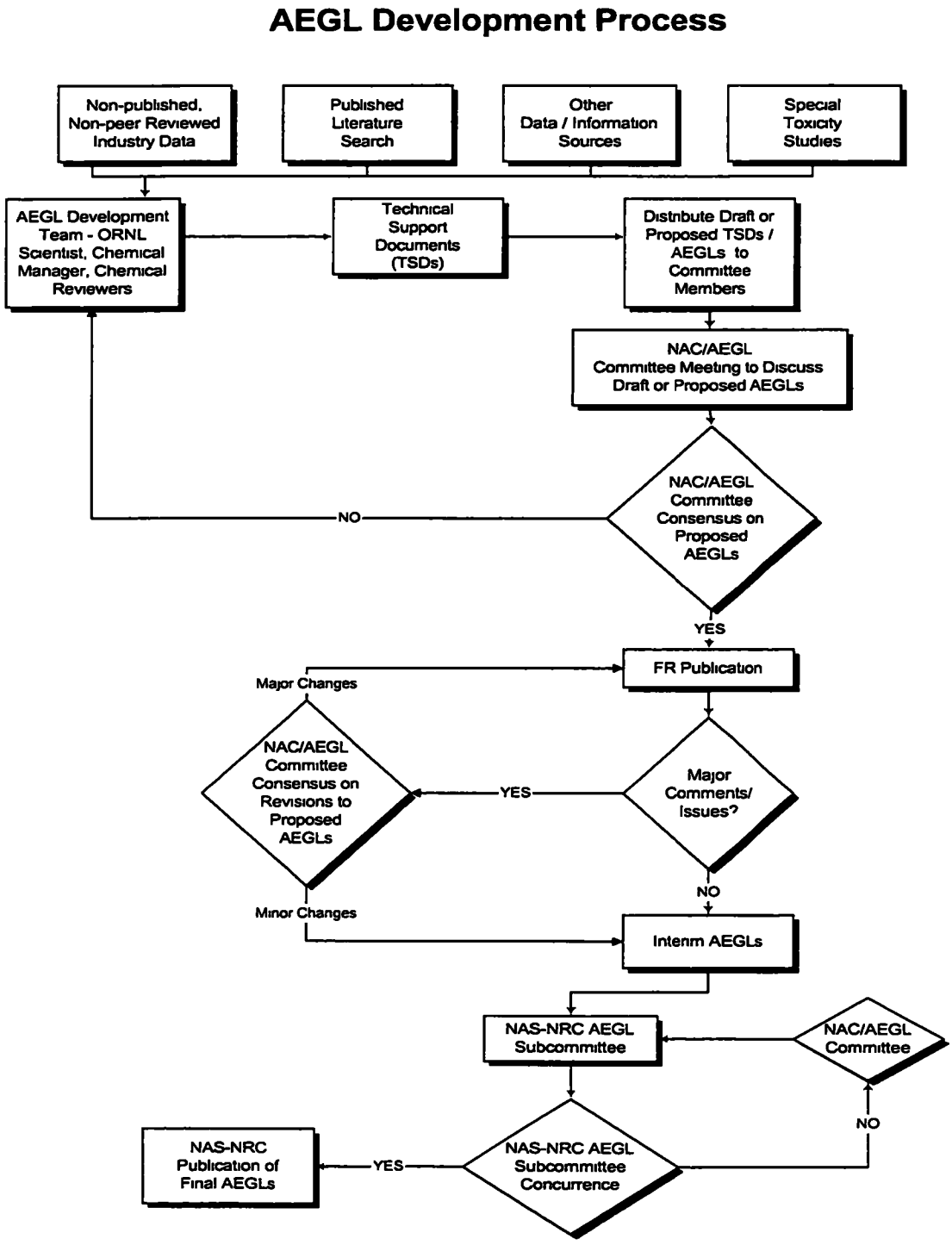
Stage 3: "Interim" AEGLs

Following resolution of relevant issues raised through public review and comment and subsequent approval of the Committee, the AEGL values are classified as "Interim". The "Interim" AEGL status represents the best efforts of the NAC/AEGL Committee to establish exposure limits and the values are available for use as deemed appropriate on an interim basis by federal and state regulatory agencies and the private sector. The "Interim" AEGLs, the supporting scientific rationale, and the TSD are subsequently presented to the U. S. National Academy of Sciences (NAS/AEGL Subcommittee) for review and concurrence. If concurrence cannot be achieved, the NAS/AEGL Subcommittee will submit its issues and concerns to the NAC/AEGL Committee for further work and resolution.

Stage 4: "Final" AEGLs

When concurrence by the NAS/AEGL Subcommittee is achieved, the AEGL values are considered "Final" and published by the U. S. NAS. Final AEGLs may be used on a permanent basis by all federal, state and local agencies and private sector organizations. It is possible that from time to time new data will become available that challenges the scientific credibility of "Final" AEGLs. If this occurs, the chemical will be resubmitted to the NAC/AEGL Committee and recycled through the review process.

1 **FIGURE 4.2-1 THE AEGL DEVELOPMENT PROCESS**
2



4.3 OPERATION OF THE COMMITTEE

The NAC/AEGL Committee meets formally four (4) times each year for two and one-half (2-1/2) days. The meetings are scheduled for each quarter of the calendar year and are generally held in the months of March, June, September, and December. Based on overall cost considerations, the meetings are generally held in Washington, D.C. However, from time to time, committee meetings may be held at other locations for justifiable reasons.

At least 15 days prior to the committee meetings, a notice of the meeting is published in the Federal Register together with a list of chemicals and other matters to be addressed by the Committee and provides dates, times and location of the meetings. The agenda is finalized and distributed to committee members approximately one week prior to the meeting. The agenda also is available to other interested parties at that time, upon request, through the Designated Federal Officer (DFO).

All NAC/AEGL Committee meetings are open to the public and interested parties may schedule individual presentations of relevant data and information by contacting the DFO to establish a date and time. Relevant data and information from interested parties also may be provided to the Committee through the DFO during the period of development of the Draft AEGLs so that it can be considered during the early stage of development. Data and information also may be submitted during the Proposed and Interim stages of AEGL development as well.

The NAC/AEGL Committee meetings are conducted by the Chair who is appointed by the U.S. Environmental Protection Agency in accordance with the Federal Advisory Committee Act (FACA). At the time of the meeting, both the Chair and all other committee members will have received the initial draft and one or more revisions of the Technical Support Document (TSD) and "Draft", "Proposed", or "Interim" AEGL values for each chemical on the agenda. Reviews, comments, and revisions are continuous up to the time of the meeting and committee members are expected to be familiar with the "Draft", "Proposed", or "Interim" AEGLs, supporting rationale, and other data and information in each TSD and to participate in the resolution of residual issues at the meeting. Procedures for the AEGL Development Teams and the other Committee members regarding work on AEGLs in the Proposed or Interim status are similar to those for Draft AEGLs.

All decisions of the NAC/AEGL Committee related to the development of Draft, Proposed, Interim, and Final AEGLs and their supporting rationale are made by consensus or a minimum of two-thirds (2/3) majority of a quorum of committee members. A quorum of the NAC/AEGL Committee is defined as fifty-one percent (51%) or more of the total NAC/AEGL Committee membership in attendance.

The highlights of each meeting are recorded by the scientists who draft the Technical Support Documents and written minutes are prepared, ratified and maintained in the

Committee's permanent records. Deliberations of each meeting also are tape-recorded and stored in the Committee's permanent records by the Designated Federal Officer (DFO) for future reference as necessary.

All Proposed AEGL values and supporting scientific rationale are published in the Federal Register. Review and comment by interested parties and the general public are requested and encouraged. The Committee's response to official comments on Federal Register notices on Proposed AEGL values consists of the discussions and deliberations that take place during the Committee meetings for elevating the AEGLs from "Proposed" to "Interim" status. This information is reflected on the tapes and in the minutes of the meetings and will be maintained for future reference. Changes in the Proposed AEGL values and the supporting rationale that are considered appropriate by the NAC/AEGL Committee based on Federal Register Comments will be made prior to elevating the AEGLs to Interim status.

As previously mentioned a "Standing Operating Procedures" Workgroup (SOP Workgroup) was established in March, 1997 to document, summarize, and evaluate the various procedures, methodologies, and guidelines employed by the Committee in the gathering and evaluation of scientific data and information and the development of the AEGL values. The SOP Workgroup performs a critical function by continually providing the Committee with detailed information on the Committee's interpretation of the NAS guidelines and the approaches the Committee has taken in the derivation of each AEGL value for each chemical addressed. This documentation enables the Committee to continually assess the basis for its decision-making, insure consistency with the NAS guidelines, and maintain the scientific credibility of the AEGL values and accompanying scientific rationale. This ongoing effort is continuously documented and is identified as the "SOP Manual".

4.4 ROLE OF THE DIRECTOR OF THE AEGL PROGRAM

The Director has the overall responsibility for the AEGL Program, including the NAC/AEGL Committee and its interface with other programs and organizations in the public and private sectors nationally and internationally. More specifically he is responsible for the overall management of the AEGL Program as it relates to:

- NAC/AEGL Committee and AEGL Program objectives of scientific credibility, quality, productivity and cost effectiveness.

- AEGL Program resource needs.

- Fostering a collaborative spirit among Committee members, Staff Scientists of the organization which drafts Technical Support Documents, and interested parties from all participating organizations in the public and private sectors.

- Matters related to the U. S National Academy of Sciences.

- Expanding the scope of the AEGL Program, including international participation.

4.5 ROLE OF THE DESIGNATED FEDERAL OFFICER

The Designated Federal Officer (DFO) serves as the administrative officer of the Committee to insure that all operations, processes, and general precedures function properly and efficiently. The DFO serves as an executive secretariat to the NAC/AEGL Committee and has the responsibility for:

- Effective communication/coordination with NAC/AEGL Committee members, the Committee Chair, the organization which drafts Technical Support Documents, and interested parties in the public and private sector.

- Day-to-day administrative management of the NAC/AEGL Committee with respect to the agenda for future meetings, distribution of Technical Support Documents and other correspondence with Committee members, maintenance of meeting minutes, tapes of meetings and other important Committee records, funding and other financial matters and Committee membership matters.

- Administrative management of quarterly meetings including responsibility for all Federal Register Notices related to NAC/AEGL Committee activities, minutes and decision making records, meeting venues, facilities, and equipment, as well as the assurance that the meetings are held in compliance of the Federal Advisory Committee Act (FACA).

- Ensuring compliance with the FACA on all matters that extend beyond the quarterly meetings such as the submission of appropriate reports to the U.S. Office of Management and Budget (OMB) and the Library of Congress.

4.6 ROLE OF THE NAC/AEGL COMMITTEE CHAIR

The NAC/AEGL Committee Chair is appointed by EPA as specified in the Federal Advisory Committee Act (FACA) and is selected from the Committee membership. The Chair's responsibilities include conducting and directing specific activities to insure the effective and efficient conduct of business by the Committee:

- Support in the planning and preparation of upcoming meetings by collaborating with the AEGL Program Director, the DFO and the organization which drafts Technical Support Documents, including the review of the meeting agenda.

- Manage the NAC/AEGL Committee meetings in an effective and efficient manner to

insure completion of the agenda for each meeting.

- Attempt to reach a consensus of the Committee by insuring adequate time for presentation of differing opinions and focusing on the major issues to break deadlocks or stalemates.

- Participation in scientific matters on AEGLs as related to the U. S. National Academy of Sciences.

- Participate with the AEGL Progam Director and the DFO in evaluating and improving Committee activities and expanding the scope of the AEGL Program.

4.7 CLASSIFICATION OF THE STATUS OF AEGL VALUES

Draft AEGL Values are AEGL values proposed by the AEGL Development Team (see section 4.8) prior to the full NAC/AEGL Committee discussion and approval.

Proposed AEGL Values are AEGL values which have been formally approved and elevated to "Proposed" status by a consensus or two-thirds majority of a quorum of the NAC/AEGL Committee.

Interim AEGL Values are AEGL values formally approved by the NAC/AEGL Committee and elevated to "Interim" status after publication in the Federal Register, response to comments, and appropriate adjustments made by the Committee. These "Interim" AEGLs are forwarded to the Committee on Toxicology, National Research Council, National Academy of Sciences for review and comment by the Subcommittee on Acute Exposure Guideline Levels (NAS/AEGL Subcommittee).

Final AEGL Values are AEGL values which have been reviewed and finalized by the U. S. National Academy of Sciences (NRC NAS) and are published inder the auspices of the NAS.

4.8 ROLE OF AEGL DEVELOPMENT TEAMS

Each AEGL Development Team consists of a Staff Scientist from the organization which drafts Technical Support Documents and a Chemical Manager and two Chemical Reviewers, who are members of the NAC/AEGL Committee. The primary function of the NAC/AEGL Development Team is to provide the NAC/AEGL Committee with Draft AEGL values and a Technical Support Document (TSD) containing relevant data and information on the chemical and the derivation of the Draft AEGLs. The Staff Scientist provides the initial effort by identifying and preliminarily evaluating available data from varied resources including on-line literature databases, other databases, journal reviews, secondary source reviews, unpublished data, federal and state documents and other sources, including accounts of accidents in the workplace or in the community (see Section 2.3). Interaction takes place among the Chemical Manager, the Chemical Reviewers, and the Staff Scientist during the development of the TSD and the Draft AEGL values. The resulting document is then distributed and reviewed by Committee Members prior to a formal meeting and attempts are made to resolve issues of concern expressed by Committee Members prior to distribution of the TSD to the NAC/AEGL Committee and formal presentation and discussion at a Committee meeting.

4.8.1 Role of a Chemical Manager

The Chemical Manager has the overall responsibility for the development of the "Draft", "Proposed", and "Interim" AEGL values and their presentation to the rest of the NAC/AEGL Committee and to the NAS Committee for evaluation of "Final" AEGLs. The Chemical Mangers serve on a rotating basis as the Committee's principal representative on the AEGL Development Team for a specific chemical. The Chemical Manager in turn selects two Committee members to serve as Chemical Reviewers.

The Chemical Manager collaborates with the Staff Scientist and the Chemical Reviewers on the development of the AEGLs, the supporting rationale, and the Technical Support Documents. In instances where the Chemical Manager has accepted the responsibilities, taken ownership for the AEGL values, resolved scientific issues, and led the discussions with Committee members, the Committee has moved rapidly toward the development of a consensus. Where the Chemical Manager's role has been less decisive, the Committee's deliberations have been more protracted, less focused, and highly inefficient. Implicit in the description of the Chemical Manager's role is the expectation that he/she will work with the Staff Scientist, the Chemical Reviewers, and the rest of the Committee members to develop exposure guidance levels that are appropriate and scientifically credible. It is expected that the Chemical Manager will achieve a consensus within the AEGL Development Team on the issues related to the development of the AEGL values prior to the meeting of the full Committee. Further, as time permits, the Chemical Manager will attempt to resolve issues raised by individual Committee Members prior to the scheduled Committee meeting.

The following is a summary outline of specific activities and responsibilities of the Chemical Manager within the NAC/AEGL Committee:

- To participate as the leader of the ad hoc AEGL Development Team.

- To select and utilize two Chemical Reviewers as technical support.

- To provide direct support to the Staff Scientist assigned to the chemical in the development of the Technical Support Documents (TSD), the "Draft" AEGL values, and the supporting rationale.

- To serve as liaison among Committee members and the Staff Scientist during the development of draft AEGL values and the Technical Support Document.

- To resolve scientific issues prior to the Committee meetings such as:
  - Completeness of data gathering (published/unpublished).
  - Selection of key and supporting data (following guidelines).
  - Interpretation of data.
  - Credibility of AEGL values (use of appropriate methodology).
  - Validity of scientific rationale for AEGLs.
  - Other (as necessary for development of scientifically credible AEGL values).

- To seek consensus of Committee members by resolving issues with individual Committee members prior to the Committee meeting.

- To frame important scientific issues related to the chemical and the AEGLs for presentation at the Committee meeting (i.e. significant issues that cannot be resolved before the meeting).

- To participate in the presentation of AEGL values, supporting rationale and important issues at the Committee meeting in collaboration with the Staff Scientist.

- To oversee appropriate follow-up activities:
  - Revisions as appropriate (AEGL values, TSD, rationales).
  - Toxicity testing.
  - FR Notice comments (conversion of "Proposed" to "Interim" values).
  - Preparation of AEGL proposal to NAS.

4.8.2 Role of a Chemical Reviewer

- To participate as a member of the ad hoc AEGL Development Team

- To conduct a detailed review of the assigned document and key references.

- To assist the Chemical Manager and Staff Scientist in evaluating the data, the candidate AEGLs, and the scientific rationale for their support.

- To participate actively in discussions of the document during AEGL Committee meetings.

- To stand in for the Chemical Manager if and when he/she is unable to perform his/her duties.

4.8.3 Role of an Staff Scientist at the Organization which Drafts Technical Support Documents

The Staff Scientist has the primary responsibility for data gathering, data evaluation, identification of potential key data and supporting data, identification of potential methodologies, calculations, and extrapolations, and the preparation of the Technical Support Document. This includes the following tasks:

- To participate as a member of the ad hoc AEGL Development Team

- To participate with the others on the AEGL Development Team in the development of "Draft" AEGL values and their presentation at the NAC/AEGL Committee meetings

- To prepare Technical Support Documents (TSD) in a timely manner and make appropriate revisions based upon discussions and decisions of the AEGL Development Team and later based upon the discussions and decisions of the NAC/AEGL Committee.

- To develop and maintain a data file on the chemical substance.

- To present a summary of the data and information on the substance in collaboration with the Chemical Manager at the AEGL Committee meetings.

- To provide continuing support to an assigned chemical through the "Draft," "Proposed," "Interim," and "Final" stages of AEGL development, including preparation for, and response to, Federal Register Notice review and comment.

4.9 ROLE OF NAC/AEGL COMMITTEE MEMBERS

- To review all Technical Support Documents in advance of meetings and to work out issues with the Chemical Manager at the earliest possible date. The importance of resolving issues before Committee meetings is greatly emphasized to increase the efficiency and productivity of the meetings.

- To circulate Technical Support Documents to other qualified scientists within their respective organizations or other organizations as appropriate to broaden the evaluation by the scientific community.

- To serve as experts in specific areas or on specific scientific issues (e.g. sensitive human sub-populations, etc.) as a member of an ad hoc task force under the SOP Workgroup chair.

- To volunteer as a Chemical Manager at least once a year and to select chemicals where a significant contribution to the development of credible AEGL values can be made based on special knowledge, expertise, or past experience.

- To assist in the application of AEGLs in appropriate programs within the organization the Committee member represents.

- To make suggestions for modification or expansion of the Chemical Priority List by providing lists of chemicals and supporting rationale for their priority to the Designated Federal Officer (DFO).

- To attend all scheduled NAC/AEGL Committee meetings and to participate in the discussions and decision making of all AEGL values. AEGL values are approved or disapproved by a vote of 2/3 majority of a quorum, with a quorum defined as the presence of more than 50 percent of the total NAC/AEGL Committee membership..

4.10 ROLE OF THE ORGANIZATION THAT DRAFTS TECHNICAL SUPPORT DOCUMENTS

The role of the organization that drafts the TSDs is to provide the principal technical support in gathering and evaluating the relevant scientific data and information from all sources, including preparation and/or revision of the Technical Support Documents (TSDs) following the guidance provided in this SOP Guidance Manual. As a member of the AEGL Development Team, to collaborate with the Chemical Manager and Chemical Reviewers in the preparation and distribution of "Draft" AEGLs, the supporting rationale, and the TSDs for the NAC/AEGL Committee members. Provide continuing technical and administrative support to assigned chemicals through the "Draft," "Proposed," "Interim," and "Final" stages of AEGL development, with revisions based upon the consensus or majority opinion of the NAC/AEGL Committee and the NAS/AEGL Subcommittee.

To provide the Staff Scientists, the administrative personnel, and the facilities and equipment necessary for data gathering, maintenance of databases, dissemination of relevant information to Committee members, presentations or co-presentations (with Chemical Managers) at the NAC/AEGL Committee meetings, development and revisions of TSDs, preparation of submissions to the Federal Register, summarization of Federal Register (F.R.) comments and identification of important scientific issues, presentations to the Committee on F.R. comments, and preparation of technical information to be entered on the Internet.

To distribute the TSDs to companies and other interested parties as directed by the DFO after review and comment by the NAC/AEGL Committee. This distribution to interested parties will be only by request through the Designated Federal Officer (DFO). This initial distributed version will be without the AEGL values and the rationale used to derive them and will occur between 1-14 days prior to the Committee meeting.

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APPENDIX A. NAC/AEGL PROGRAM PERSONNEL.

ADMINISTRATIVE MANAGEMENT:

Roger Garrett ..... Director, AEGL Program, U.S. Environmental Protection Agency
Paul S. Tobin ..... Designated Federal Officer, NAC/AEGL Committee,
..... U.S. Environmental Protection Agency

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George Rusch ..... Chair, Honeywell, Inc.
Ernest Falke ..... Chair, SOP Workgroup, U S. Environmental Protection Agency

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Steven Barbee ..... Olin Corporation
Lynn Beasley ..... U.S. Environmental Protection Agency (5204G)
David Belluck ..... Minnesota Pollution Control Agency
Robert Benson ..... U.S. Environmental Protection Agency Region VIII
Jonathan Borak ..... American College of Occupational and Environmental Medicine
..... (ACOEM)
William Bress ..... Vermont Department of Health
George Cushmac ..... Department of Transportation
Larry Gephart ..... Exxon Mobil Biomedical Sciences, Inc.
Doan Hanson ..... Brookhaven National Laboratory (DOE Alternate)
John P. Hinz ..... Armstrong Laboratory/Occupational and Environmental Health Directorate (AF)
Jim Holler ..... Agency for Toxic Substances Disease Registry
Thomas C. Hornshaw ..... Illinois Environmental Protection Agency
Nancy K. Kim ..... New York State Department of Health
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John Morawetz ..... International Chemical Workers Union
Richard Niemeier ..... National Institute for Occupational Safety and Health
Marinelle Payton ..... Harvard Medical School
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George Rodgers ..... American Association of Poison Control Centers (AAPCC)
Michelle Schaper ..... Mine Safety and Health Administration
Robert Snyder ..... Environmental and Occupational Health Sciences Institute
Thomas J. Sobotka ..... Food and Drug Administration HFS-507
Kenneth Still ..... Medical Service Corp/U.S. Navy
Judy Strickland ..... U.S. Environmental Protection Agency (Pending)
Richard Thomas ..... International Ctr for Environmental Hlth
Thomas Tuccinardi ..... U.S. Department of Energy

PAST COMMITTEE MEMBERS

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Luz Claudio ..... Mt. Sinai Medical Center
Benjamin Jackson ..... Consultant
William Pepelko ..... U.S. Environmental Protection Agency
Patricia Talcott ..... University of Idaho, Dept of Food Science & Toxicology

APPENDIX B. PRIORITY LISTS OF CHEMICALS

A master list of approximately 1,000 acutely toxic chemicals was initially compiled through the integration of individual priority lists of chemicals submitted by each U. S. federal agency placing a representative on the Committee. The master list was subsequently reviewed by individuals from certain state agencies and representatives from organizations in the private sector and modified as a result of comments and suggestions received. The various priority chemical lists were compiled separately by each federal agency based on their individual assessments of the hazards, potential exposure, risk, and relevance of a chemical to their programmatic needs.

On May 21, 1997, a list of 85 chemicals was published in the Federal Register. This list identified those chemicals to be of highest priority across all U. S. federal agencies and represented the selection of chemicals for AEGL development by the NAC/AEGL Committee for the first two to three years of the program. The Committee has now addressed these chemicals and they are presently in the Proposed, Interim, or Final stages of development. Certain chemicals did not contain an adequate database for AEGL development and, consequently, are on hold pending decisions regarding further toxicity testing. This initial "highest" priority list of 85 chemicals is shown below.

A second "working list" of approximately 100 priority chemicals is being selected from the original master list, or from new, high priority candidate chemicals submitted by U. S. Agencies and organizations and by OECD member countries that are planning to participate in the AEGL Program. Although "working lists" will be published in the U. S. Federal Register and elsewhere from time-to-time to indicate the NAC/AEGL Committee's agenda, the priority of chemicals addressed, and , hence, the "working list" is subject to modification if priorities of the NAC/AEGL Committee or individual stakeholder organizations, including international members, change during that period.

Initial List of 85 Priority Chemicals for Acute Exposure Guideline Level (AEGL) Development*

ORGANIZATION LISTS USED TO COMPILE THE MASTER LIST AND THE INITIAL LIST OF 85 PRIORITY CHEMICALS

[1]ATSDR Medical Managment	Agency for Toxic Substances and Disease Registry M = Chemicals with an ATSDR Medical Management Guideline T = Chemicals with an ATSDR Toxicology Profile

[2]DOD	Department of Defense A = Army Toxicity Summary Chemical C = Chemical Weapons Convention Schedule 3.A Toxic Chemical Cs = Chemical Stockpile Emergency Preparedness Program (CSEPP) Chemical I = Air Force Installation Restoration Program Chemical N = Navy Chemical S = Strategic Environmental Research and Development Program (SERDP) Chemical
[3]DOE SCAPA	DOE Subcommittee for Consequence Assessment and Protective Action Chemical
[4]DOT ERP	Department of Transportation Emergency Response Guidebook P = Priority DOT ERG Chemical O = Other ERG Chemical
[5]EPA CAA 112b	Environmental Protection Agency Clean Air Act 112b Chemical
[6]EPA CAA 112r	Environmental Protection Agency Clean Air Act 112b Chemical (+ = SARA s.302 also)
[7]EPA Superfund	Environmental Protection Agency Superfund Chemical
[8]OSHA PSM	OSHA Process Safety Management Chemical
[9]OSHA STEL	OSHA Short-term Exposure Limit Chemical
[10]NIOSH IDLH	NIOSH Immediately Dangerous to Life or Health Chemical
[11]Seveso Annex III	International Seveso Convention List

* The initial list of 85 priority chemicals shown below has been created by identifying the highest priority hazardous chemicals from the Master List. This initial list is a starting point for the development of AEGL values by the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Chemicals (NAC/AEGL). However, the list of chemicals is subject to modification, pending changes in priorities recommended by the various stakeholders that make up the NAC/AEGL. While it is anticipated that most of these chemicals will remain as

high priority for AEGL development, changes to the list could occur. The NAC/AEGL hopes to select 30 to 40 chemicals per year to address in the AEGL development process. Consequently, the initial list will expand as the NAC/AEGL continues to address chemicals of interest to its member organizations.

TABLE B-1. PRIORITY LIST OF CHEMICALS

CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Superfund	[8]OSHA PSM	Seveso Annex III	[9]OSHA STEL	[10]NIOSH IDLH
56-23-5	Carbon tetrachloride	T	AIS			X		X				X
57-14-7	1,1-Dimethyl hydrazine				P	X	X+		X			X
60-34-4	Methyl hydrazine				P	X	X+	X	X			X
62-53-3	Aniline	M			P	X	+	X				X
67-66-3	Chloroform	T	AIS			X	X+	X				X
68-12-2	Dimethylformamide			X		X						
71-43-2	Benzene	X	AIS	X		X		X				
71-55-6	1,1,1-Trichloroethane	T	X	X		X		X				
74-90-8	Hydrogen cyanide	M	C		P	X	X+		X	X		X
74-93-1	Methyl mercaptan	T			P		X+		X			X
75-09-2	Methylene chloride	MT	AIS	X		X		X				
75-21-8	Ethylene oxide	MT			P	X	X+		X	X		X
75-44-5	Phosgene	M	C		P	X	X+		X	X		X
75-55-8	Propyleneimine					X	X+			X		X
75-56-9	Propylene oxide					X	X+			X		X

	CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Superfund	[8]OSHA PSM	Seveso Annex III	[9]OSHA STEL	[10]NIOSH IDLH
1	75-74-1	Tetramethyllead					X	X+		X	X		X
2	75-77-4	Trimethychlorosilane						X+					
3	75-78-5	Dimethyldichlorosilane			X			X+		X			
4	75-79-6	Methyltrichlorosilane						X+		X			
5	78-82-0	Isobutyronitrile						X+					
6	79-01-6	Trichloroethylene	MT	AIS	X		X		X				
7	79-21-0	Peracetic acid						X+		X	X		
8	79-22-1	Methy chloroformate						X+					
9	91-08-7	Toluene 2,6-diisocyanate	M					X+					
10	106-89-8	Epichlorohydrin					X	X+					X
11	107-02-8	Acrolein	T			P	X	X+	X	X	X	X	X
12	107-11-9	Allyl amine				P		X+		X	X		
13	107-12-0	Propionitrile						X+					
14	107-15-3	Ethylenediamine						X+					X
15	107-18-6	Allyl alcohol				P		X+			X	X	X
16	107-30-2	Chloromethyl methyl ether				O	X	X+		X	X		

	CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Super fund	[8]OSHA PSM	Seves o Annex III	[9]OSHA STEL	[10]NIOSH IDLH
1	108-23-6	Isopropyl chloroformate				P		X+					
2	108-88-3	Toluene	MT	AINS			X		X				
3	108-91-8	Cyclohexylamine						X+					
4	109-61-5	Propyl chloroformate				O		X+					
5	110-00-9	Furan						X+	X	X			
6	110-89-4	Piperidine						X+					
7	123-73-9	Crotonaldehyde, (E)						X+					X
8	126-98-7	Methacrylonitrile				O		X+		X			
9	127-18-4	Tetrachloroethylene	T	AIS	X		X		X				
10	151-56-4	Ethyleneimine				P	X	X+			X	X	X
11	302-01-2	Hydrazine	T	I	X		X	X+					X
12	353-42-4	Boron triflouride compound with methyl ether (1 1)						X+					X
13	506-77-7	Cyanogen chloride						X+		X			
14	509-14-8	Tetranitromethane						X+					X
15	540-59-0	1,2-Dichloroethylene	T		X								X
16	540-73-8	1,2-Dimethylhydrazine				P	X	X+		X			X

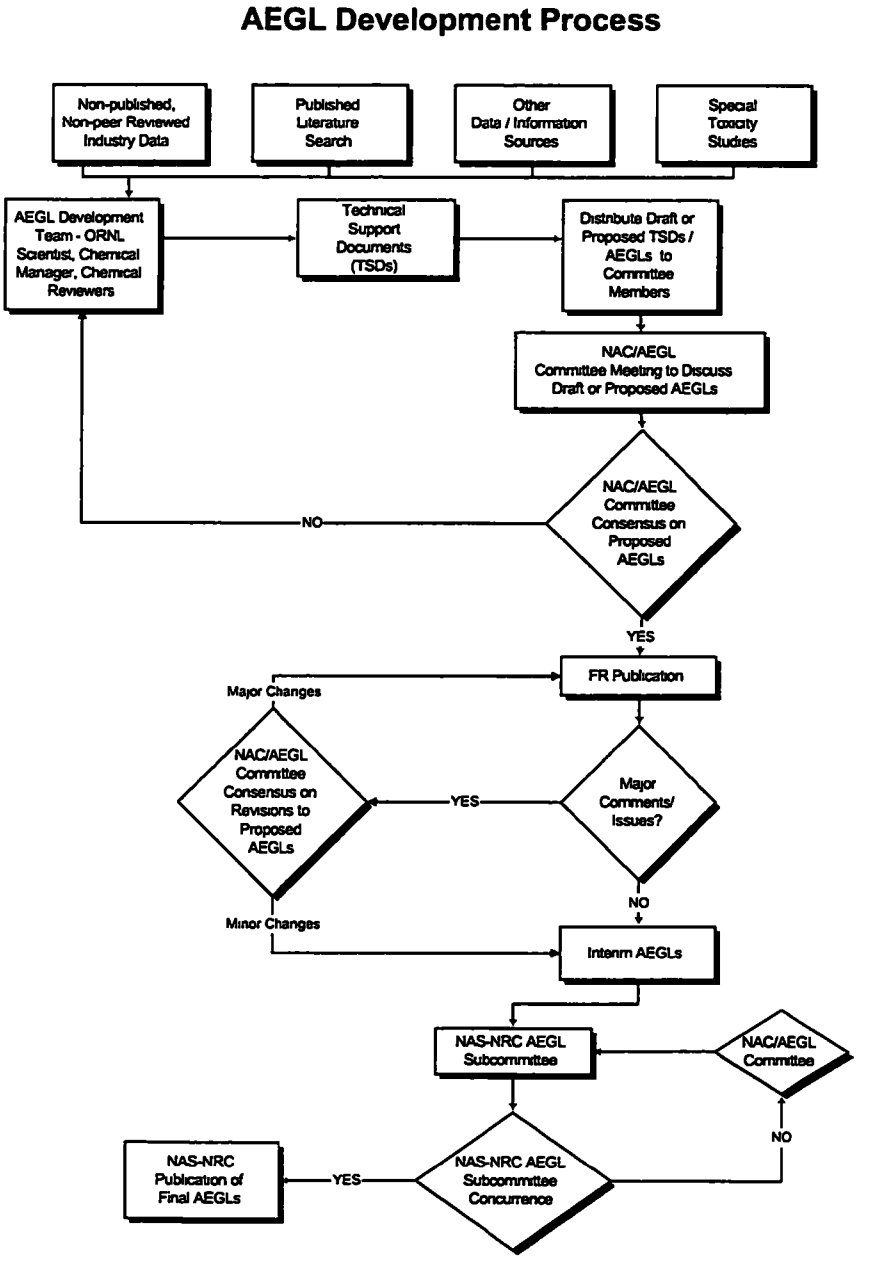
	CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Superfund	[8]OSHA PSM	Seveso Annex III	[9]OSHA STEL	[10]NIOSH IDLH
1	584-84-9	Toluene 2,4-diisocyanate	M				X	X+	X			X	X
2	594-42-3	Perchloromethylmercaptan						X+		X	X		X
3	624-83-9	Methyl isocyanate				P	X	X+		X	X		X
4	811-97-2	HFC 134A (1,1,1,2-Tetrafluoroethane)		N									
5	814-68-6	Acrylyl chloride						X+		X			
6	1330-20-7	Xylenes (mixed)	X	AIN			X		X				
7	1717-00-6	HCFC 141b (1,1-Dichloro-1-fluoroethane)		N									
8	4170-30-3	Crotonaldehyde cis & trans mixture				P		X+					X
9	6423-43-4	Propylene glycol dinitrate (Otto Fuel II)	T	Navy									
10	7446-09-5	Sulfur dioxide				P		X+		X	X	X	X
11	7446-11-9	Sulfur trioxide				P		X+		X	X		
12	7647-01-0	Hydrogen chloride				P	X	X+	X	X	X	X	X
13	7647-01-0	Hydrochloric acid				P	X	X+	X	X		X	X
14	7664-39-3	Hydrogen fluoride	M			P	X	X+		X	X	X	X

	CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Super fund	[8]OSHA PSM	Seves o Annex III	[9]OSHA STEL	[10]NIOSH IDLH
1	7664-41-7	Ammonia	MT					X+	X	X	X		X
2	7664-93-9	Sulfuric acid				P		+	X				X
3	7697-37-2	Nitric acid			X	P		X+		X		X	X
4	7719-12-2	Phosphorus trichloride				P		X+		X		X	X
5	7726-95-6	Bromine				P		X+		X	X	X	X
6	7782-41-4	Fluorine				P		X+		X			X
7	7782-50-5	Chlorine	M			P	X	X+	X	X	X	X	X
8	7783-06-4	Hydrogen sulfide	M				X	X+		X			
9	7783-60-0	Sulfur tetrafluoride				P		X+					
10	7783-81-5	Uranium hexafluoride			X								
11	7784-34-1	Arsenous trichloride				P		X+					
12	7784-42-1	Arsine	M		X	P	X	X+	X	X	X		X
13	7790-91-2	Chlorine trifluoride			X	O				X			X
14	7803-51-2	Phosphine	M		X	P	X	X+		X	X	X	X
15	8014-95-7	Oleum				P		X+		X			
16	10025-87-3	Phosphorus oxychloride				O		X+		X			

	CAS NO.	CHEMICAL	[1]ATSDR	[2]DOD	[3]DOE SCAPA	[4]DOT ERG	[5]EPA CAA 112b	[6]EPA CAA 112r	[7]EPA Superfund	[8]OSHA PSM	Seveso Annex III	[9]OSHA STEL	[10]NIOSH IDLH
1	10049-04-4	Chlorine dioxide						X		X		X	X
2	10102-43-9	Nitric oxide				P		X+		X			X
3	10102-44-0	Nitrogen dioxide			X	X		X		X			
4	10294-34-5	Boron trichloride				P		X+		X			
5	13463-39-3	Nickel carbonyl				P	X	X+		X	X	X	
6	13463-40-6	Iron, pentacarbonyl-				P		X+		X		X	
7	19287-45-7	Diborane			X	P		X+		X			X
8	25323-89-1	Trichloroethane	T	AS	X		X		X				
9	70892-10-3	Jet fuels (JP-5 and JP-8)		N									
10	163702-07-6	Methyl nonafluorobutyl ether (HFE 7100 component)		N									
11	163702-08-7	Methyl nonafluorobutyl ether (HFE 7100 component)		N									
12													

APPENDIX C. DIAGRAM OF THE AEGL DEVELOPMENT PROCESS

FIGURE C-1 THE AEGL DEVELOPMENT PROCESS



APPENDIX D. GLOSSARY - ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	--	American Association of Poison Control Centers
ACGIH	--	American Conference of Government Industrial Hygienist
ACOEM	--	American College of Occupational and Environmental Medicine
ADI	--	Acceptable Daily Intake
AEGL	--	National Advisory Committee for Acute Exposure Guidelines Levels for Hazardous Substances (AEGL Committee)
AFL-CIO	--	American Federation of Labor - Congress of Industrial Organizations
AIHA	--	American Industrial Hygienist Association
ATSDR	--	Agency for Toxic Substances and Disease Registry (U. S.)
BMC	--	Benchmark Concentration
BMC_{05}	--	Benchmark Concentration, 5% response
BMC_{10}	--	Benchmark Concentration, 10% response
CAAA	--	Clean Air Act Amendments (U. S. EPA)
CAER	--	Community Awareness and Emergency Response
CAS	--	Chemical Abstract Service (U. S.)
CDC	--	Centers for Disease Control and Prevention (U. S. HHS)
CEEL	--	Community Emergency Exposure Levels (U. S. NAS)
CEL	--	Emergency Exposure Limits (U. S. NAS)
CMA	--	Chemical Manufacturers Association (U. S.)
CORR	--	Chemicals on Reporting Rules
COT	--	Committee on Toxicology (U. S. NAS)
Ct or Cxt	--	Measure of cumulative exposure
CURE	--	Chemical Unit Record Estimates
DFO	--	Designated Federal Official
DOD	--	Department of Defense (U. S.)
DOE	--	Department of Energy (U. S.)
DOT	--	Department of Transportation (U. S.)
DTIC	--	Defense Technical Information Center (U. S.)
ECETOC	--	European Chemical Industry Ecology and Toxicology Centre
EEGL	--	Emergency Exposure Guideline Levels (U. S NAS)
EEL	--	Emergency Exposure Limits (U. S. NAS)
Einsatztoleranzwert	--	[Action Tolerance Levels] Federation for the Advancement of German Fire Prevention (Germany)
EPA	--	Environmental Protection Agency (U. S.)
ERP	--	Emergency Response Planning, (U. S.) American Industrial Hygiene Association (AIHA)
ERPG	--	Emergency Response and Planning Guidelines, (U. S.) American

			Industrial Hygiene Association (AIHA)
	FACA	--	Federal Advisory Committee Act (U. S.)
	FDA	--	Food and Drug Administration (U. S.)
	FEDRIP	--	Federal Research in Progress
	FEMA	--	Federal Emergency Management Agency (U. S.)
	FEV_1	--	Forced Expiratory Volume
	FR	--	Federal Register (U. S.)
	FYI	--	For Your Information
	GLP	--	Good Laboratory Practice Standards
	GSA	--	General Services Administration (U. S.)
	HEAST	--	Health Effects Assessment Tables
	HSDB	--	Hazardous Substances Data Base
	HUD	--	Department of Housing and Urban Development (U. S.)
	IARC	--	International Agency for Research on Cancer
	IDLH	--	Immediately Dangerous to Life and Health (U. S. NIOSH)
	IPCS	--	International Programme for Chemical Safety
	IRIS	--	Integrated Risk Information System
	LC_{01}	--	Lethal Concentration, 1 % kill
	LC_{50}	--	Lethal Concentration, 50 % kill
	LCL	--	Lower Confidence Limit
	LOAEL	--	Lowest-observe-adverse effect level
	MAC	--	Mean Alveolar Concentration
	MAC	--	Maximum Acceptable Concentration (The Netherlands)
	MAK	--	[Maximale Arbeitsplatzkonzentration] Maximum Workplace Concentration, 8 hour time weighted average German Research Association (Germany)
	MAK S.	--	Spitzenbegrenzung (Kategorie II,2) [Peak Limit II,2] 30 minute x 2 per day (Germany)
	MCS	--	Multiple Chemical Sensitivity
	MF	--	Modifying Factor
	MLE	--	Maximum Likelihood Estimate
	MLE_{01}	--	Maximum Likelihood Estimate, 1% response
	MTD	--	Maximum Tolerated Dose
	N/A	--	Not Applicable
	NAAQS	--	National Ambient Air Quality Standards, U.S.
	NAC	--	National Advisory Committee
	NAC/AEGL	--	National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee)
	NAS	--	National Academy of Sciences (U. S.)
	NAS/AEGL	--	National Academy of Sciences Subcommittee on Acute Exposure Guideline Levels (NAS/AEGL Subcommittee) (U. S.)
	NASA	--	National Aeronautical and Space Administration (U. S.)

NCI	--	National Cancer Institute (U. S.)
NIOSH	--	National Institute for Occupational Safety and Health (U. S.)
NOAEL	--	No Observed-Adverse-Effect Level
NRC	--	National Resource Council (U. S.)
NSF	--	National Science Foundation (U. S.)
NTIS	--	National Technical Information Services (U. S.)
NTP	--	National Toxicology Program (U. S.)
OECD	--	Organization for Economic Cooperation and Development
ORNL	--	Oak Ridge National Laboratories (U. S.)
OSHA	--	Occupational Safety and Health Administration (U. S.)
OSWER	--	Office of Solid Waste and Emergency Response
PEL-TWA	--	Permissible Exposure Limits - Time Weighted Average (U. S. OSHA)
PEL-STEL	--	Permissible Exposure Limits - Short Term Exposure Limit (U. S. OSHA)
QA	--	Quality Assurance
QC	--	Quality Control
QSARs	--	Quantitative Structure Activity Relationships
REL-STEL	--	Recommended Exposure Limits-Short Term Exposure Limit (U. S. NIOSH)
REL-TWA	--	Recommended Exposure Limits-Time Weighted Average (U. S. NIOSH)
RfC	--	Reference Concentration (U. S. EPA)
RfD	--	Reference Dose (U. S. EPA)
RTECS	--	Registry of Toxic Effects of Chemical Substances
SARA	--	Superfund Amendments and Reauthorization Act (CERCLA)
SMAC	--	Spacecraft Maximum Allowable Concentrations
SOP	--	Standing Operating Procedures Manual
SPEGL	--	Short-term Public Exposure Guideline Levels (U. S. NRC, NAS)
STPL	--	Short Term Public Limits (U. S. NAS)
TARA	--	Toxicology And Risk Assessment Document List (ORNL)
TLV-STEL	--	Threshold Limit Value - Short Term Exposure Limit (U. S. ACGIH)
TLV-TWA	--	Threshold Limit Value - Time Weighted Average (U. S. ACGIH)
TSD	--	Technical Support Document
UF	--	Uncertainty Factor
WEELS	--	Workplace Environmental Exposure Levels (AIHA)

>	Greater than
≥	Greater than or equal to
<	Less than

1	≤		Less than or equal to
2	%		Percent
3			
4	dl	--	Deciliter
5	g or gm	--	Gram
6	hr.	--	Hour
7	um	--	Micrometer
8	ug	--	Microgram
9	mg	--	Milligram
10	min	--	Minute
11	mL	--	Milliliter
12	mm	--	Millimeter
13	ppb	--	Parts per billion
14	ppm	--	Parts per million
15	ppt	--	Parts per trillion
16			

APPENDIX E. EXAMPLE OF A TABLE OF CONTENTS IN A TECHNICAL SUPPORT DOCUMENT

TABLE OF CONTENTS

APPENDIX F. EXAMPLE OF AN EXECUTIVE SUMMARY IN A TECHNICAL SUPPORT DOCUMENT

EXECUTIVE SUMMARY

Dimethylhydrazine occurs as a symmetrical (1,2-dimethylhydrazine) and unsymmetrical (1,1-dimethylhydrazine) isomer. Unless otherwise specified, dimethylhydrazine refers to unsymmetrical dimethylhydrazine in this document. Both compounds are clear, colorless liquids. Unsymmetrical dimethylhydrazine (1,1-dimethylhydrazine) is a component of rocket fuels and is also used as an absorbent for acid gas, as a plant growth control agent, and in chemical synthesis. Although it has been evaluated as a high-energy rocket fuel, commercial use of the symmetrical isomer (1,2-dimethylhydrazine) is limited to small quantities and it is usually considered to be a research chemical. Because data are limited for 1,2-dimethylhydrazine (symmetrical dimethylhydrazine), the AEGL values for both isomers are based upon 1,1-dimethylhydrazine (unsymmetrical). Limited data suggest that 1,1-dimethylhydrazine may be somewhat more toxic than 1,2-dimethylhydrazine.

Data on acute exposures of humans to both isomers of dimethylhydrazine are limited to case reports of accidental exposures. Signs and symptoms of exposure include respiratory irritation, pulmonary edema, nausea, vomiting, and neurological effects. However, definitive exposure data (concentration and duration) were unavailable for these exposures. The limited data in humans suggest that the nonlethal toxic response to acute inhalation of dimethylhydrazine is qualitatively similar to that observed in animals. No information was available regarding lethal responses in humans. In the absence of quantitative data in humans, the use of animal data is considered a credible approach for developing AEGL values.

Toxicity data of varying degrees of completeness are available for several laboratory species, including, rhesus monkeys, dogs, rats, mice, and hamsters (Weeks et al., 1963). Most of the animal studies were conducted using 1,1-dimethylhydrazine, although limited data suggest that 1,2-dimethylhydrazine exerts similar toxic effects. Minor nonlethal effects such as respiratory tract irritation appear to occur at cumulative exposures of <100 ppm-hrs. At cumulative exposures of 100 ppm-hrs, or slightly greater than this level more notable effects have been reported, including, muscle fasciculation, behavioral changes, tremors, and convulsions. Lethality has been demonstrated when cumulative exposures exceed these levels only slightly. The available data suggest that there is a very narrow margin between exposures resulting in no significant toxicity and those causing substantial lethality (LC_{50} ≈ 900-2,000 ppm-hrs).

Developmental toxicity of dimethylhydrazines has been demonstrated in rats following parenteral administration of maternally toxic doses.

Both isomers of dimethylhydrazine have been shown to be carcinogenic in rodents following oral exposure and 6-month inhalation exposure to 1,1-dimethylhydrazine. Increased tumor incidence was observed in mice, although these findings are compromised by the contaminant exposure to dimethylnitrosamine. An increased incidence of lung tumors and hepatocellular carcinomas was also seen in rats but not in similarly exposed hamsters. Inhalation slope factors are currently unavailable.

AEGL-1 values for dimethylhydrazine are not recommended. This is due to inadequate data to develop health-based criteria, and because the concentration-response relationship for dimethylhydrazine indicated a very narrow margin exists between exposures producing no toxic response and those resulting in significant toxicity.

Behavioral changes and muscle fasciculations in dogs exposed for 15 minutes to 360 ppm 1,1-dimethylhydrazine (Weeks et al., 1963) served as the basis for deriving AEGL-2 values. Available lethality data in dogs and rats indicated a near linear temporal relationship (n=0.84 and 0.80 for dogs and rats, respectively). For temporal scaling ($C^1 \times t = k$) to derive values for AEGL-specific exposure durations a linear concentration-response relationship; n=1 was used. This value was adjusted by an uncertainty factor of 30. An uncertainty factor of 3 for interspecies variability was applied because the toxic response to dimethylhydrazine was similar across the species tested. This was especially true for lethality responses among rats, mice, dogs, and hamsters with LC_{50} values for time periods ranging from 5 minutes to 4 hours. A comparison of LC_{50} values for the same exposure durations in these species did not vary more than 3-fold. An uncertainty factor of 10 was used for intraspecies variability. This was based primarily on the variability in the toxic response observed in dogs where responses varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Additionally, experiments by Weeks et al. (1963) indicated that dogs previously stressed by auditory stimuli may have potentiated their response to dimethylhydrazine. Based on these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine as a result of similar stresses.

The AEGL-3 values were derived from the 1-hr LC_{50} (981 ppm) for 1,1-dimethylhydrazine in dogs (Weeks et al., 1963). Because of the steep slope of the dose-response curve of 1,1-dimethyl hydrazine, the 1 hour LC_{50} of 981 ppm was adjusted downward to estimate the lethality threshold of 327 ppm. An uncertainty factor of 3-fold for interspecies variability was applied for several reasons. The 4-hr LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 hr using n=1. The more sensitive species, the dog, was used to derive the AEGL-3 values. An uncertainty factor of 10 for intraspecies variability was used since a broad spectrum of effects were seen including behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals may vary. Following identical exposures, the responses of the dogs varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Temporal scaling as

previously described was applied to obtain exposure values for AEGL-specific exposure periods.

Verified inhalation and oral slope factors were unavailable for dimethylhydrazine. A cancer assessment based upon the carcinogenic potential (withdrawn cancer slope factors) of dimethylhydrazine revealed that AEGL values for a 10^{-4} carcinogenic risk exceeded the AEGL- 2 values that were based on noncancer endpoints. Because the cancer risk for dimethylhydrazine was estimated from nonverified cancer estimates, and because AEGLs are applicable to rare events or single once-in-a-lifetime exposures to a limited geographic area and small population, the AEGL values based on noncarcinogenic endpoints were considered to be more appropriate.

SUMMARY OF AEGL VALUES FOR 1,1- and 1,2-DIMETHYLHYDRAZINES

Classification	30-min	1-hour	4-hour	8-hour	Endpoint(Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	Not recommended due to insufficient data, concentration-response relationships suggest little margin between exposures causing minor effects and those resulting in serious toxicity [a]
AEGL-2 (Disabling)	6 ppm 14.7 mg/m^3	3 ppm 7 4 mg/m^3	0 75 ppm 2 mg/m^3	0 38 ppm 1 mg/m^3	Behavioral changes and muscle fasciculations in dogs exposed to 360 ppm for 15 minutes (Weeks et al , 1963)
AEGL-3 (Lethal)	22 ppm 54 mg/m^3	11 ppm 27 mg/m^3	2 7 ppm 6 6 mg/m^3	1 4 ppm 3 4 mg/m^3	Lethality threshold of 327 ppm for 1 hr estimated from 1-hr LC_{50} in dogs (Weeks et al , 1963)

NR: Not Recommended. Analysis of dimethylhydrazine toxicity data in total revealed that significant toxicity may occur at or below the odor threshold. Furthermore, the available data indicate that there is there an almost nonexistent margin between exposures resulting in no response and those causing lethality. Therefore, AEGL-1values for dimethylhydrazine are not recommended (NR) Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects

[a]Refer to AEGL-1 for hydrazine if hydrazine is also present.

References

Weeks, M.H., Maxey, G.C., Sicks, Greene, E.A. 1963. Vapor toxicity of UDMH in rats and dogs from short exposures. *American Industrial Hygiene Association Journal* 24: 137-143.

APPENDIX G. EXAMPLE OF THE DERIVATION OF AEGL VALUES APPENDIX IN A TECHNICAL SUPPORT DOCUMENT

DERIVATION OF AEGL-1 VALUES

Key study	None. An AEGL-1 was not recommended due to inadequate data for developing health-based criteria and because exposure-response relationships suggest little margin between exposures resulting in no observable adverse effects and those producing significant toxicity. The absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects. In situations where hydrazine may also be present, the AEGL-1 values (0.1 ppm for all exposure periods) for hydrazine should be used.

DERIVATION OF AEGL-2 VALUES

Key study: Weeks et al., 1963

Toxicity endpoint: Dogs exposed to 360 ppm 1,1-dimethylhydrazine for 15 minutes exhibited behavioral changes and muscle fasciculations

Uncertainty factors: An uncertainty factor of 3 for interspecies variability was applied because the toxic response to dimethylhydrazine was similar across the species tested. This was especially true for lethality responses (LC_{50} values for varying time periods ranging from 5 minutes to 4 hours) among rats, mice, dogs, and hamsters. A comparison of LC_{50} values for the same exposure durations in these species did not vary more than 3-fold.
An uncertainty factor of 10 was retained for intraspecies variability (protection of sensitive populations). A broad spectrum of effects were seen which included behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals regarding these effects may vary. Following identical exposures, the responses of the dogs varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. A factor of 10 was also retained because experiments by Weeks et al. (1963) indicated that dogs that had been previously stressed (auditory stimuli) were more sensitive to the adverse effects of dimethylhydrazine.

Calculations:

$$360 \text{ ppm}/30 = 12 \text{ ppm}$$
$$C^1 \times t = k$$
$$12 \text{ ppm} \times 15 \text{ min} = 180 \text{ ppm-min}$$

Time scaling: $C^1 \times t = k$ (ten Berge, 1986)
$(12 \text{ ppm})^1 \times 15 \text{ min} = 180 \text{ ppm-min}$
LC_{50} data were available for 5, 15, 30, 60, and 240-minute exposures in rats and 5, 15, and 60 minutes for the dog. Exposure-response data indicated a near linear concentration-response relationship (n=0 84 for rats, n=0.80 for dogs) For time-scaling, a linear relationship was assumed and a value of n=1 was selected

<u>30-min AEGL-2</u>
$C^1 \times 30 \text{ min} = 180 \text{ ppm-min}$
$C = 6 \text{ ppm}$

<u>1-hr AEGL-2</u>
$C^1 \times 60 \text{ min} = 180 \text{ ppm-min}$
$C = 3 \text{ ppm}$

<u>4-hr AEGL-2</u>
$C^1 \times 240 \text{ min} = 180 \text{ ppm-min}$
$C = 0.75 \text{ ppm}$

<u>8-hr AEGL-2</u>
$C^1 \times 480 \text{ min} = 180 \text{ ppm-min}$
$C = 0.38 \text{ ppm}$

DERIVATION OF AEGL-3 VALUES

Key study: Weeks et al., 1963

Toxicity endpoint: 1-hr LC_{50} of 981 ppm in dogs reduced by a factor of three to 327 ppm as an estimate of a lethality threshold. Weeks et al. (1963) provided data showing that 15-minute exposure of dogs to 36-400 ppm produced only minor, reversible effects (behavioral changes and mild muscle fasciculations)

Uncertainty factors: An uncertainty factor of 3 for interspecies variability was applied because the toxic response to dimethylhydrazine was similar across the species tested. This was especially true for lethality responses (LC_{50} values for varying time periods ranging from 5 minutes to 4 hours) among rats, mice, dogs, and hamsters. A comparison of LC_{50} values for the same exposure durations in these species did not vary more than 3-fold.

An uncertainty factor of 10 was retained for intraspecies variability (protection of sensitive populations). A broad spectrum of effects were seen which included behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals regarding these effects may vary. Following identical exposures, the responses of the dogs varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. A factor of 10 was also retained because experiments by Weeks et al. (1963) indicated that dogs that had been previously stressed (auditory stimuli) were more sensitive to the adverse effects of dimethylhydrazine.

Calculations:

$$327 \text{ ppm}/30 = 10.9 \text{ ppm}$$

$$C^1 \times t = k$$

$$11.9 \text{ ppm} \times 60 \text{ min} = 654 \text{ ppm-min}$$

Time scaling.

$C^1 \times t = k$ (ten Berge, 1986)

$11.9 \text{ ppm}^1 \times 60 \text{ min} = 654 \text{ ppm-min}$

LC_{50} data were available for 5, 15, 30, 60, and 240-minute exposures in rats and 5, 15, and 60 minutes for the dog. Exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats, n=0 80 for dogs). For time-scaling, a linear relationship was assumed and a value of n=1 was selected.

30-min AEGL-2

$C^1 \times 30 \text{ min} = 654 \text{ ppm-min}$

$C = 22 \text{ ppm}$

1-hr AEGL-2

$C^1 \times 60 \text{ min} = 654 \text{ ppm-min}$

$C = 11 \text{ ppm}$

4-hr AEGL-2

$C^1 \times 240 \text{ min} = 654 \text{ ppm-min}$

$C = 2.7 \text{ ppm}$

8-hr AEGL-2

$C^1 \times 480 \text{ min} = 654 \text{ ppm-min}$

$C = 1.4 \text{ ppm}$

APPENDIX H. EXAMPLE OF A TIME SCALING CALCULATIONS APPENDIX IN A TECHNICAL SUPPORT DOCUMENT

APPENDIX B

TIME SCALING CALCULATIONS FOR DIMETHYLHYDRAZINE AEGLS

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law (NRC, 1993a) or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs t. Ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, these workers showed that the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where n = 1. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

Two data sets of LC_{50} values for different time periods of exposure were analyzed using a linear regression analysis of the log-log transformation of a plot of C vs t to derive values of n for dimethylhydrazine.

Dog data from Weeks et al.,1963

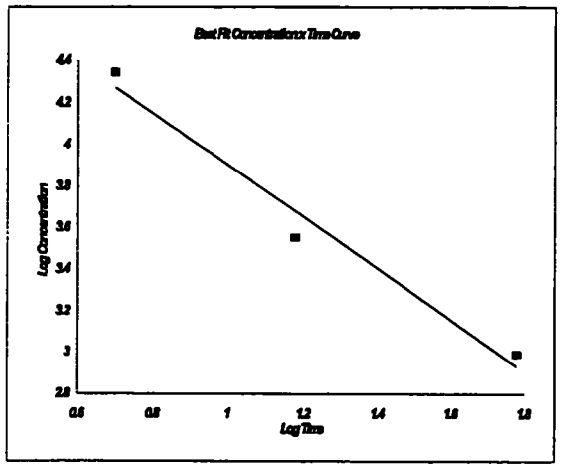
The LC_{50} values for 5, 15, and 60-minute exposures were 22,300, 3580, and 981 ppm, respectively.

Time	Conc.	Log Time	Log Conc.
5	22300	0.6990	4.3483
15	3580	1.1761	3.5539
60	981	1.7782	2.9917

n = 0.8

Calculated LC_{50} values:

Minutes	Conc.
30	2036.15
60	860.12
240	153.48
480	64.83



Rat data from Weeks et al., 1963

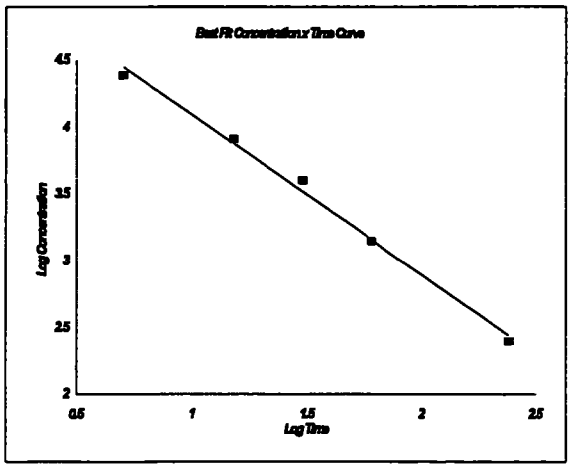
For the 5, 15, 30, 60, and 240-minute exposure periods, LC_{50} values of 24,500, 8,230, 4,010, 1,410, and 252 ppm were reported by the study authors.

Time	Conc.	Log Time	Log Conc.
5	24500	0.6990	4.3892
15	8230	1.1761	3.9154
30	4010	1.4771	3.6031
60	1410	1.7782	3.1492
240	252	2.3802	2.4014

n = 0.84

Calculated LC_{50} values:

Minutes	Conc.
30	3323.28
60	1449.93
240	276.00
480	120.42



APPENDIX I. EXAMPLE OF A CARCINOGENICITY ASSESSMENT APPENDIX IN A TECHNICAL SUPPORT DOCUMENT

CARCINOGENICITY ASSESSMENT OF DIMETHYLHYDRAZINE

Slope factors for 1,1-dimethylhydrazine and 1,2-dimethylhydrazine were available but have been withdrawn from the U.S. EPA Integrated Risk Information System (IRIS). For a preliminary carcinogenicity assessment, the withdrawn inhalation slope factor for 1,1-dimethylhydrazine (cited in ATSDR, 1994) will be used. The assessment follows previously described methodologies (NRC, 1985; Henderson, 1992).

The withdrawn slope factor for 1,1-dimethylhydrazine was 3.5 $(mg/kg\text{-}day)^{-1}$ which, based upon a human inhalation rate of 20 m^3/day and a body weight of 70 Kg, is equivalent to 1 $(mg/m^3)^{-1}$.

To convert to a level of monomethylhydrazine that would cause a theoretical excess cancer risk of 10^{-4}:

$$\text{Risk of } 1 \times 10^{-4} = (1 \times 10^{-4}/1) \times 1\ mg/m^3 = 1 \times 10^{-4}\ mg/m^3$$
(virtually safe dose)

To convert a 70-year exposure to a 24-hour exposure:

$$\text{24-hr exposure} = d \times 25{,}600$$
$$= (1 \times 10^{-4}\ mg/m^3) \times 25{,}600 \text{ days}$$
$$= 2.56\ mg/m^3$$

To account for uncertainty regarding the variability in the stage of the cancer process at which monomethylhydrazine or its metabolites may act, a multistage factor of 6 is applied (Crump and Howe, 1984):

$$(2.56\ mg/m^3)/6 = 0.43\ mg/m^3\ (0.18\ ppm)$$

Therefore, based upon the potential carcinogenicity of monomethylhydrazine, an acceptable 24-hr exposure would be 0.9 mg/m^3 (0.5 ppm).

If the exposure is limited to a fraction (f) of a 24-hr period, the fractional exposure becomes 1/f x 24 hrs (NRC, 1985).

24-hr exposure = 0.43 mg/m^3 (0.18 ppm)
8-hr = 1.3 mg/m^3 (0.5 ppm)

4-hr	=	2.6 mg/m^3 (1.1 ppm)
1-hr	=	10.3 mg/m^3 (4.2 ppm)
0.5 hr	=	20.6 mg/m^3 (8.5 ppm)

Because the AEGL-2 values based upon acute toxicity were equivalent to or lower than the 10^{-4} risk values derived based on potential carcinogenicity, the acute toxicity data were used for the AEGLs for dimethylhydrazine. For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

APPENDIX J. EXAMPLE OF THE DERIVATION SUMMARY APPENDIX IN A TECHNICAL SUPPORT DOCUMENT

DERIVATION SUMMARY
(CAS NO. 57-14-7; 1,1-DIMETHYLHYDRAZINE)
(CAS NO. 540-73-8; 1,2-DIMETHYLHYDRAZINE)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
Not recommended	Not recommended	Not recommended	Not recommended
Reference: Not applicable.			
Test Species/Strain/Number: Not applicable			
Exposure Route/Concentrations/Durations: Not applicable			
Effects: Not applicable			
Endpoint/Concentration/Rationale: Not applicable			
Uncertainty Factors/Rationale: Not applicable			
Modifying Factor: Not applicable			
Animal to Human Dosimetric Adjustment: Not applicable			
Time Scaling: Not applicable			
Data Adequacy: Analysis of dimethylhydrazine toxicity data in total revealed that significant toxicity may occur at or below the odor threshold. Furthermore, the available data indicate that there is there an almost nonexistent margin between exposures resulting in no response and those causing lethality. Therefore, AEGL-1values for dimethylhydrazine are not recommended (NR). Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.			

NOTE: If an AEGL-1 value is not recommended, there should be a short discussion of the rationale for that choice. The rationale should include as appropriate a discussion that numeric values for AEGL-1 are not recommended because (1) relevant data are lacking, (2) the margin of safety between the derived AEGL-1 and AEGL-2 values is inadequate, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the

AEGL-2 is without adverse effects.

DERIVATION SUMMARY
(CAS NO. 57-14-7; 1,1-DIMETHYLHYDRAZINE)
(CAS NO. 540-73-8; 1,2-DIMETHYLHYDRAZINE)

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
6.0 ppm	3.0 ppm	0.75 ppm	0.38 ppm

Reference: Weeks, M.H., G.C. Maxey, M.E. Sicks, E.A. Greene. 1963. Vapor toxicity on UDMH in rats and dogs from short exposures. Am. Ind. Hyg. Assoc. J. 24: 137-143.

Test Species/Strain/Sex/Number: mongrel dogs, 2-4/group, sex not specified

Exposure Route/Concentrations/Durations: Inhalation; 1,200-4,230 ppm for 5 minutes; 360, 400 or 1,530 ppm for 15 minutes; 80-250 ppm for 60 minutes

Effects:

Exposure (15 min)	Effect
360 ppm	muscle fasciculations in 1 of 4 dogs (determinant for AEGL-2)
400 ppm	behavioral changes in 2 of 4 dogs
1,530 ppm	tremors, convulsions, vomiting in 2 of 2 dogs

Endpoint/Concentration/Rationale: 15-min exposure to 360 ppm considered a threshold for potentially irreversible effects or effects that would impair escape. At this exposure, muscle fasciculations were observed in 1 of 4 exposed dogs and at 400 ppm behavioral changes were observed.

Uncertainty Factors/Rationale:

Total uncertainty factor: 30

Interspecies: 3 - The toxic response to dimethylhydrazine (LC_{50} values) was similar across species. The 4-hr LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 hr using n=1. The more sensitive species, the dog, was used to derive the AEGL-2 values.

Intraspecies: 10 – A broad spectrum of effects were seen which included behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals regarding these effects may vary. This variability was especially demonstrated in dogs wherein responses varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Therefore, a factor of 10 was retained. A factor of 10 was also retained because experiments by Weeks et al. (1963) indicated that dogs that had been previously stressed (auditory stimuli) which may have affected their response to dimethylhydrazine. Based upon these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$ where n = 1 and k = 180 ppm-min; LC_{50} data were available for 5, 15, 30, 60, and 240-minute exposures in rats and 5, 15, and 60 minutes for the dog. Exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats, n=0.80 for dogs). For time-scaling, a linear relationship was assumed and a value where n=1 was selected.

Data Adequacy: Information regarding the human experience for acute inhalation exposure to dimethylhydrazine are limited to qualitatively case reports indicating nasal and respiratory tract irritation, breathing difficulties, and nausea.. Data in animals have shown concentration-dependent effects ranging from respiratory tract irritation, pulmonary edema and neurological effects to lethality. Because the nonlethal effects in humans and animals are qualitatively similar, the animal data were considered relevant and appropriate for development of AEGL values. The AEGL values for dimethylhydrazine reflect the steep exposure-response relationship suggested by available data.

DERIVATION SUMMARY
(CAS NO. 57-14-7; 1,1-DIMETHYLHYDRAZINE)
(CAS NO. 540-73-8; 1,2-DIMETHYLHYDRAZINE)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
22 ppm	11 ppm	2.7 ppm	1.4 ppm

Reference:	Weeks, M.H., G.C. Maxey, M.E. Sicks, E.A. Greene. 1963. Vapor toxicity of UDMH in rats and dogs from short exposures. Am. Ind. Hyg. Assoc. J. 24: 137-143.
Test Species/Strain/Sex/Number: mongrel dogs, 3-4/group; sex not specified	
Exposure Route/Concentrations/Durations:	Inhalation; exposure to various concentrations (80-22,300 ppm) for 5, 15, or 60 minutes
Effects:	
1-hr LC_{50}	981 ppm (reduction by 1/3 was basis for AEGL-3 derivation)
15-min LC_{50}	3,580 ppm
5-min LC_{50}	22,300 ppm
Endpoint/Concentration/Rationale:	1-hr LC_{50} (981 ppm) reduced by 1/3 was considered an estimate of the lethality threshold (327 ppm). Based on the available exposure-response data for this chemical (Jacobson et al., 1955) a three fold reduction in LC50 values results in exposures which would not be associated with lethality.

Uncertainty Factors/Rationale: Total uncertainty factor: 30 Interspecies: 3 -The toxic response to dimethylhydrazine (LC_{50} values) was similar across species. The 4-hr LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 hr using n=1. The more sensitive species, the dog, was used to derive the AEGL-3 values. Intraspecies: 10 – A broad spectrum of effects were seen which included behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals regarding these effects may vary. This variability was especially demonstrated in dogs wherein responses varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Therefore, a factor of 10 was used. A factor of 10-fold was also used because experiments by Weeks et al. (1963) indicated that dogs previously stressed by auditory stimuli may have a potentiated response to dimethylhydrazine. Based upon these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine subsequent to similar stresses.
Modifying Factor: None
Animal to Human Dosimetric Adjustment: None applied, insufficient data
Time Scaling: $C^n \times t = k$ where n = 1 and k = 654 ppm-min; LC_{50} data were available for 5, 15, 30, 60, and 240-minute exposures in rats and 5, 15, and 60 minutes for the dog. Exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats, n=0.80 for dogs). For time-scaling, a linear relationship was assumed and a value where n=1 selected by the National Advisory Committee.
Data Adequacy: Information regarding the lethality of dimethylhydrazine in humans were not available. Lethality data for several animal species allowed for a defensible development of the AEGL-3 values but uncertainties remain regarding individual variability in the toxic response to dimethylhydrazines.

APPENDIX K. LIST OF EXTANT STANDARDS AND GUIDELINES IN A TECHNICAL SUPPORT DOCUMENT

Section 8.2 of the Technical Support Document compares the AEGL values for a chemical with other standards and guidelines previously published for exposure durations ranging from 10 minutes to 8 hours. A summary discussion of important comparisons should be presented in the text and the values for recognized standards and guidelines, if available, should be presented on the table. The statement "All currently available standards and guidelines are shown in Table ..." should be included in the text to affirm completeness of the table. Only those standards or guidelines with published values for a given chemical should be included in the table. In cases where the exposure duration of a published standard or guideline differs from those designated for AEGLs (e.g., 15 minute PEL-STEL), the value should be placed in parentheses in the column of the closest AEGL exposure duration category and footnoted to indicate its true exposure duration. A list of recognized standards and guidelines and the order in which they should appear in the table is shown below.

List and Order of Presentation of Extant Standards and Guidelines in the TSD Table.

AEGL-1
AEGL-2
AEGL-3
ERPG-1 (AIHA)
ERPG-2 (AIHA)
ERPG-3 (AIHA)
SPEGL (NRC)
EEL (NRC)
STPL (NRC)
CEL (NRC)
EEGL (NRC)
SMAC (NRC)
PEL-STEL (OSHA)
PEL-TWA (OSHA)
IDLH (NIOSH)
REL-STEL (NIOSH)
TLV-STEL (ACGIH)
TLV-TWA (ACGIH)
MAC (THE NETHERLANDS)
MAK (GERMANY)
MAK S. (GERMANY)
EINSATZTOLERANZWERT (ACTION TOLERANCE LEVELS - GERMANY)